NOVARTIS

Regulatory Affairs

UPERIO(ENTRESTO)® (sacubitril/valsartan) 50 mg, 100 mg, 200 mg Film-coated tablets

Core Data Sheet (CDS)

Version 2.2

NOTICE

The Novartis Core Data Sheet (CDS) displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

The Novartis CDS contains all relevant information relating to indications, dosage regimen, pharmacology and Core Safety Information which Novartis requires to be listed for the product in all countries where the product is registered.

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Deletions are crossed out
Additions/changes are underlined
Essential hypertension text in grey

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1 Trade name

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

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

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

2 Description and composition

Pharmaceutical form [1]

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.

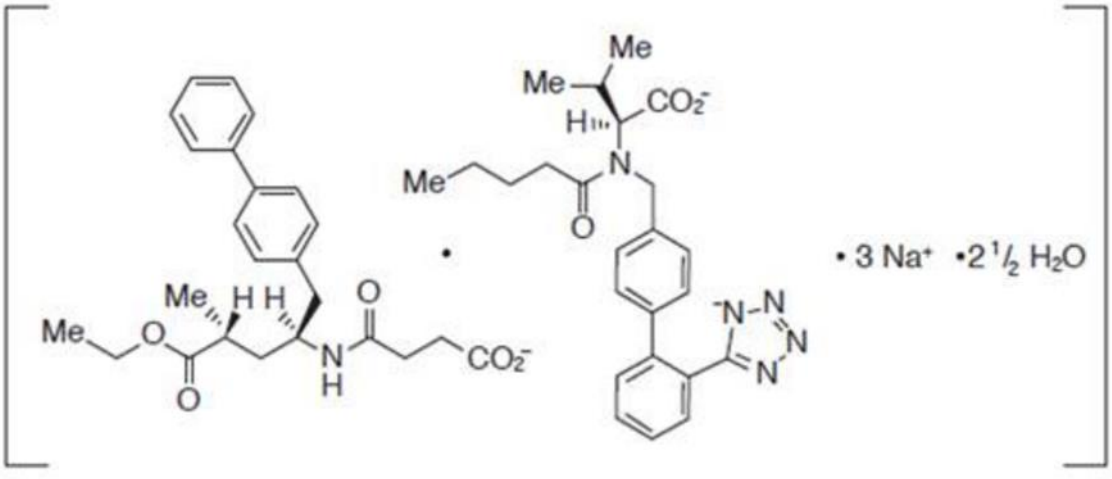
100 mg: Pale yellow ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with "NVR" on one side and "L1" on the other side.

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 or local designated active substance name as applicable.

Entresto® contains a 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 [2]:



Following oral administration, the complex dissociates into sacubitril (which is further metabolized to sacubitrilat) and valsartan [2].

Single dose strengths

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)*[1].

Fixed dose strengths

Entresto 24 mg/26 mg film-coated tablets*

Each film-coated tablet contains 24.3 mg sacubitril and 25.7 mg valsartan.

Entresto 49 mg/51 mg film-coated tablets*

Each film-coated tablet contains 48.6 mg sacubitril and 51.4 mg valsartan.

Entresto 97 mg/103 mg film-coated tablets*

Each film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan.

**Information may differ in some countries.*

Excipients [29]

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

Excipients of film-coating: [5,29]

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).

3 Indications

Heart failure

Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure.[3,81,143, 144]. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal [143, 144]. 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 [3].

Hypertension

Entresto is indicated for the treatment of essential hypertension [141].

4 Dosage regimen and administration

Dosage regimen

Heart Failure

The target dose of Entresto is 200 mg twice daily [6].

The recommended starting dose of Entresto is 100 mg twice daily [65]. 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 12 Clinical studies) [65].

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 [65].

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 5 Contraindications) [26].

Entresto should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of Entresto (see sections 6 Warnings and precautions and 8 Drug interactions) [4].

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 [7].

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 [141]. 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 5 Contraindications) and angiotensin II receptor blockers (ARBs) (see section 6 Warnings and precautions) [141].

Special populations

Renal impairment

A starting dose of 50 mg twice daily is recommended in heart failure patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) [138]. Caution is recommended when using Entresto in these patients due to limited data (see section 11 Clinical pharmacology) [13].

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 11 Clinical pharmacology) [141].

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 [12].

Hepatic impairment

A starting dose of 50 mg twice daily is recommended for patients with heart failure patients with moderate hepatic impairment (Child-Pugh B classification) [138].

A starting dose of 100 mg once daily is recommended for essential hypertensive patients with moderate hepatic impairment (Child-Pugh B classification) [141].

No dose adjustment is required when administering Entresto to patients with mild hepatic impairment (Child-Pugh A classification) [14].

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 11 Clinical pharmacology) [15].

Pediatric patients (below 18 years of age)

The safety and efficacy of Entresto in pediatric 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 [16].

Method of administration

For oral use. Entresto may be administered with or without food (see section 11 Clinical pharmacology) [51].

5 Contraindications

- Hypersensitivity to the active substance, sacubitril, valsartan, or to any of the excipients [18].
- Concomitant use with ACE inhibitors (see sections 6 Warnings and precautions, 4 Dosage regimen and administration, and 8 Interactions). Entresto must not be administered until 36 hours after discontinuing ACE inhibitor therapy [26].
- Known history of angioedema related to previous ACE inhibitor or ARB therapy [26].
- Hereditary angioedema [139].
- Concomitant use with aliskiren in patients with Type 2 diabetes (see sections 6 Warnings and precautions and 8 Interactions) [4].
- Pregnancy (see section 9 Pregnancy, lactation, females and males of reproductive potential) [18].

6 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 sections 5 Contraindications, 4 Dosage regimen and administration, and 8 Interactions) [26].
- Caution is required while co-administering Entresto with direct renin inhibitors such as aliskiren (see sections 5 Contraindications, and 8 Interactions). Entresto must not be administered with aliskiren in patients with Type 2 diabetes (see section 5 Contraindications) [4].

- Entresto should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of Entresto (see sections 4 Dosage regimen and administration, and 8 Interactions) [4].

Hypotension

Cases of symptomatic hypotension have been reported in patients treated with Entresto during clinical trials [26]. If hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g. hypovolemia) should be considered [26]. If hypotension persists despite such measures, the dosage of Entresto should be reduced or the product should be temporarily discontinued (see section 4 Dosage regimen and administration) [26]. Permanent discontinuation of therapy is usually not required [24]. 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%) [22]. Down titration of Entresto should be considered in patients who develop a clinically significant decrease in renal function [7]. Caution should be exercised when administering Entresto in patients with severe renal impairment (see sections 4 Dosage regimen and administration, and 11 Clinical Pharmacology) [10,13].

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 [24]. Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used with caution when co-administered with Entresto [28]. If clinically significant hyperkalemia occurs, measures such as reducing dietary potassium, or adjusting the dose of concomitant medications should be considered [7]. 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 4 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 [26]. 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 [11].

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 [26]. 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 5 Contraindications) [26,139].

Black patients may have increased susceptibility to develop angioedema [25].

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 [18].

7 Adverse drug reactions

Heart Failure

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 [145].

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=4,203) or enalapril 10 mg (n=4,229) [19,38]. Patients randomized to Entresto received treatment for up to 4.3 years, with a median duration of exposure of 24 months [36]; 3,271 patients were treated for more than one year [37]. 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 [24]. The events most commonly associated with dosage adjustment or treatment interruption were hypotension, hyperkalemia and renal impairment [40].

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 [44].

The overall frequency of adverse reactions was not related to gender, age, or race [41].

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 7-1 Adverse Drug Reactions in the PARADIGM-HF, Safety Set [42]

Adverse drug reactions	Entresto 200 mg twice daily (%)*	Enalapril 10 mg twice daily (%)*	Frequency category
Metabolism and nutrition disorders			
Hyperkalaemia	11.61	14.00	Very common
Hypokalaemia	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 [143,145].

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) [142].

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 7-2) [142].

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 7-2 Adverse Drug Reactions in the pooled hypertension clinical studies [142].

Adverse drug reactions	Entresto N= 3272 n (%)	Olmesartan monotherapy N=1352 n (%)	Frequency category
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 7-3 Adverse Drug Reactions from spontaneous reports and literature cases (frequency not known)

Immune system disorders
Hypersensitivity (including rash, pruritus, and anaphylaxis) [139]

8 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 sections 5 Contraindications, and 4 Dosage regimen and administration) [26].

Aliskiren: The concomitant use of Entresto with aliskiren is contraindicated in patients with Type 2 diabetes (see section 5 Contraindications) [4].

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 6 Warnings and precautions) [4].

Concomitant use with aliskiren should be avoided in patients with renal impairment (eGFR <60 mL/min/1.73 m^2) (see section 6 Warnings and precautions) [4].

Observed interactions to be considered

Statins: *In vitro* data indicates that sacubitril inhibits OATP1B1 and OATP1B3 transporters [43]. 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 [45,80]. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered [140].

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 [45,46].

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 6 Warnings and precautions) [4].

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 [4].

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 [4].

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 [67].

No significant interactions

No clinically meaningful drug-drug interaction was observed upon co-administration of Entresto and furosemide [52], digoxin [53], warfarin [137], hydrochlorothiazide [56], amlodipine [55], metformin [57], omeprazole [58], carvedilol [59], intravenous nitroglycerin [60] or a combination of levonorgestrel/ethinyl estradiol [61]. No interaction is expected with atenolol, indomethacin, glyburide, or cimetidine [4].

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 [63].

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk Summary

As for other drugs that also act directly on the RAAS, Entresto must not be used during pregnancy (see section 5 Contraindications) [10]. 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 [136]. 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] [89,91]. 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 [89]. 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] [87] and valsartan [86] 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.

9.2 Lactation

Risk Summary

It is not known whether the components of Entresto are transferred into human milk. The components of Entresto, sacubitril [49] and valsartan [50], 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 [10]. 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.

9.3 Females and males of reproductive potential

Female 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 [10].

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) [48].

10 Overdosage

Limited data are available with regards to overdosage in human subjects with Entresto [79]. In healthy volunteers, a single dose of Entresto 1200 mg, and 900 mg multiple doses (14 days) have been studied and were well tolerated [88].

Hypotension is the most likely symptom of overdosage due to the blood pressure lowering effects of Entresto. Symptomatic treatment should be provided [79].

Entresto is unlikely to be removed by hemodialysis due to high protein binding [21].

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II antagonists, other combinations, ATC code: C09DX04.

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 [8,74]. 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 [8,68]. Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release [74].

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 [68]. 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 [69]. 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 [70]. In PARADIGM-HF, Entresto decreased plasma NT-proBNP and increased plasma BNP and urine cGMP compared with enalapril [71]. In PARAGON-HF, Entresto decreased NT-proBNP, troponin and soluble ST2 (sST2) and increased urine cGMP compared to valsartan [143,144]. 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 [72].

In a thorough QTc clinical study in healthy male subjects, single doses of 400 mg and 1,200 mg Entresto had no effect on cardiac repolarization [9].

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 13 Nonclinical safety data) [75].

Pharmacokinetics (PK)

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 [45]. The oral absolute bioavailability of sacubitril and valsartan is estimated to be ≥60% [83] and 23% [47,108], respectively. The valsartan in Entresto is more bioavailable than the valsartan in other marketed tablet formulations [108].

Following twice daily dosing of Entresto, steady state levels of sacubitril, sacubitrilat, and valsartan are reached in 3 days [53,54,135]. At steady state, sacubitril and valsartan do not accumulate significantly, while sacubitrilat accumulates by 1.6-fold [80]. 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 [141]. Entresto administration with food has no clinically significant impact on the systemic exposures of sacubitril, sacubitrilat and valsartan [51]. 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 [39]. Entresto can therefore be `administered with or without food [51].

Distribution

Entresto is highly bound to plasma proteins (94% - 97%) [82]. Based on the comparison of plasma and CSF exposures, sacubitrilat does cross the blood brain barrier to a limited extent (0.28%) [75]. Entresto has an apparent volume of distribution ranging from 75 L to 103 L [45].

Biotransformation/metabolism

Sacubitril is readily converted to sacubitrilat by esterases; sacubitrilat is not further metabolized to a significant extent [83]. Valsartan is minimally metabolized, as only about 20% of the dose is recovered as metabolites [90]. A hydroxyl metabolite has been identified in plasma at low concentrations (<10%) [33]. 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 [23].

Elimination

Following oral administration, 52 to 68% of sacubitril (primarily as sacubitrilat) [83] and ~13% of valsartan and its metabolites [34,90] are excreted in urine; 37 to 48% of sacubitril (primarily as sacubitrilat) [83], and 86% of valsartan and its metabolites are excreted in feces [47,90].

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 [31].

Linearity/non-linearity

The pharmacokinetics of sacubitril, sacubitrilat, and valsartan are linear in the dose range tested (50 to 400 mg of Entresto) [32].

Special populations

Pediatric patients (aged below 18 years of age)

Entresto has not been studied in pediatric patients.

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 [16]. However, this is not associated with clinically relevant effects and therefore no dosage adjustment is necessary [20].

Gender

The pharmacokinetics of Entresto (sacubitril, sacubitrilat and valsartan) are similar between male and female subjects [16].

Race/Ethnicity

The pharmacokinetics of Entresto (sacubitril, sacubitrilat and valsartan) are comparable across different race and ethnic groups (Caucasians, Blacks, Asians, Japanese and others) [35].

Renal impairment

A correlation was observed between renal function and systemic exposure to sacubitrilat, but not to valsartan [12]. In 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 [12]. A 2.7-fold higher AUC for sacubitrilat was observed in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) [13]. A starting dose of 50 mg twice daily is recommended in heart failure patients with severe renal impairment [138]. Caution is recommended when administering Entresto to these patients due to limited data [13]. Safety and efficacy of Entresto in patients with essential hypertension and with severe renal impairment have not been established [141].

No studies have been performed in patients undergoing dialysis. However, sacubitrilat and valsartan are highly bound to plasma protein [82] and, therefore, unlikely to be effectively removed by dialysis.

Hepatic impairment

In 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 [14]. No dosage adjustment is recommended when administering Entresto to patients with mild hepatic impairment (Child-Pugh A classification) including patients with biliary obstructive disorders [14]. In patients with moderate hepatic impairment (Child-Pugh B classification), a starting dose of 50 mg twice daily is recommended in patients with heart failure and 100 mg once daily in hypertensive patients [138,141]. Entresto has not been studied in patients with severe hepatic impairment. Therefore, its use is not recommended in patients with severe hepatic impairment.

12 Clinical studies

Dosing in clinical trials was based on the total amount of both components of Entresto, i.e., 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively [64].

Heart Failure

PARADIGM-HF

PARADIGM-HF was a multinational, randomized, double-blind study of 8,442 patients [64] 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 [19]. The primary endpoint was the composite of cardiovascular (CV) death or hospitalization for heart failure (HF) [27].

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%) [92]. The median follow-up duration was 27 months and patients were treated for up to 4.3 years [36].

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 [19]. 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)] [64].

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 [93].

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) [66].

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 [94]. This effect was observed early and was sustained throughout the duration of the trial [98]. The absolute risk reduction was 4.69% [62]. 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) [94]; see Table 12-1 and Figure 12-1. 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) [78]. 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) [77].

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 [96].

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 12-1). The absolute risk reduction was 2.84% [97].

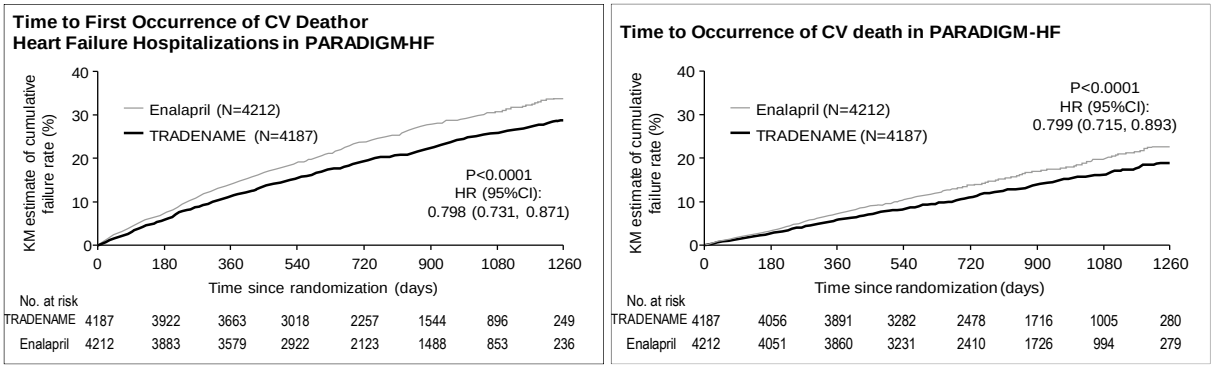
Table 12-1 Treatment effect for the primary composite endpoint, its components and all-cause mortality - PARADIGM-HF [94]

	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 [97]	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 12-1 Kaplan-Meier curves for the primary composite endpoint and the CV death component - PARADIGM-HF [98,99]



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) [100,101].

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 [102]. 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) [103].

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 enlargment (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

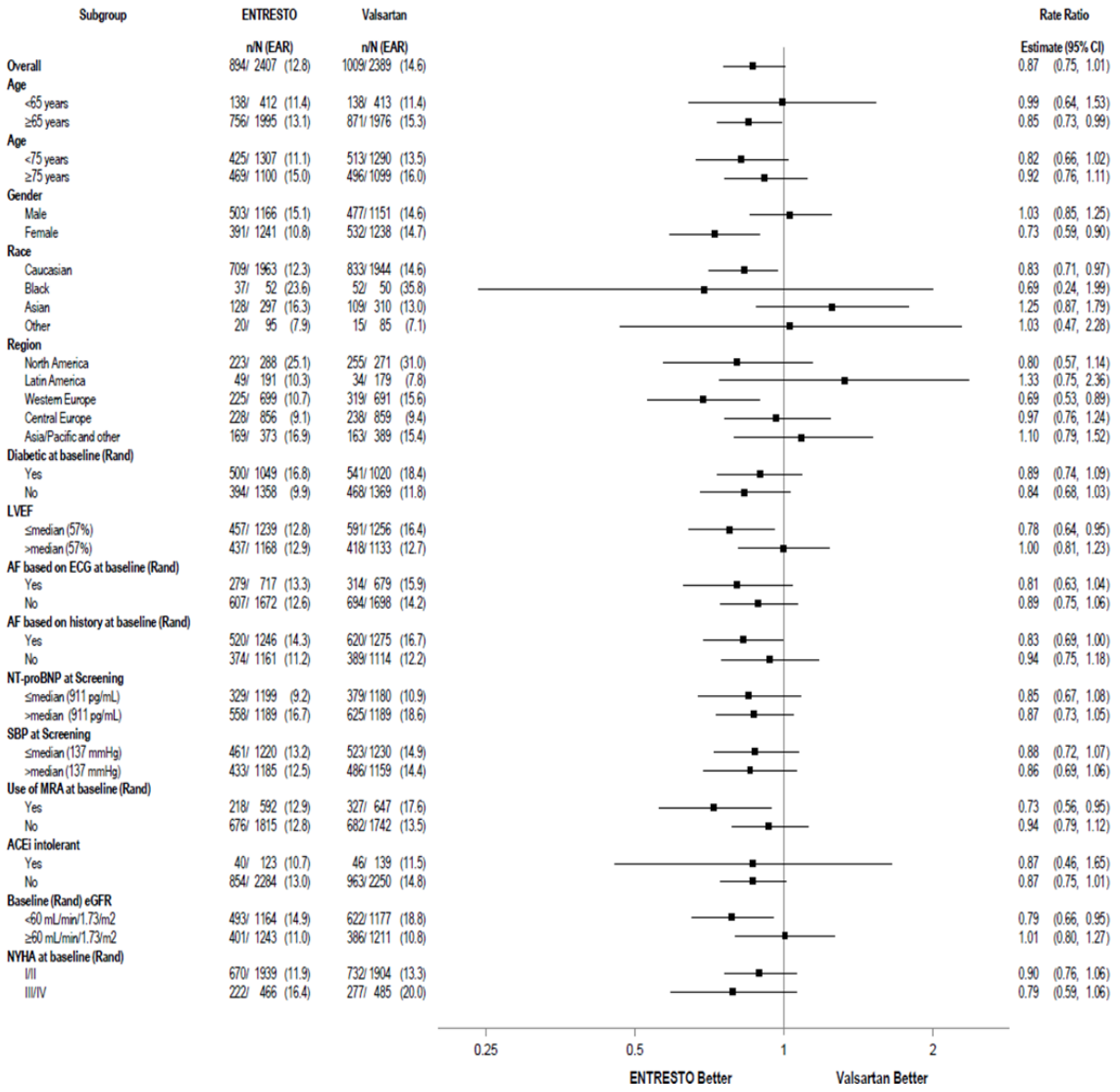
IV. The median left ventricular ejection fraction was 57%. The underlying cause of heart failure was of ischemic etiology in 36% of patients. Furthermore, 96% had a history of hypertension, 23% had a history of myocardial infarction, 46% had an eGFR < 60 mL/min/1.73 m^2, and 43% had diabetes mellitus. 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]) [143,144].

A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes (Figure 12-2).

Figure 12-2 Primary Composite Endpoint of Total HF Hospitalizations and CV Death – Subgroup Analysis - PARAGON-HF [143,144]



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 12-2 and Figure 12-3, and Figure 12-4). 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 12-1 and 12-4).

Table 12-2 Treatment Effect for Composite Endpoints (Primary and Expanded) and Components for LVEF ≤ 60% - PARAGON-HF [143,144]

	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 12-3 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 [143,144]

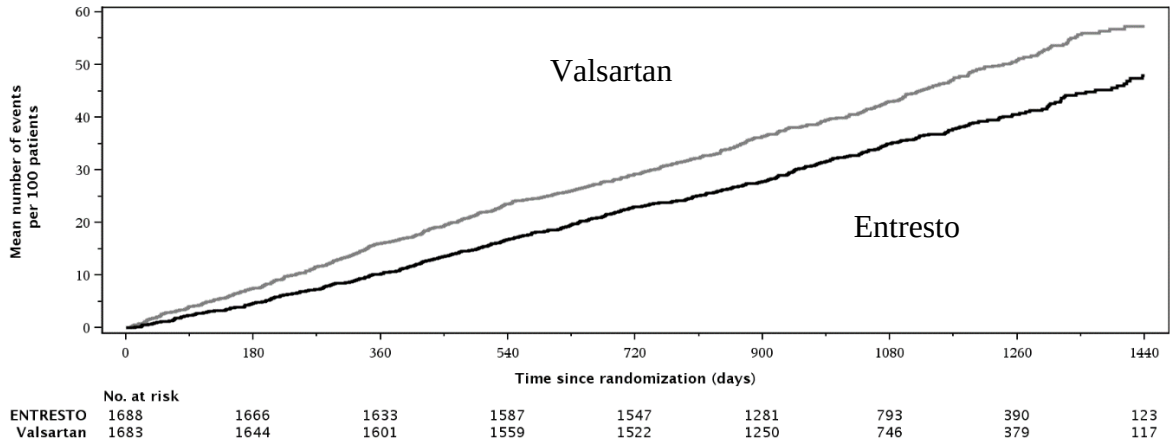
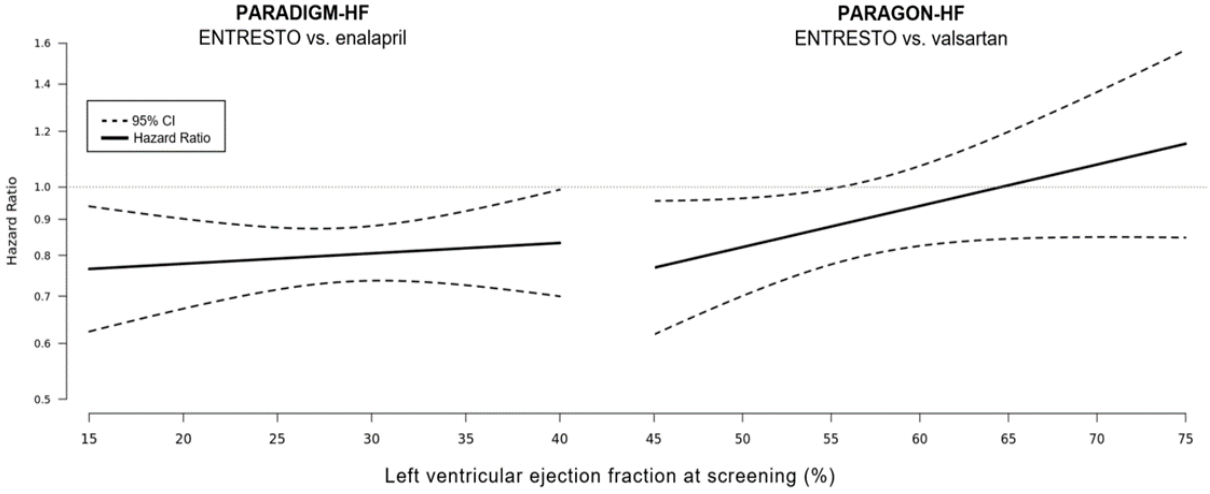


Figure 12-4 Treatment Effect for the Composite Endpoint of Time to First HF Hospitalization or CV Death by LVEF in PARADIGM-HF and PARAGON-HF [143,144]



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%) naïve to ACE inhibitor or ARB therapy or on varying doses of ACE inhibitors or ARBs prior to study entry [104,105]. 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 [105].

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 [106]. 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 [107,142].

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 [30,73,76]. 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 [109]. 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 [110]. A statistically significant improvement in NYHA class was noted at Week 36 (p=0.0488) [111].

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 [142]. 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 [141]. Consistent results were observed in mean diastolic BP [141].

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 [141].

13 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 [112,113,114,115]. Most findings seen in repeated toxicity studies were reversible and attributable to the pharmacology of AT_1 receptor blockade [116,117,118,119,120,121].

Carcinogenicity, mutagenesis and genetic toxicity

Carcinogenicity studies conducted in mice and rats with sacubitril [122,123] and valsartan [124,125] did not identify any carcinogenic potential for Entresto. The doses of sacubitril studied (high dose of 1,200 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, [126,127,128] sacubitril, [129,130,131] and valsartan [95,132,133,134] did not reveal any effects at either the gene or chromosome level.

Fertility, reproduction and development

See section 9 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 to 4 years old) cynomolgus monkeys treated with Entresto (50 mg/kg/day) for 2 weeks [85,84]. In this study, Entresto had a pharmacodynamic effect on CSF A-beta clearance in cynomolgus monkeys, increasing CSF A-beta 1-40, 1-42, and 1-38 levels; there was no corresponding increase in A-beta levels in the brain [84]. Increases in CSF A-beta 1-40 and 1-42 were not observed in a 2 week healthy volunteer study in humans (see section 11 Clinical pharmacology) [75]. 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 [121].

14 Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Storage requirements: Do not store above 30°C. Store in the original package to protect from moisture [31].

Entresto must be kept out of the reach and sight of children.

Information might differ in some countries.

Instructions for use and handling

Not applicable.

Special precautions for disposal

Not applicable.

15 References

1.	[Quality Overview Summary Drug Product] 2.3P Quality overall summary- 6002752_23P_M_966_1. Novartis Pharma AG, Basel, Switzerland. 21-Nov-2014-EU	2.3	Table 1.1
2.	[Quality Overview Summary Drug Substance] 2.3S Quality overall summary- 5001226_23S_M_966_1. Novartis Pharma AG, Basel, Switzerland. 21-Nov-2014-EU	2.3	Section1.1
3.	[Clinical Overview] 2.5- EU	2.5	Section 6.3.1
4.	[Clinical Overview] 2.5- EU	2.5	Section 5.1.10
5.	[Quality Overview Summary Drug Product] 2.3P Quality overall summary- 6002752_23P_M_966_1. Novartis Pharma AG, Basel, Switzerland. 21-Nov-2014-EU	2.3	section 2.1.2
6.	[Clinical Overview] 2.5- EU	2.5	Section 6.3.2
7.	[Clinical Overview] 2.5- EU	2.5	Section 6.3.2.2
8	[Clinical Pharmacology Summary] 2.7.2 -EU	2.7.2	Section 1.2
9.	[Study LCZ696B2123 report (2013)] A randomized, partially blinded, placebo-controlled crossover study to assess the effects of single therapeutic and supratherapeutic doses of LCZ696 on baseline- and placebo-corrected QTc intervals in healthy male volunteers		Section 13
10.	[Clinical Overview] 2.5- EU	2.5	Section 6.3.3
11.	[Summary of Clinical Safety] 2.7.4- EU	2.7.4	Section 2.1.5.5
12.	[Study LCZ696A2204 report (2010)] An open label, parallel-group study to determine multiple dose pharmacokinetics of LCZ696 and its metabolites in subjects with mild and moderate renal impairment compared to matched healthy subjects with normal renal function.		Section 13
13.	[Study LCZ696A2205 report (2010)] An open label, parallel-group study to determine multiple dose pharmacokinetics of LCZ696 and its metabolites in subjects with severe renal impairment compared to matched healthy subjects with normal renal function.		Section 13
14.	Study LCZ696B2203 report (2013) A single-dose, open-label, parallel-group study to assess the pharmacokinetics of LCZ696 in subjects with hepatic impairment compared to matched healthy subjects.		Section 13
15.	[Clinical Pharmacology Summary] 2.7.2 -EU	2.7.2	Section 3.1.9.8
16.	[Study LCZ696B2109 report (2013)] An open-label, single dose study to assess the effect of age and gender on the pharmacokinetics of LCZ696 in healthy volunteers.		Section 13
17.	[Study LCZ696B2314 report (2014)]: A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure (HF) and reduced ejection fraction.		Section 12.3.3.4.4
18.	[Study LCZ696B2314 report (2014)] : A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure (HF) and reduced ejection fraction.		Section 9.3.2

19.	[Study LCZ696B2314 report (2014)] : A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure (HF) and reduced ejection fraction.		Section 9.1
20.	[Clinical Overview] 2.5- EU	2.5	Section 3.1.3.1
21.	[Study LCZ696A2102 report (2009)]: A randomized, double-blind, placebo controlled, time-lagged, parallel group, interwoven single- and multiple-ascending dose study to assess safety, tolerability, and pharmacokinetics of LCZ696 in healthy volunteers.		Section 8.2
22.	[Study LCZ696B2314 report (2014)]: A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure (HF) and reduced ejection fraction.		Table 12-18
23.	[Clinical Pharmacology Summary] 2.7.2-EU	2.7.2	Section 1.5.1.1
24.	[Study LCZ696B2314 report (2014)]: A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure (HF) and reduced ejection fraction.		Table 14.3.1-1 .13
25.	[Clinical Overview] 2.5- EU	2.5	Section 5.1.5.4
26.	[Clinical Overview] 2.5- EU	2.5	Section 6.2
27.	[Study LCZ696B2314 report (2014)]: A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure (HF) and reduced ejection fraction.		Section 8.1
28.	[Clinical Overview] 2.5- EU	2.5	Section 5.1.5.3
29.	[Quality Overview Summary Drug Product] 2.3P Quality overall summary- 6002752_23P_M_966_1 Novartis Pharma AG, Basel, Switzerland. 21-Nov-2014-EU	2.3	Table 1.2
30.	[Study LCZ696B2214 report (2013)] A 36-Week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the efficacy, safety and tolerability of LCZ696 compared to valsartan in patients with CHF and preserved left-ventricular ejection fraction		Table10-1
31.	[Clinical Pharmacology Summary] 2.7.2-EU	2.7.2	Table 3-2
32.	[Clinical Pharmacology Summary] 2.7.2-EU	2.7.2	Section 3.1.4
33.	[Clinical Pharmacology Summary] 2.7.2-EU	2.7.2	Section 3.1.7
34.	[Clinical Pharmacology Summary] 2.7.2-EU	2.7.2	Section 3.1.8
35.	[Clinical Pharmacology Summary] 2.7.2-EU	2.7.2	Section 3.1.9.4

36.	[Study LCZ696B2314 report (2014)]: A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure (HF) and reduced ejection fraction.		Table 14.3-1.1
37.	[Study LCZ696B2314 report (2014)]: A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure (HF) and reduced ejection fraction.		Table 14.3-1.6
38.	[Study LCZ696B2314 report (2014)]: A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure (HF) and reduced ejection fraction.		Table 10-1
39.	[Protocol 17 report (1994)] Double-blind, randomized, placebo-controlled, parallel design trial of twelve to fourteen weeks duration to determine the effect of food on the antihypertensive response of CGP 48933 80 mg in patients with mild to moderate essential hypertension.		Section 11
40.	[Study LCZ696B2314 report (2014)]: A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure (HF) and reduced ejection fraction.		Table 14.3.1-1.14
41.	[Study LCZ696B2314 report (2014)]: A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure (HF) and reduced ejection fraction.		Section 12.2.1
42.	[Clinical Overview] 2.5- EU	2.5	Table 5-8
43.	[Study 1200043 report (2013)] Assessment of LBQ657 (active metabolite of AHU377) as a substrate of human organic anion transporting polypeptides 1B1 (OATP1B1) and 1B3 (OATP1B3).		Section 4
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46.	[Study LCZ696B2225 report (2013)] An open-label, three-period, single sequence study to evaluate the pharmacokinetic drug-drug interaction between LCZ696 and sildenafil in subjects with mild to moderate hypertension.		Section 13
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48.	[Study 0970613 report (2010)]. LCZ696: An oral (gavage) fertility and early embryonic development study in rats.		Section 5
49.	[DMPK R1200622 report (2013)]. Excretion in milk after a single oral dose of [14C] LCZ696 in the rat.		Section 4
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53.	[Study LCZ696B2111 report (2010)] An open label, two-period, single sequence study to evaluate the Pharmacokinetic drug-drug interaction between LCZ696 and Digoxin in healthy adult subjects.		Section 11
54.	[Study LCZ696B2112 report (2010)] A single blind, randomized, two-period, two-treatment crossover study to assess the pharmacokinetic and pharmacodynamic drug-drug interaction between LCZ696 and warfarin in healthy adult subjects.		Section 11.4.1, Table 11-2
55.	[Study LCZ696A2119 report (2013)] An open label, three-period, single sequence study to evaluate the pharmacokinetic drug-drug interaction between LCZ696 and amlodipine in healthy volunteers.		Section 13
56.	[Study LCZ696A2120 report (2013] An open label, three-period, single sequence study to evaluate the pharmacokinetic drug-drug interaction between LCZ696 and hydrochlorothiazide in healthy volunteers.		Section 13
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58.	[Study LCZ696B2113 report (2013)] An open-label, two-period, single-sequence study to evaluate the effect of omeprazole on the pharmacokinetics of LCZ696 in healthy volunteers.		Section 13
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63.	[Study R0300252 report (2004)]: In vitro assessment of cytochrome P450 enzyme inhibition by NVP-AHU377 and its metabolite NVP-LBQ657.		Section 4

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65.	[Clinical Overview] 2.5- EU	2.5	Section 6.3.2
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80.	[Study LCZ696B2115 report (2012)]: An open-label study to evaluate the single and multiple dose pharmacokinetics of LCZ696 and the drug-drug interaction potential between LCZ696 and atorvastatin in healthy Chinese subjects.		Section 13
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84.	[Study 1270586A report (2014)] LCZ696: A 16-day oral (gavage) investigational study of cerebrospinal fluid drug levels and amyloid beta in the female cynomolgus monkey. Determination of Amyloid Beta Clearance.		Section 5
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86.	[Study 936207 report (1994)] CGP 48 933. A modified perinatal and postnatal reproductive (Segment III) study in rats.		Section 5
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90.	[Protocol 16 report (1995)] Pharmacokinetics, disposition and biotransformation of CGP 48 933 in healthy male volunteers after a single oral dose of 80 mg 14C-radiolabelled preparation.		Section 7
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98.	[Study LCZ696B2314 report (2014)]: A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure (HF) and reduced ejection fraction.	Figure14.2-1.2
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102.	[Study LCZ696B2314 report (2014)]: A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure (HF) and reduced ejection fraction.	Table 14.2-2.4

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115.	[Study 0670464 report (2007)] LCZ696: A neuropharmacological profile (NPP) after oral (gavage) administration in male rats.		Section 5
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135.	[Clinical Pharmacology Summary] 2.7.2 -EU	2.7.2	Section 3.1.5.1
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16 CDS history table

Version	Effective date	GLC/PSB approval date	SLC Tracking No.	Section keyword	Refs.	Authors GLM/GPRD/GPRM
1.0	04-Dec-2014	12-Nov-2014 21-Nov-2014	N/A	CDS Creation	1-137	M. Abraham, M. Berkhin, M. Weitbruch
1.1	10-Aug-2015	04-Aug-2015	2015-PSB/GLC-0769-s	CDS Amendment –dose adjustment for patients with severe renal impairment and moderate hepatic impairment Section 4 and Section 11 modification	138	M. Abraham, M. Berkhin, M. Weitbruch, M. Romano, A. Zhang
1.2	10-Jul-2017	16-May-2017	2017-PSB/GLC-0871-s	CDS Amendment – ADR	139-140	M. Abraham, M. Berkhin, M. Weitbruch, A. Parakh, C. Hauschka, T. Armstrong

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2.0	N/A released to archive but not dispatched	4-Dec-2018	N/A	CDS Update Section 9 conversion: Based on CDS Sect 9 template Administrative changes to references and text	N/A	H. Baker Henry
2.1	24-Jun-2020	19-May-2020	N/A	CDS Amendment – Essential Hypertension indication	141—142	J. Holzer L. Heinrich A. Parekh
2.2	19-May-2021	27-April -2021	N/A	CDS Amendment –expansion of CHF indication (preserved ejection fraction)and chemical formula and structure	143-145	J. Holzer A. Parekh