NEW DRUGS

Sacubitril/valsartan

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Approved indication: chronic heart failure

Entresto (Novartis)
24.3/25.7 mg, 48.6/51.4 mg, 97.3/102.8 mg film-coated tablets
Australian Medicines Handbook section 6.3.4

This product is a fixed-dose combination of sacubitril and valsartan and comes in three strengths. It is indicated for people with heart failure who have a reduced ejection fraction. The combination is given in place of an ACE inhibitor or other angiotensin receptor antagonist, with other drugs for heart failure.

The combination is designed to simultaneously inhibit neprilysin (sacubitril) and the renin–angiotensin system (valsartan).[1] Neprilysin is an enzyme that degrades vasoactive substances such as bradykinin and natriuretic peptides. By inhibiting neprilysin, sacubitril increases the concentration of these peptides which promotes vasodilation, an increased glomerular filtration rate and anti-fibrotic and anti-hypertrophic effects.

The combination of sacubitril and valsartan (49/51 mg increased to 97/103 mg twice daily) has been compared to the ACE inhibitor enalapril (10 mg twice daily) in a large phase III trial in patients with chronic systolic heart failure (PARADIGM-HF).[2] The average left ventricular ejection fraction of participants was 29% and most had New York Heart Association class II or III symptoms. Before enrolment, patients were already taking an ACE inhibitor or angiotensin receptor antagonist and most were also on a beta blocker. During a run-in period, all patients received enalapril for two weeks. If tolerated, they were then given sacubitril/valsartan for a further 4–6 weeks. Only patients who could tolerate both products were randomly switched to sacubitril/valsartan or enalapril. They were then followed for a median of 27 months.

There were fewer cardiovascular deaths and hospitalisations due to worsening heart failure in patients receiving sacubitril/valsartan than in those receiving enalapril. This was reflected in the primary outcome which was a composite of the two outcomes (see Table).[2] All-cause mortality and scores on a validated symptom questionnaire were also lower with the combination than with enalapril. However, the rate of decline in renal function or new-onset atrial fibrillation was not significantly different between study treatments.[2] The trial was stopped prematurely because of the observed benefit of sacubitril/valsartan over enalapril.

Drug intolerance was common during the trial. During the run-in period, just over 10% of participants (1138/10 513) discontinued because of an adverse event to one of the study treatments. After randomisation, a similar proportion discontinued sacubitril/valsartan because of an adverse event.[2] The most common events relating to the combination included hypotension (17.61%), hyperkalaemia (11.61%) renal impairment (10.14%) and cough (8.78%).

Hypotension was more common with sacubitril/valsartan than with enalapril (17.61% vs 11.97%). The risk of it occurring is higher in older age (≥75 years), low baseline systolic blood pressure, renal disease, use of high-dose diuretics, diarrhoea and vomiting. Blood pressure should be monitored at baseline and during dose titration. If hypotension persists despite adjusting the dose of other treatments (e.g. diuretics), reduce the sacubitril/valsartan dose or temporarily discontinue.

Renal function should be checked before and during treatment, especially in those with renal artery stenosis. Decrease or interrupt the sacubitril/valsartan dose if renal function declines.

Because of the risk of hyperkalaemia, serum potassium should be monitored and treatment

Table **Efficacy of sacubitril/valsartan compared to enalapril in chronic heart failure**

Outcome	Sacubitril/valsartan 97/103 mg twice daily	Enalapril 10 mg twice daily
Composite primary outcome: death from cardiovascular causes or hospitalisation from worsening heart failure	21.5% (914/4187)	26.5% (1117/4212)
Death from cardiovascular causes	13.3% (558/4187)	16.5% (693/4212)
Hospitalisation from worsening heart failure	12.8% (537/4187)	15.6% (658/4212)

Source: Reference 2

should not be started if concentrations are more than 5.4 mmol/L. Hyperkalaemia is more likely to occur in patients with severe renal impairment, diabetes, hypoaldosteronism or on a high potassium diet.

Neprilysin is involved in the clearance of amyloid-beta. Increased concentrations were found in the cerebrospinal fluid of healthy adults taking sacubitril/valsartan. The clinical relevance of this is currently unknown.

Angioedema was found to be a serious adverse event with previous combination therapies that inhibit neprilysin and the renin–angiotensin system simultaneously.[3] Although rare in the PARADIGM-HF trial, angioedema was more common with sacubitril/valsartan than with enalapril (0.5% vs 0.2%).[2] If angioedema occurs, treatment should be permanently stopped. Sacubitril/valsartan is contraindicated in patients with a history of angioedema with an ACE inhibitor or other angiotensin receptor antagonist, and in those with hereditary angioedema.

Concomitant use of an ACE inhibitor is contraindicated because of the risk of angioedema. A washout period of 36 hours is recommended before sacubitril/valsartan is initiated in patients switching from an ACE inhibitor. Angiotensin receptor antagonists should not be taken with sacubitril/valsartan.

Sacubitril/valsartan has numerous other drug interactions. Co-administration of potassium-sparing diuretics may lead to increased serum potassium. Use of non-steroidal anti-inflammatory drugs may increase renal impairment, and there is a theoretical risk of lithium toxicity with concomitant use. Other drugs that may interact with the combination include aldosterone antagonists, frusemide, rifampicin, cyclosporin, ritonavir, metformin, statins and sildenafil.

Following oral administration, the combination dissociates into sacubitril and valsartan, and sacubitril is metabolised to the active metabolite (LBQ657) by esterases. Steady-state drug concentrations are reached after three days of twice daily dosing. Up to 68% of sacubitril (mainly as LBQ657) and 13% of valsartan are excreted in the urine with the rest excreted in the faeces. The elimination half-lives of sacubitril, LBQ657 and valsartan are 1.4, 11.5 and 9.9 hours.

The recommended starting dose of sacubitril/valsartan is 49 mg/51 mg twice daily. A lower starting dose (24 mg/26 mg) should be considered in patients not currently taking an ACE inhibitor or angiotensin receptor antagonist, or who have risk factors for hypotension such as those aged 75 years and over or with low systolic blood pressure. A lower dose is also recommended for patients with severe renal impairment or moderate hepatic impairment. Valsartan is more bioavailable in this formulation than in other valsartan products. This should be considered for patients switching over to this formulation.

The drug is contraindicated in patients with severe hepatic impairment, biliary cirrhosis and cholestasis. It should also not be used in pregnancy.

The combination of sacubitril and valsartan lowered the risk of death or hospitalisation due to worsening heart failure compared to enalapril in a large phase III trial. However, the enalapril dose (20 mg/day) in the trial was at the lower end of the recommended dose (20–40 mg/day) in Australia. This raises the question of whether it was a valid comparator. Another concern about the trial design was that many patients discontinued because they could not tolerate the drug during the run-in period and after randomisation so the patients that completed the trial may not be representative of the general population of patients with heart failure. Patient monitoring is very important, particularly when treatment is initiated and during dose titration and when there is a change in the patient's other medicines. Before starting this drug in patients switching from an ACE inhibitor, there should be a washout period of at least a day to reduce the risk of angioedema.

T T manufacturer provided additional useful information

REFERENCES

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The Transparency Score (T) is explained in 'New drugs: transparency', Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration (www.fda.gov) and the European Medicines Agency (www.ema.europa.eu).