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ENTRESTO helps patients stay out of the hospital, live longer, and feel better.[1-3]

ENTRESTO reduced the risk of CV death or HF hospitalisation as a first event by 20% vs enalapril (primary end point)[1]*

ENTRESTO provided an estimated 1 to 2 additional years of life expectancy and survival free from HF events† vs enalapril for patients aged 45 to 75 years[2†]

ENTRESTO reduced the risk of a primary end point event in both the most and least stable patients[5‡]

ENTRESTO helped slow the clinical progression of HF vs enalapril[15§]

* PARADIGM-HF was a multinational, randomised, double-blind, active-controlled, 2-arm event-driven trial comparing the long-term efficacy and safety of enalapril and ENTRESTO in 8442 patients in NYHA classes II-IV with chronic symptomatic HF and reduced EF (LVEF ≤40%. This was changed to ≤35% by an amendment to the protocol on 15 December, 2010). 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 49 mg/51 mg twice daily, increasing to 97 mg/103 mg twice daily. Patients were then randomised to the double-blind period of the study to receive either ENTRESTO 97 mg/103 mg (n=4209) or enalapril 10 mg twice daily (n=4233). Patients received treatment for up to 4.3 years, with a median duration of follow-up of 27 months; 3271 ENTRESTO patients were treated for more than 1 year.1

‡ This post hoc analysis of PARADIGM-HF examined the risk of the primary outcome based on presence of and time from a prior HF hospitalisation as a measure of clinical stability. Patients having their most recent HF hospitalisation within 3 months of screening (n=1611) were defined as least stable, while patients who had no prior HF hospitalisation (n=3125) were defined as the most stable. Compared to patients in the enalapril group, patients in the ENTRESTO group, regardless of presence of and time from a prior HF hospitalisation, had a reduction of at least 19% in the risk of a primary end point event.1,5

§ This post hoc analysis of PARADIGM-HF focused on prespecified measure of nonfatal clinical deterioration. In comparison with the enalapril group, fewer ENTRESTO patients required intensification of medical treatment for HF (520 for ENTRESTO vs 604 for enalapril; HR, 0.84; 95% CI, 0.74-0.94; *P*=0.003) or an ED visit for worsening HF (HR, 0.66; 95% CI, 0.52-0.85; *P*=0.001).1,15

† Post hoc analysis of PARADIGM-HF estimating the long-term treatment effects of ENTRESTO vs enalapril by deriving actuarial estimates of age-specific event rates and expected survival times using data regarding the age at randomisation and the age at the time of an outcome event. Survival analysis was performed using the patients' age as the time scale (rather than the time since randomisation) to estimate the projected effect of ENTRESTO vs enalapril over the duration of patients' lifetimes. The effect of treatment on the average duration of event-free survival was estimated by comparing the area under the survival curves.1,2

ENTRESTO™ ▼ (sacubitril/valsartan)
Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex).
Indications: In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.
Dosage & administration: The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water.
Contraindications: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy.
Warnings/Precautions: Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased 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. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing product. Hypotension: Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with Entresto during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with Entresto. If hypotension occurs, temporary down-titration or discontinuation of Entresto is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m2). There is no experience in patients with end-stage renal disease and use of Entresto is not recommended. Use of Entresto may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. Entresto is not recommended in patients with end-stage renal disease. Hyperkalaemia: Entresto should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation of Entresto. If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with Entresto. If angioedema occurs, discontinue Entresto immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. Entresto must not be re 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. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with Entresto because it is a neprilysin substrate.
Interactions: Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Should not be co-administered with another ARB. Use with caution when co-administering Entresto with statins or PDE5 inhibitors. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered. Monitoring serum potassium is recommended if Entresto is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on Entresto who are taking NSAIDs concomitantly. Interactions between Entresto and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of Entresto and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and Entresto was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of Entresto with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of Entresto with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with Entresto in patients receiving metformin, the clinical status of the patient should be evaluated.
Fertility, pregnancy and lactation: The use of Entresto is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether Entresto is excreted in human milk, but components were excreted in the milk of rats. 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.
Undesirable effects: *Very common (≥1/10):* Hyperkalaemia, hypotension, renal impairment. *Common (≥1/100 to <1/10):* Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. *Uncommon (≥1/1,000 to <1/100):* Hypersensitivity, postural dizziness, pruritis, rash, angioedema.
Packs sizes: Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets.
Legal classification: POM.
Marketing Authorisation Holder: Novartis Europharm Ltd, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.
Marketing Authorisation Numbers: Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007.
Please refer to the Summary of Product Characteristics (SmPC) before prescribing. Full Prescribing Information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872.
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References: 1. Novartis Europharm Ltd. Entresto Summary of Product Characteristics. 2. Claggett B, et al. *N Engl J Med*. 2015;373(23):2289-2290. 3. Lewis EF, et al. *Circ Heart Fail*. 2017;10(8):e003430. **5.** Solomon SD, et al. *JACC Heart Fail*. 2016;4(10):816-822. **15.** Packer M, et al.*Circulation*. 2015;131(1):54-61

Identify candidates sooner and help protect their lives with ENTRESTO.

Entresto™ sacubitril/valsartan

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