Technology Guidance

Eltrombopag

for treating immune thrombocytopenia and severe aplastic anaemia

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Eltrombopag 25 mg and 50 mg tablets for treating:
  - **immune thrombocytopenia** lasting six months or longer from diagnosis in patients who are intolerant or refractory to other treatments (e.g. corticosteroids, immunosuppressants); and
  - **severe aplastic anaemia** in patients who are refractory to immunosuppressive therapy (comprising horse anti-thymocyte globulin plus ciclosporin for at least three months) and have marrow cellularity <25% (or 25 to 50% with <30% residual haematopoietic cells), with at least two of the following:
    - neutrophils $<0.5 \times 10^9$/l
    - platelets $<20 \times 10^9$/l
    - reticulocyte count $<20 \times 10^9$/l ($<60 \times 10^9$/l for automated reticulocyte counting).

Eltrombopag should be prescribed by a haematologist with experience in managing immune thrombocytopenia and severe aplastic anaemia.

Subsidy status

Eltrombopag 25 mg and 50 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indications.

MAF assistance **does not** apply to the use of eltrombopag for treating newly diagnosed severe aplastic anaemia.

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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 eltrombopag for treating immune thrombocytopenia (ITP) and severe aplastic anaemia (SAA). The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for eltrombopag was considered in line with its 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. Immune thrombocytopenia

The Committee noted that there are approximately 270 patients who have been diagnosed with ITP in Singapore. In line with international clinical practice guidelines, eltrombopag and rituximab (off-label) are used in local practice to treat ITP in patients who are refractory or intolerant to corticosteroids. They are also used if oral immunosuppressants are unsuitable. Although rituximab biosimilar is already listed on the Standard Drug List (SDL) and provides a subsidised treatment option for patients with ITP, the Committee agreed that there was a clinical need to improve the affordability of other treatment options.

2.2. Severe aplastic anaemia

The Committee acknowledged that SAA is a rare condition with fewer than 10 new cases diagnosed annually. In local practice, eltrombopag is used in combination with immunosuppressive therapy to treat newly diagnosed SAA or as monotherapy for refractory SAA. The Committee acknowledged that there were no subsidised treatment options for SAA, representing a therapeutic gap in the MOH List of Subsidised Drugs; therefore, there was an unmet clinical need to improve the affordability of treatment options to ensure appropriate patient care.

Clinical effectiveness and safety

3.1. Immune thrombocytopenia

The Committee reviewed the available clinical evidence from six randomised controlled trials (RCTs) which compared eltrombopag with placebo in children and adults with ITP. Eltrombopag was associated with statistically significant improvements in platelet response rates and led to significant reductions in the incidences of any bleeding (WHO Grades 1 to 4) and use of rescue therapy compared with placebo.

3.2. The Committee also considered clinical evidence from a phase III RCT that showed no significant differences in treatment failure and platelet response rates between rituximab and placebo. The Committee heard that there were no available head-to-head studies directly comparing eltrombopag to rituximab and indirect comparisons were not appropriate to conduct due to the significant heterogeneity between the trials. Despite these limitations, the Committee agreed that the clinical data supported the use of eltrombopag in patients with refractory ITP.

3.3. Severe aplastic anaemia

The Committee noted that a phase II, single-arm trial in patients with newly diagnosed SAA showed that eltrombopag in combination with standard immunosuppressive therapy was associated with significant improvements in overall response rates at six months compared with a historical control group treated with immunosuppressive therapy alone. Likewise, another randomised, open-label phase III trial showed that eltrombopag combined with immunosuppressive therapy led to a statistically significant increase in complete response rates at three months compared to immunosuppressive therapy alone. However, there was no significant difference in overall survival at two years between the two treatment arms.

3.4. For patients with refractory SAA, results from a phase II, single-arm trial showed that eltrombopag led to improvement in some haematological responses (such as an increase in blood counts and decreased transfusion requirements). Although the available evidence was limited, the Committee considered that eltrombopag was likely to provide some clinical benefits to patients with refractory SAA who lack other therapeutic options.

3.5. Safety

The Committee agreed that eltrombopag was generally well-tolerated and most adverse events in the trials were mild to moderate in severity. While hepatotoxicity-related adverse events were more commonly reported with eltrombopag, they were transient and resolved when treatment was discontinued.

Cost effectiveness

4.1. The Committee noted that cost-effectiveness analyses of eltrombopag for treating ITP conducted by overseas reference HTA agencies included populations and comparators that differed from clinical practice in Singapore and therefore, the results were not generalisable to the local context. No cost-effectiveness analyses were conducted by reference HTA agencies for treating SAA.

4.2. The manufacturer of eltrombopag offered a price reduction contingent on an MAF listing for both ITP and SAA as part of their value-based pricing proposal. The Committee acknowledged that the price proposed for eltrombopag was lower than prices accepted for subsidy in other reference jurisdictions; therefore, eltrombopag was likely to be cost-effective in the local context.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact in the first year of listing eltrombopag on the MAF for treating ITP or SAA was estimated to be less than SG$1 million for each indication.

Recommendations

6.1. Based on the available evidence, the Committee recommended eltrombopag 25 mg and 50 mg tablets be listed on the MAF for treating ITP in patients who are intolerant or refractory to other treatments (e.g. corticosteroids, immunosuppressants), in view of the clinical need and favourable clinical and cost effectiveness.

6.2. The Committee also recommended eltrombopag 25 mg and 50 mg tablets be listed on the MAF for treating patients with clinically defined SAA that is refractory to immunosuppressive therapy (comprising horse anti-thymocyte globulin plus ciclosporin for at least three months), in view of the high clinical need to provide patients with a subsidised treatment option to ensure appropriate care.

6.3. Eltrombopag in combination with immunosuppressive therapy for newly diagnosed SAA was not recommended for listing on the MAF due to uncertain clinical effectiveness.

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 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.

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

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