Endothelin receptor antagonists

for treating pulmonary arterial hypertension

Technology Guidance from the MOH Drug Advisory Committee

Guidance recommendations

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

✓ Ambrisentan 5 mg and 10 mg tablets for treating adults with a confirmed diagnosis of WHO Functional Class II or III pulmonary arterial hypertension (PAH) who have one of the following PAH aetiologies:
  ▪ Idiopathic PAH;
  ▪ Heritable or familial PAH;
  ▪ PAH associated with connective tissue disease;
  ▪ Anorexigen-induced PAH; or
  ▪ PAH associated with HIV infection.

Subsidy status

Ambrisentan 5 mg and 10 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication.

MAF assistance does not apply to bosentan 62.5 mg and 125 mg tablets, and macitentan 10 mg tablet.
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 endothelin receptor antagonist (ERA; ambrisentan, bosentan and macitentan) monotherapy for treating pulmonary arterial hypertension (PAH). The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from public healthcare institutions. Published clinical evidence for ERAs was considered in line with their registered indications.

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.

Clinical need

2.1 The Committee acknowledged that PAH is a rare, progressive disease which can cause right ventricular failure and eventually death if untreated. Given the significant morbidity and mortality associated with the disease, treatment aims to prevent progression of the disease and pulmonary artery thrombosis, relieve the symptoms of PAH, improve exercise capacity and prolong survival.

2.2 Local clinical practice is in line with international clinical practice guidelines which recommend ERAs for treating non-vasoreactive WHO Functional Class II, III or IV PAH, either as monotherapy for patients who are unsuitable for phosphodiesterase type 5 (PDE-5) inhibitors or as add-on therapy to other agents (such as PDE-5 inhibitors or prostanoids) to slow disease progression.
The Committee acknowledged that no ERAs for PAH are currently included on the MOH List of Subsidised Drugs, and agreed that there is a high clinical to provide patients with a subsidised treatment option to address this therapeutic gap.

Clinical effectiveness and safety

ERA versus placebo
The Committee considered the available clinical evidence and acknowledged that randomised controlled trials showed that all ERAs (ambrisentan, bosentan and macitentan) were statistically superior to placebo in reducing the composite outcome of clinical worsening (comprising all-cause mortality, non-elective hospitalisation for PAH, disease progression, need for additional PAH therapies, and lung and/or heart transplantation). For 6-minute walk distance (6MWD), all ERAs also showed statistically significant improvement when compared to placebo. However, the results were only considered to be clinically significant for ambrisentan and bosentan (not macitentan). Extension studies of the pivotal trials showed sustained efficacy and no additional safety signals. The Committee concluded that all ERAs were clinically superior to placebo.

ERA versus ERA
The Committee noted that head-to-head trials comparing the ERAs were lacking. Indirect evidence from network meta-analyses showed no significant differences in clinical worsening between the ERAs. For 6MWD, ambrisentan 10 mg daily showed a statistically significantly greater improvement in 6MWD compared to macitentan 10 mg daily. There were no statistically significant differences between all other interventions.

The safety profiles of the ERAs were largely comparable; however, indirect comparisons showed that bosentan was associated with a higher incidence of elevated liver enzymes compared to ambrisentan and macitentan. The Committee concluded that all ERAs were clinically comparable and generally well tolerated.

Cost effectiveness

Cost-minimisation among the ERAs
The Committee agreed that a cost-minimisation approach was appropriate to select the lowest priced ERA for subsidy consideration in view of comparable efficacy and safety among the drug class. It noted that the manufacturer of ambrisentan offered the lowest price as part of their value-based pricing proposal.
Estimated annual technology cost

5.1 The Committee estimated the annual cost impact to be less than SG$500,000 in the first year of listing ambrisentan on the MAF.

Additional considerations

6.1 The Committee expressed concerns that ambrisentan may be used to treat other forms of pulmonary hypertension, outside of its approved indication, if it is listed on SDL. It therefore agreed that an MAF listing in line with specific clinical criteria was needed to ensure appropriate use.

Recommendation

7.1 Based on available evidence, the Committee recommended ambrisentan 5 mg and 10 mg tablets be listed on the MAF for treating PAH in line with specific clinical criteria, in view of favourable clinical and cost-effectiveness, and the high clinical need for this treatment to ensure appropriate patient care.

7.2 Bosentan 62.5 mg and 125 mg tablets, and macitentan 10 mg tablet were not recommended due to their higher costs compared with ambrisentan that were not justified by the clinical outcomes they provide over ambrisentan.

About the Agency

The Agency for Care Effectiveness (ACE) is the national health technology assessment agency in Singapore residing within the Ministry of Health. It conducts evaluations to inform the subsidy of treatments, and produces guidance on the appropriate use of treatments for public hospitals and institutions in Singapore. When using the guidance, the responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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