Commissioning Support
Sacubitril-valsartan
(Entresto®▼)

Treatment of heart failure

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of sacubitril valsartan:

- The need to ensure that the patient's current treatment regime is optimal and that they are taken as agreed.
- The NICE guidance on sacubitril valsartan[1] advises that it is used as an option for treating people with heart failure with reduced ejection fraction, only in those:
  - with New York Heart Association (NYHA) class II to IV chronic heart failure and
  - with a left ventricular ejection fraction (LVEF) of 35% or less and
  - who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB).
- The guidance also advises that treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be performed by the most appropriate team member as defined in NICE's guideline on chronic heart failure in adults: management.[1]
- Acquisition costs are £1,194 per year with sacubitril valsartan (200mg, twice daily; excluding VAT).
- The need to implement the NICE technology appraisal guidance on sacubitril valsartan within 30 days of final publication. This decision has been taken because sacubitril valsartan was available as part of an early access to medicines scheme.

Strength of the evidence for efficacy: relatively strong

The Paradigm-HF was a large well-designed trial with patient-oriented outcomes (mortality, hospitalisation) that showed a significant clinical benefit for sacubitril valsartan *vs*. enalapril. The NICE evidence review group commented on factors affecting the validity of the findings to UK clinical practice:

- that the mean age of trial participants was younger than heart failure patients in the UK,
- that there was lower level of cardiac device use in the trial than in the UK,
- the choice of valsartan dose and use of enalapril instead of ramipril as comparator,
- the low percentage of participants from Western Europe (25%).

It was agreed during clinical discussion, however, that the results of the PARADIGM-HF trial were relevant to routine clinical practice.

Description of technology

Sacubitril/valsartan is an angiotensin receptor neprilysin inhibitor, including a neprilysin inhibitor (sacubitril) and an angiotensin II receptor blocker (ARB; valsartan); both components act to lower blood pressure. It is licensed for use in adult patients for the treatment of symptomatic chronic heart failure (CHF) with reduced ejection fraction.[1,2]

The recommended starting dose of sacubitril valsartan is either 100 mg twice daily (oral combination tablet containing 48.6 mg sacubitril and 51.4 mg valsartan), or 50 mg twice daily for people not currently taking (or on low doses of) an ACE inhibitor or an ARB (Summary of Product Characteristics [SPC] states limited experience with this group[2]). The dose should be doubled every 2 to 4 weeks to the target of 200 mg twice daily, as tolerated by the patient.[1,2] A washout period of at least 36 hours is required between discontinuing an ACE inhibitor and starting sacubitril valsartan. For full details see the SPC.[2]

Background

Heart failure is a complex clinical syndrome relating to any structural or functional disorder that impairs the ability of the heart to maintain blood circulation.[3,4]

Common symptoms include fatigue, dyspnoea, swollen ankles and exercise intolerance.[4]

According to 2014/15 QOF prevalence data, there are about 410,783 people in England registered with heart failure;[5] NICE estimates that there are 900,000 people with heart failure in the UK as a whole[3]. The average prevalence of heart failure is 0.79% in the Midlands and East of England Commissioning region and the number of patients registered with HF on QOF registers is 129,219. An estimated 50% of patients with heart failure have reduced ejection fraction.[4]

Overall prognosis depends on factors such as severity of symptoms (New York Heart Association [NYHA] functional classification), age, LVEF, and the presence of co-morbidities. About 40% of people admitted to hospital with heart failure die or are re-admitted within one year, and about 50% of people with heart failure die within five years of diagnosis.[4]

Patients with heart failure require life-long treatment. Current NICE guidance on the management of chronic heart failure (CG108) advises that for a person with CHF and left ventricular systolic dysfunction, a diuretic is recommended to relieve symptoms of fluid overload. An ACE inhibitor and a beta-blocker (bisoprolol, carvedilol, or nebivolol) are

recommended to reduce morbidity and mortality. The choice of which drug to start first is dependent on the patient's comorbidities and clinical judgement. An ARB is recommended if the person has previously used an ACE inhibitor but was unable to tolerate this due to persistent troublesome cough.[3,4] If the patient remains symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker, seek specialist advice and consider adding:

- an aldosterone antagonist (spironolactone or eplerenone) licensed for heart failure (especially if the patient has moderate to severe heart failure [NYHA class III–IV] or has had an MI within the past month) or
- an ARB licensed for heart failure (especially if the patient has mild to moderate heart failure [NYHA class II–III]) or
- hydralazine in combination with nitrate (especially if the patient is of African or Caribbean origin and has moderate to severe heart failure [NYHA class III–IV]).

Clinical evidence for efficacy

Sacubitril valsartan has been evaluated in a single, pivotal, phase 3 RCT; PARADIGM-HF[6]. The trial compared sacubitril valsartan with enalapril in adults with symptomatic heart failure (NYHA class II to IV) with reduced LVEF of 40% or lower (later changed to 35%; LVEF >35% in 13% participants[6]). Eligible patients were on a stable dose of a beta-blocker and an ACE inhibitor, or an ARB equivalent to enalapril 10 mg per day for 4 weeks or more before screening. During a single-blind run-in phase, all participants were first given enalapril 10mg twice daily for 2 weeks, then switched to sacubitril valsartan 100 to 200 mg twice daily for 4 to 6 weeks. Participants without unacceptable side effects to either of the study medications during run-in were randomised to double-blind treatment with enalapril 10 mg twice daily (n = 4,212), or sacubitril valsartan 200 mg twice daily (n = 4,187), in addition to ongoing stable treatment (e.g. beta-blocker).

The primary outcome was a composite of death from cardiovascular (CV) causes or a first hospitalization for worsening heart failure. The secondary outcomes were the time to death from any cause, the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ; a scale from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure), the time to a new onset of atrial fibrillation, and the time to the first occurrence of a decline in renal function (which was defined as end-stage renal disease or as a decrease in the eGFR of at least 50% or a decrease of more than 30 ml per minute per 1.73 m^2 from randomisation to less than 60 ml per minute per 1.73 m^2).[6]

Main results

The composite primary end point significantly favoured sacubitril valsartan compared with enalapril (hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.73 to 0.87, p < 0.001).[1] It was statistically significant in favour of sacubitril valsartan compared with enalapril across most subgroups, except in people aged 75 years and older (HR 0.86, 95% CI 0.72 to 1.04), and people with NYHA class III or IV heart failure (HR 0.92, 95% CI 0.79 to 1.08). There was also no significant difference between sacubitril valsartan compared with enalapril when patients were divided into subgroups by region. For the Western European subgroup the hazard ratio for the primary composite outcome was 0.89 (95% CI 0.74 to 1.07).

Secondary outcomes data showed that sacubitril valsartan had a significantly reduced risk of all-cause mortality compared with enalapril (HR 0.84; 95% CI 0.76 to 0.93, p < 0.001), first all cause hospitalisation (HR 0.88; 95% CI 0.82 to 0.94, p < 0.0001), and first CV hospitalisation (HR 0.88; 95% CI 0.81 to 0.95, p < 0.0008). The KCCQ patient scores were lower for both sacubitril valsartan and enalapril; however, this reduction was less with sacubitril valsartan (by 2.99 points) than with enalapril (by 4.63 points).[1]

Adverse events

The most commonly reported adverse reactions during treatment with sacubitril valsartan were hypotension, hyperkalaemia and renal impairment. Reported adverse events were generally in line with that reported for other medicinal products acting on the renin-angiotensin-aldosterone system.[2]

Considerations for cost impact

Table of ACE inhibitors and ARBs recommended for the treatment of heart failure. Note the considerable drug acquisition cost of sacubitril valsartan.

Costs for one year's treatment with*:

Enalapril (generic)	10 -20 mg daily	£ 13-19
Ramipril (generic)	10 mg once daily or 5 mg twice daily	£ 14-25
Lisinopril (generic)	20 -35 mg once daily	£ 11-31
Valsartan (generic)	160 mg twice daily	£ 23
Candesartan (generic)	32 mg once daily	£ 23
Losartan (generic)	150 mg once daily	£ 25
Sacubitril valsartan (Entresto®▼)	200 mg twice daily	£1,194

**Recommended for heart failure by Clinical Knowledge Summaries*
Maintenance or maximum doses stated, other doses are available; doses shown do not imply therapeutic equivalence. Prices are rounded to nearest pound, from MIMS August 2016.

References

1. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. NICE 2015
2. Entresto film-coated tablets. EMC 2015
3. Chronic heart failure in adults: management. NICE 2010
4. Heart failure - chronic. NICE 2015
5. Quality and Outcomes Framework (QOF) - 2014-15. HSCIC 2015
6. McMurray JJ et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371(11):993-1004.

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