Technology Guidance

Tafamidis

for treating transthyretin amyloid cardiomyopathy

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended tafamidis for inclusion on the MOH List of Subsidised Drugs for treating wild-type or hereditary transthyretin amyloid cardiomyopathy. The decision was based on the unfavourable cost-effectiveness of tafamidis at the price proposed by the company, compared with standard management.

Published: 2 January 2024

Factors considered to inform the recommendations for funding

Technology evaluation

1.1. At the October 2023 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of tafamidis for treating transthyretin amyloid cardiomyopathy (ATTR-CM). The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions and patient experts from local patient and voluntary organisations. Clinical and economic evidence for tafamidis was considered in line with its registered indication.

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 funding considerations.

Clinical need

2.1. The Committee heard that ATTR-CM is an underdiagnosed, progressive disease, characterised by extracellular deposition of misfolded transthyretin amyloid fibrils in the myocardium, which results in heart failure. Median survival in untreated patients with ATTR-CM is poor.

2.2. According to local clinicians, tafamidis is the only available disease-modifying agent for treating ATTR-CM. However, due to its high cost, most patients are only prescribed symptomatic treatments, such as diuretics. Diflunisal or doxycycline in combination with ursodeoxycholic acid is also sometimes prescribed (due to their lower cost), despite the lack of high-quality clinical evidence or regulatory approval supporting their efficacy and safety in this setting. Hence, the Committee acknowledged that there was a high clinical need for a subsidised treatment for ATTR-CM, especially since diagnosis rates have been increasing in recent years.

2.3. The Committee considered a testimonial from a local patient expert about their lived experience with ATTR-CM and the treatment they have received. The Committee heard that ATTR-CM had negatively impacted the patient's physical ability to walk and

caused water retention that required hospitalisation. The Committee acknowledged that the patient was treated with doxycycline and ursodeoxycholic acid combination therapy to manage symptoms but experienced acid reflux as a side effect. Treatment was subsequently stopped as the water retention worsened and it was not considered to be effective for the patient's condition. The Committee noted that the patient considered tafamidis was the only treatment currently available that could prevent or slow disease progression. However, its affordability was a significant concern.

Clinical effectiveness and safety

3.1. The Committee reviewed published clinical evidence from a phase III randomised controlled trial (ATTR-ACT), comparing tafamidis meglumine (80 mg and 20 mg doses) with placebo, as add-on treatment to standard management in patients with ATTR-CM.

3.2. While the doses and formulations studied in the ATTR-ACT trial differed from that marketed in Singapore (tafamidis 61 mg), the Committee noted that tafamidis 61 mg and tafamidis meglumine 80 mg are considered bioequivalent by HSA. Given that the trial primary efficacy analysis compared pooled tafamidis (20 mg and 80 mg) treatment results with placebo, and was not designed or powered to compare tafamidis dose strengths, the Committee agreed it would be appropriate for the clinical effectiveness of tafamidis to be informed by results of the pooled group.

3.3. In the primary outcome of the ATTR-ACT trial at 30 months, the Finkelstein-Schoenfeld prioritised pairwise comparison of all-cause mortality and frequency of cardiovascular (CV) hospitalisations showed a statistically significant effect in favour of the pooled tafamidis treatment group compared with placebo. Statistically significant improvements in the individual components of the primary outcome and for risk of CV mortality were also shown for the pooled group compared to placebo.

3.4. However, the Committee noted that the magnitude of benefit from tafamidis treatment was uncertain for the subgroup of patients with baseline New York Heart Association (NYHA) class III. Tests for interaction indicated that NYHA class at baseline was a treatment effect modifier for CV hospitalisation, with results indicating an increased risk for patients with NYHA class III treated with tafamidis compared to placebo. Furthermore, compared to patients in the NYHA class I/II subgroup, patients in the NYHA class III subgroup experienced a numerically smaller improvement in all-cause mortality with tafamidis compared to placebo. Nonetheless, the Committee noted advice from clinical experts that patients could transition between NYHA class II and III throughout the course of the disease and hence patients with NYHA class III could benefit from tafamidis treatment.

3.5. The Committee also considered that the optimal dosing of tafamidis remained uncertain as the proportion of events for all-cause mortality, CV mortality and

frequency of CV-related hospitalisations in ATTR-ACT were numerically in favour of the 20 mg dose over the 80 mg dose. While surrogate outcomes from ATTR-ACT and survival outcomes of the extension study (ATTR-ACT LTE) favoured the 80 mg dose, the Committee agreed that these results were difficult to interpret due to unclear clinical significance and methodological limitations, respectively.

3.6. Based on the available evidence, the Committee concluded that tafamidis was superior in efficacy compared to standard management alone. However, the magnitude of benefit in the NYHA baseline class III subgroup and the optimal dosing of tafamidis remained uncertain.

3.7. In terms of safety, the Committee noted that tafamidis was generally well tolerated and acknowledged that PBAC (Australia) considered tafamidis to be inferior in safety compared to standard management alone, given the limited clinical safety dataset.

Cost effectiveness

4.1. The Committee reviewed a cost-effectiveness analysis conducted by ACE that compared tafamidis with placebo as an add-on to standard management in patients with ATTR-CM. At the price proposed by the company, tafamidis had an unacceptably high base-case incremental cost-effectiveness ratio (ICER) between SG$245,000 and SG$285,000 per quality-adjusted life year (QALY) gained. The Committee noted that the cost of tafamidis was a key driver in the model. Majority of scenario analyses conducted also resulted in high ICERs between SG$245,000 and SG$285,000 per QALY gained.

4.2. Therefore, the Committee considered that tafamidis did not represent a cost-effective use of healthcare resources for treating ATTR-CM at the price proposed by the company.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact to the public healthcare system was estimated to be between SG$1 million and SG$3 million over the first 5 years of listing tafamidis on the MOH List of Subsidised Drugs for treating ATTR-CM. However, the Committee was concerned with the budget uncertainty as these estimates could potentially be substantially higher.

Recommendations

6.1. Based on available evidence, the Committee recommended not listing tafamidis on

the MOH List of Subsidised Drugs for treating ATTR-CM. This decision was based on unfavourable cost effectiveness at the price proposed by the company compared with standard management.

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

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 funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance 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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