

Prescribing Information:

ENTRESTO® (sacubitril/valsartan)

Important note: Before prescribing, consult Summary of Product Characteristics (SmPC).

Presentation: Film-coated tablets of 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg of 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 sacubitril/valsartan 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 \geq 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. Sacubitril/valsartan 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. Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan. Combination of sacubitril/valsartan with direct renin inhibitors such as aliskiren is not recommended. Sacubitril/valsartan should not be co-administered with another ARB containing medicinal product. Hypotension: Treatment should not be initiated unless SBP is \geq 100 mmHg. Patients with SBP $<$ 100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with sacubitril/valsartan during clinical studies, especially in patients \geq 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 sacubitril/valsartan. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartan 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 sacubitril/valsartan is not recommended. Use of sacubitril/valsartan may be associated with decreased renal function, and down-titration should be considered in these patients. Hyperkalaemia: sacubitril/valsartan 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 sacubitril/valsartan. If serum potassium level is $>$ 5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with sacubitril/valsartan. If angioedema occurs, discontinue sacubitril/valsartan immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. sacubitril/valsartan 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 sacubitril/valsartan 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 sacubitril/valsartan 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 sacubitril/valsartan with statins or PDE5 inhibitors. Monitoring serum potassium is recommended if sacubitril/valsartan 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 sacubitril/valsartan who are taking NSAIDs concomitantly. Interactions between sacubitril/valsartan 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 sacubitril/valsartan and furosemide reduced C_{max} and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and sacubitril/valsartan was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerin alone, no dose adjustment is required. Co-administration of sacubitril/valsartan 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 sacubitril/valsartan with metformin reduced both C_{max} and AUC of metformin by 23%. When initiating therapy with sacubitril/valsartan in patients receiving metformin, the clinical status of the patient should be evaluated. **Fertility, pregnancy and lactation:** The use of sacubitril/valsartan 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 sacubitril/valsartan is excreted in human milk, but components were excreted in the milk of rats. Sacubitril/valsartan is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue sacubitril/valsartan while breast feeding, taking into account the importance of sacubitril/valsartan to the mother. **Undesirable effects:** *Very common (\geq 1/10):* Hyperkalaemia, hypotension, renal impairment. *Common (\geq 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 (\geq 1/1,000 to $<$ 1/100):* Hypersensitivity, postural dizziness, pruritis, rash, angioedema. **Legal classification:** POM. **Marketing Authorisation Numbers, quantities and price:** Entresto 24 mg/26 mg film-coated tablets £45.78 per 28 tablet pack (EU/1/15/1058/001); Entresto 49 mg/51 mg film-coated tablets £45.78 per 28 tablet pack, £91.56 per 56 tablet pack (EU/1/15/1058/002-003); Entresto 97 mg/103 mg film-coated tablets £91.56 per 56 tablet pack (EU/1/15/1058/006). **Date of last revision of prescribing information: June 2020.** ENT15-C019(4). **Full prescribing information (SmPC) is available from:** Novartis Pharmaceuticals UK Ltd, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Tel: 01276 692255.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard

Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the Patient Safety Information (PSI) tool at <https://psi.novartis.com>.

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com