The 2010 NICE clinical guideline on the management of heart failure due to left ventricular dysfunction recommends a diuretic, a beta-blocker and an ACE inhibitor (or, if this is not appropriate an angiotensin II-receptor antagonist – AIIRA) as first-line therapy together with lifestyle change.1

In a draft appraisal (final guidance expected May 2016), NICE was minded to recommend sacubitril/valsartan an option for treating people with New York Heart Association (NYHA) Class II–III chronic heart failure with reduced ejection fraction who are already taking a stable dose of an ACE inhibitor or an AIIRA, and with left ventricular ejection fraction ≤35 per cent.2 Treatment should be initiated only by a specialist; dose titration and monitoring should be carried out by the specialist or, in primary care, by a GP with a special interest in heart failure or a heart failure specialist nurse.

**Properties**

Entresto is a combined formulation of valsartan and sacubitril. The AIIRA valsartan blocks the action of angiotensin II at AT1 receptors, thus inhibiting the activation of the renin-angiotensin-aldosterone system (RAS), and preventing vasoconstriction, renal sodium and fluid retention and maladaptive cardiac remodelling. Sacubitril’s active metabolite, LBQ657, inhibits the enzyme neprilysin, thus enhancing levels of natriuretic peptides, which in turn leads to RAS inhibition, vasodilation and reduced sympathetic activity, and potentially exerts favourable effects on renal function.

Entresto is licensed for the treatment of symptomatic chronic heart failure with reduced ejection fraction in adults. It is used in place of an ACE inhibitor or an AIIRA; it should not be co-prescribed with these agents.

Tablets are available in three strengths: sacubitril/valsartan 24/26mg (‘50mg’), 49/51mg (‘100mg’) and 97/103mg (‘200mg’). Valsartan in the Entresto formulation is more bioavailable than in other formulations; 26mg, 51mg, and 103mg valsartan in Entresto are equivalent to 40mg, 80mg and 160mg valsartan respectively in other tablets.
The recommended dosage is 100mg twice daily, doubled after two to four weeks to 200mg twice daily depending on tolerability. The starting dosage should be reduced to 50mg twice daily and increased at intervals of three to four weeks in patients who previously did not take or who were taking a low dose of an ACE inhibitor or an Alira. A reduced initial dose is also recommended for patients with systolic blood pressure ≥100 to 110mmHg; moderate or severe renal impairment; or moderate hepatic impairment. The dosage in older people should be adjusted according to renal function.

Valsartan/sacubitril is contraindicated in patients with serum potassium >5.4mmol/L; systolic pressure <100mmHg; patients with severe hepatic impairment, biliary cirrhosis or cholestasis; current treatment with or within 36 hours of an ACE inhibitor; a history of angioedema; and in patients with diabetes or renal impairment who are taking aliskiren. Among its clinically significant drug interactions, sacubitril/valsartan is associated with an increased risk of angioedema with ACE inhibitors, hyperkalaemia with potassium-sparing diuretics and renal impairment when taken with an NSAID; full details are provided in the summary of product characteristics. Valsartan/sacubitril does not induce or inhibit CYP450 enzymes.

**Efficacy**

Evidence for the efficacy of sacubitril/valsartan comes from the PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in chronic heart failure) trial, which randomised 8442 patients with heart failure (71 per cent NYHA Class II) and an ejection fraction of ≤40 per cent (mean 29–30 per cent) to either sacubitril/valsartan 100–200mg twice daily or the ACE inhibitor enalapril 10mg twice daily in addition to recommended therapy. The study was terminated after a median follow-up of 27 months when an interim analysis demonstrated overwhelming benefit of sacubitril/valsartan.

Sacubitril/valsartan significantly reduced the combined risk of the primary endpoint (death from cardiovascular cause or first hospitalisation for heart failure) with enalapril in the PARADIGM-HF trial (n=8442). It also reduced the risk of sudden cardiac death (HR 0.80; 95% CI 0.68–0.94; p=0.008), death due to worsening heart failure (HR 0.79; 95% CI 0.64–0.98; p=0.034) and all-cause mortality (17.0 vs 19.8 per cent; HR 0.81; 95% CI 0.73–0.93; p=0.004). The number needed to treat to prevent one primary event and one death from cardiovascular causes compared with enalapril over the period of the trial was 21 and 32 respectively.

**Adverse effects**

In PARADIGM-HF, about 10 per cent of patients in each group had been withdrawn due to adverse events during the prerandomisation phase; of those randomised, 11 per cent of patients taking sacubitril/valsartan and 12 per cent of those assigned to enalapril prematurely discontinued treatment due to adverse events (p=0.03) or renal impairment (0.7 vs 1.4 per cent; p=0.002). Sacubitril/valsartan was associated with a higher frequency (vs enalapril) of angioedema (2.4 vs 0.5 per cent in patients of African-Caribbean origin) or symptomatic hypotension (14 vs 9 per cent) but fewer cases of hyperkalaemia (serum potassium >6.0mmol/L, 4.3 vs 5.6 per cent) or renal impairment (10 vs 12 per cent).

**References**


**Declaration of interests**

None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics.