Great Britain Prescribing Information:

ENTRESTO® (sacubitril/valsartan)

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

Indications: Adult heart failure: In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. Paediatric heart failure: In children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction. **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); granules in capsules for opening of 6 mg/6 mg and 15 mg/16 mg of sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). **Dosage & administration:** General considerations: 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. Adult heart failure: 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. Paediatric heart failure: Please see table below for recommended dose for paediatric 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. The lowest recommended dose is 6 mg/6 mg. Doses can be rounded up or down to the closest combination of full 6 mg/6 mg and/or 15 mg/16 mg capsules. When rounding the dose up or down during the up-titration phase, consideration should be given to ensuring progressive increase to the target dose. Sacubitril/valsartan film-coated tablets are not suitable for children weighing less than 40 kg. Sacubitril/valsartan granules are available for these patients.

Paediatric patient weight	To be given twice daily			
	Half the starting dose*	Starting dose	Intermediate dose	Target dose
Paediatric patients less than 40 kg	0.8 mg/kg#	1.6 mg/kg#	2.3 mg/kg#	3.1 mg/kg#
Paediatric patients at least 40 kg, less than 50 kg	0.8 mg/kg#	24 mg/ 26 mg	49 mg/ 51 mg	72 mg/ 78 mg
Paediatric patients at least 50 kg	24 mg/ 26 mg	49 mg/ 51 mg	72 mg/ 78 mg	97 mg/ 103 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 renal impairment and patients who have moderate hepatic impairment; #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 granules.

Half the starting dose is recommended in patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products. After initiation, the dose should be increased to the standard starting dose following the recommended dose titration in the above table and adjusted every 3 – 4 weeks. Special populations: Half of the starting dose should be considered for adult patients with SBP ≥ 100 to 110 mmHg, moderate (eGFR 30 – 60 mL/min/1.73 m^2) or severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (use with caution in severe renal impairment) and moderate hepatic impairment. In paediatric patients weighing 40 kg to less than 50 kg, a starting dose of 0.8 mg/kg twice daily is recommended in moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. After initiation, the dose should be increased following the recommended dose titration every 2 – 4 weeks. Method of administration: *Tablets:* Sacubitril/valsartan tablets may be administered with or without food. The tablets must be swallowed with a glass of water. Splitting or crushing of the tablets is not recommended. *Granules:* Sacubitril/valsartan granules are administered by opening the capsule and sprinkling the contents onto a small amount of soft food (1 to 2 teaspoons). Food containing the granules must be consumed immediately. Patients may receive either the 6 mg/6 mg (white cap) or 15 mg/16 mg (yellow cap) capsules or both to reach the required doses. The capsule must not be swallowed. The empty shells must be discarded after use and not swallowed. **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 m^2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. **Warnings/Precautions:** Dual blockade of the renin angiotensin-aldosterone system: Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Do not administer until 36 hours after discontinuing 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 ≥ 100 mmHg for adult patients or ≥ 5th percentile SBP for the age of the paediatric patient. Patients with SBP below these values were not studied. Cases of symptomatic hypotension have been reported in adult patients treated with sacubitril/valsartan 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 therapy 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 (eGFR < 30 mL/min/1.73 m^2). 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 in adult patients and > 5.3 mmol/L in paediatric patients. 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. Psychiatric disorders: Hallucinations, paranoia and sleep disorders, in the context of psychotic events, have been associated with sacubitril/valsartan use. If a patient experiences such events, discontinuation of sacubitril/valsartan treatment should be considered. **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 m^2). 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. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or ARBs including sacubitril/valsartan. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased further. Co-administration of sacubitril/valsartan and furosemide reduced Cmax 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 nitroglycerine 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 Cmax 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 (≥ 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, hyponatraemia, postural dizziness, pruritis, rash, angioedema. *Rare (≥ 1/10,000 to < 1/1,000):* Hallucinations (including auditory and visual hallucinations), sleep disorders. *Very rare (< 1/10,000):* Paranoia.

Legal classification: POM. **Marketing Authorisation numbers, quantities and price:** Entresto 24 mg/26 mg film-coated tablets £45.78 per 28 tablet pack (PLGB 00101/1041); Entresto 49 mg/51 mg film-coated tablets £45.78 per 28 tablet pack, £91.56 per 56 tablet pack (PLGB 00101/1042); Entresto 97 mg/103 mg film-coated tablets £91.56 per 56 tablet pack (PLGB 00101/1043); Entresto 6 mg/6 mg granules in capsules for opening £10.14 per 60 capsule pack (PLGB 00101/1225); Entresto 15 mg/16 mg granules in capsules for opening £25.36 per 60 capsule pack (PLGB 00101/1226). **Date of last revision of prescribing information: March 2024**. Content ID: 417491. **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 Event Reporting:

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 pharmacovigilance intake (PVI) tool at www.novartis.com/report. If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Northern Ireland Prescribing Information:

ENTRESTO® (sacubitril/valsartan)

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

Indications: Adult heart failure: In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. Paediatric heart failure: In children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction. **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); granules in capsules for opening of 6 mg/6 mg and 15 mg/16 mg of sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). **Dosage & administration:** General considerations: 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. Adult heart failure: 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. Paediatric heart failure: Please see table below for recommended dose for paediatric 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. The lowest recommended dose is 6 mg/6 mg. Doses can be rounded up or down to the closest combination of full 6 mg/6 mg and/or 15 mg/16 mg capsules. When rounding the dose up or down during the up-titration phase, consideration should be given to ensuring progressive increase to the target dose. Sacubitril/valsartan film-coated tablets are not suitable for children weighing less than 40 kg. Sacubitril/valsartan granules are available for these patients.

Paediatric patient weight	To be given twice daily			
	Half the starting dose*	Starting dose	Intermediate dose	Target dose
Paediatric patients less than 40 kg	0.8 mg/kg#	1.6 mg/kg#	2.3 mg/kg#	3.1 mg/kg#
Paediatric patients at least 40 kg, less than 50 kg	0.8 mg/kg#	24 mg/ 26 mg	49 mg/ 51 mg	72 mg/ 78 mg
Paediatric patients at least 50 kg	24 mg/ 26 mg	49 mg/ 51 mg	72 mg/ 78 mg	97 mg/ 103 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 renal impairment and patients who have moderate hepatic impairment; #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 granules.

Half the starting dose is recommended in patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products. After initiation, the dose should be increased to the standard starting dose following the recommended dose titration in the above table and adjusted every 3 – 4 weeks. Special populations: Half of the starting dose should be considered for adult patients with SBP ≥ 100 to 110 mmHg, moderate (eGFR 30 – 60 mL/min/1.73 m^2) or severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (use with caution in severe renal impairment) and moderate hepatic impairment. In paediatric patients weighing 40 kg to less than 50 kg, a starting dose of 0.8 mg/kg twice daily is recommended in moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. After initiation, the dose should be increased following the recommended dose titration every 2 – 4 weeks. Method of administration: *Tablets:* Sacubitril/valsartan tablets may be administered with or without food. The tablets must be swallowed with a glass of water. Splitting or crushing of the tablets is not recommended. *Granules:* Sacubitril/valsartan granules are administered by opening the capsule and sprinkling the contents onto a small amount of soft food (1 to 2 teaspoons). Food containing the granules must be consumed immediately. Patients may receive either the 6 mg/6 mg (white cap) or 15 mg/16 mg (yellow cap) capsules or both to reach the required doses. The capsule must not be swallowed. The empty shells must be discarded after use and not swallowed. **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 m^2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. **Warnings/Precautions:** Dual blockade of the renin angiotensin-aldosterone system: Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Do not administer until 36 hours after discontinuing 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 ≥ 100 mmHg for adult patients or ≥ 5th percentile SBP for the age of the paediatric patient. Patients with SBP below these values were not studied. Cases of symptomatic hypotension have been reported in adult patients treated with sacubitril/valsartan 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 therapy 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 (eGFR < 30 mL/min/1.73 m^2). 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 in adult patients and > 5.3 mmol/L in paediatric patients. 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. Psychiatric disorders: Hallucinations, paranoia and sleep disorders, in the context of psychotic events, have been associated with sacubitril/valsartan use. If a patient experiences such events, discontinuation of sacubitril/valsartan treatment should be considered. **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 m^2). 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. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or ARBs including sacubitril/valsartan. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased further. Co-administration of sacubitril/valsartan and furosemide reduced Cmax 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 nitroglycerine 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 Cmax 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 (≥ 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, hyponatraemia, postural dizziness, pruritis, rash, angioedema. *Rare (≥ 1/10,000 to < 1/1,000):* Hallucinations (including auditory and visual hallucinations), sleep disorders. *Very rare (< 1/10,000):* Paranoia.

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); Entresto 6 mg/6 mg granules in capsules for opening £10.14 per 60 capsule pack (EU/1/15/1058/023); Entresto 15 mg/16 mg granules in capsules for opening £25.36 per 60 capsule pack (EU/1/15/1058/024). **Date of last revision of prescribing information: March 2024**. Content ID: 417492. **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.

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