Technology Guidance

Sacubitril/valsartan

for treating chronic heart failure with reduced ejection fraction

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Sacubitril/valsartan 50 mg, 100 mg and 200 mg tablets to reduce the risk of cardiovascular death and hospitalisation for heart failure in patients:
  - with chronic heart failure classified by New York Heart Association (NYHA) Class II-IV symptoms; and
  - with left ventricular ejection fraction of 40% or less; and
  - who are receiving concomitant optimal standard chronic heart failure treatment, which includes a beta-blocker, unless contraindicated or not tolerated; and
  - who remain symptomatic despite already receiving a stable dose of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), unless such treatment is contraindicated or cannot be tolerated.

Sacubitril/valsartan must not be co-administered with an ACE inhibitor or an ARB.

Subsidy status

Sacubitril/valsartan 50 mg, 100 mg and 200 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication.

Updated: 4 January 2022

Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of sacubitril/valsartan for treating chronic heart failure with reduced ejection fraction (HFrEF) in December 2018. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from public healthcare institutions.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

1.4. Following a negative recommendation on the basis of uncertain cost-effectiveness and potentially high budget impact, the manufacturer of sacubitril/valsartan submitted a revised price proposal, which the Committee considered in August 2021.

Clinical need

2.1. The American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guideline recommends sacubitril/valsartan at the same line of therapy as ACE inhibitors or ARBs to reduce morbidity and mortality in patients with HFrEF. Guidelines from the European Society of Cardiology (ESC) recommend it as a replacement for ACE inhibitors in ambulatory patients with HFrEF who remain symptomatic despite receiving optimal standard treatment for heart failure (HF) and as a treatment option for patients with HFrEF who have not previously received an ACE inhibitor or ARB.

2.2. The Committee noted that in local practice, sacubitril/valsartan is mainly given after ACE inhibitors, or less commonly, after ARBs if patients remain symptomatic. Sacubitril/valsartan is typically initiated at a low dose of 25 mg twice daily by local clinicians, with dose escalation based on clinical response and tolerability. Clinical experts suggested that only one-third of the local patient population could tolerate the maximum recommended dose of 200 mg twice daily.

Clinical effectiveness and safety

3.1. The Committee agreed that enalapril, which is listed on the MOH Standard Drug List (SDL), was the appropriate comparator for sacubitril/valsartan for people with HFrEF.

3.2. The Committee heard that the clinical effectiveness of sacubitril/valsartan was solely derived from the pivotal PARADIGM-HF trial for patients treated with ACE inhibitors or ARBs for at least 4 weeks, prior to study entry. Results showed that sacubitril/valsartan significantly reduced the primary composite endpoint of death from cardiovascular (CV) causes or first hospitalisation for worsening HF by 20% (HR 0.80; 95% CI: 0.73 to 0.87; p<0.001) compared to enalapril over a median follow-up of 27 months. The Committee noted however, that this outcome was not statistically significant in a post-hoc subgroup analysis of patients with East Asian origin, including 32 patients from Singapore (n=812; HR 0.81; 95% CI: 0.62 to 1.06). While the Committee considered that the subgroup analyses may have been underpowered to detect the true effect size due to the small sample, they noted that the PARALLEL-HF trial also showed no difference in the primary composite outcome of CV death or HF hospitalisation among Japanese patients (n = 225; HR 1.09; 95% CI: 0.65 to 1.82; p = 0.6260).

3.3. The Committee acknowledged that the PARADIGM-HF trial population was highly selective and may not be representative of the local HF population. It was noted that lower doses of sacubitril/valsartan, consistent with local practice, were not studied. Furthermore, while the trial enrolled patients with NYHA class II-IV symptoms, only 0.7% of patients were class IV, which was considerably lower than the estimated proportion (25%) of class IV patients with HF in Singapore.

3.4. The Committee noted that the adverse event profiles for the two drugs differed. Sacubitril/valsartan was associated with a higher risk of hypotension whereas the more commonly reported adverse events associated with enalapril were hyperkalaemia, renal impairment and cough. Overall, the Committee agreed that sacubitril/valsartan was generally well-tolerated.

3.5. While noting that local cardiologists consider PARADIGM-HF was a well-conducted trial and that sacubitril/valsartan would be a useful additional treatment option, the Committee considered that the early termination of the study after 27 months gave rise to uncertainty in the magnitude and long-term nature of the clinical benefits associated with sacubitril/valsartan, as well as its long-term safety profile. Potential long-term safety issues such as effects on cognitive function and risk of dementia remain to be answered in an ongoing global trial (PERSPECTIVE) involving patients with HF and preserved ejection fraction. However, the Committee noted that recent post-hoc analyses from PARAGON-HF showed cognitive change (measured by Mini-Mental State Examination [MMSE]) did not differ between the sacubitril/valsartan and valsartan groups.

Cost effectiveness

4.1. Following value-based pricing (VBP) discussions in 2018, the manufacturer of sacubitril/valsartan did not offer any price reduction for subsidy consideration of use after an ACE inhibitor or ARB. At the cost price in 2018, the daily treatment cost of sacubitril/valsartan per patient (assuming two full tablets daily) was significantly higher than generic enalapril.

4.2. Based on an in-house cost-effectiveness analysis, the Committee acknowledged that the base-case incremental cost-effectiveness ratio (ICER) for sacubitril/valsartan compared with enalapril was between SG$45,000 to less than SG$75,000 per QALY gained. The Committee noted that there was high uncertainty surrounding the ICER, mainly driven by the uncertainty in the treatment effect of sacubitril/valsartan to reduce risk of CV death in the East Asian subgroup, and the long-term extrapolation of treatment effectiveness beyond the follow-up period of PARADIGM-HF. At the meeting in December 2018, the Committee concluded that sacubitril/valsartan did not represent a cost-effective use of healthcare resources in Singapore's context.

4.3. In August 2021, following a revised price proposal for sacubitril/valsartan, the ICER reduced to be between SG$15,000 to less than SG$45,000/QALY gained. The Committee agreed that the revised cost of sacubitril/valsartan was reasonable and could be considered an acceptable use of healthcare resources.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact was estimated to be less than SG$1 million in the first year of listing sacubitril/valsartan on MAF for use after an ACE inhibitor or ARB.

5.2. The Committee noted the uncertainty surrounding the annual cost impact calculations, and considered the amount could increase substantially between SG$3 million to less than SG$5 million following listing, when existing patients who are likely to switch from an ACE inhibitor or an ARB to sacubitril/valsartan were taken into account.

Additional considerations

6.1. Given the large price difference between sacubitril/valsartan and ACE inhibitors or ARBs, the Committee agreed that sacubitril/valsartan was unlikely to be cost-effective when used in a first-line setting. Therefore, the Committee concluded that an MAF listing for sacubitril/valsartan was needed to limit the use of sacubitril/valsartan to patients who remain symptomatic despite being treated with an ACE inhibitor or ARB.

Recommendations

7.1. Based on available evidence presented in December 2018, the Committee recommended not listing sacubitril/valsartan on the MAF because of uncertain cost-effectiveness and potentially high budget impact at the price proposed by the manufacturer at that time.

7.2. In August 2021, following an acceptable price reduction from the manufacturer which improved the cost-effectiveness and addressed the previous uncertainties, the Committee recommended sacubitril/valsartan for listing on the MAF for treating chronic heart failure with reduced ejection fraction in patients who meet certain clinical criteria.

VERSION HISTORY

Guidance on sacubitril/valsartan for treating chronic heart failure with reduced ejection fraction

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

1. **Publication of guidance**

   Date of Publication 2 May 2019

2. **Guidance updated to extend MAF listing to sacubitril/valsartan**

   Date of Publication 4 Jan 2022

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 17 December 2018 and 18 August 2021. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

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