Epoprostenol

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:

✓ epoprostenol (Veletri) 1.5 mg powder for solution for infusion for treating idiopathic or heritable pulmonary arterial hypertension (PAH) or PAH associated with connective tissue diseases, in patients with WHO Functional Class III–IV symptoms.

Subsidy status

Epoprostenol 1.5 mg powder for solution for infusion is recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication.

MAF assistance **does not** apply to Veletri 0.5 mg vial or Flolan 0.5 mg and 1.5 mg vials.

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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 epoprostenol (Veletri) for pulmonary arterial hypertension (PAH). The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from public healthcare institutions. Published clinical and economic evidence for epoprostenol was considered in line with its registered indication. The Committee acknowledged that another brand of epoprostenol (Flolan) is available in Singapore but does not have HSA approval for PAH; therefore, it was excluded from the evaluation.

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.

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

1.3 The Committee agreed that PAH was a rare disease in the local context and also considered the following additional criteria to inform their subsidy considerations:

1) Rare disease treatments which are unlikely to be cost effective due to the small number of patients who require them will still be considered for SDL/MAF if they meet **all** of the following criteria:
   a) Treatment is for a rare but clinically defined condition that is chronically debilitating, life-threatening or has a significant impact on a patient's quality of life; and
   b) Treatment is considered to be standard of care and clinically essential for the condition under evaluation in line with local and/or international clinical practice guidelines; and
   c) Treatment is registered by the Health Sciences Authority (HSA) or a reputable international regulatory authority (e.g. US Food and Drug Administration (FDA) and/or European Medicines Agency (EMA)) for the condition under evaluation (i.e. treatment has proven therapeutic modality); and

d) There is a lack of affordable treatment alternatives (including non-drug therapy) for patients with the condition; and
e) There is sufficient evidence available to robustly assess the safety and clinical effectiveness of the treatment for patients with the condition.

2) The Committee will also consider whether the budget impact to list the treatment on SDL/MAF if it is funded for all eligible patients is reasonable.

Clinical need

2.1 The Committee noted that PAH is a group of very rare diseases characterised by a progressive increase in pulmonary vascular resistance, leading to right ventricular failure and premature death. Initial symptoms include chest pain, breathlessness during exertion and fainting; however, due to the non-specific nature of symptoms, patients often have severe disease by the time an accurate diagnosis is made and treatment is started.

2.2 PAH may be idiopathic, hereditary, drug- or toxin-induced or associated with other diseases like congenital heart disease, connective tissue disease or HIV. There are four WHO functional classes (one is lowest, four is highest) that are used to describe the severity of PAH and the level of urgency for treatment. Prognosis varies between different forms of PAH, but is generally poor. The mean survival rate after diagnosis is less than three years without treatment.

2.3 Early therapeutic intervention may lead to improved exercise capacity, prevention of pulmonary artery thrombosis, and better survival. The Committee heard that epoprostenol is typically used as monotherapy or add-on therapy to oral PAH medications (endothelin receptor agonists (ERAs) and/or phosphodiesterase type 5 [PDE5] inhibitors) after failure of maximum oral treatment options, as bridging therapy for patients with WHO Class III or IV PAH who are awaiting a heart and lung transplant. Without treatment the average length of survival for patients with WHO Class IV PAH is 6-12 months. In view of the severity of the disease and lack of treatment options, the Committee agreed that there was a high clinical need to consider epoprostenol for subsidy.

Clinical effectiveness and safety

3.1 Three open-label parallel trials conducted in the US showed that epoprostenol in combination with conventional therapy (including anticoagulants, diuretics, calcium channel blockers and supplemental oxygen) significantly improved exercise capacity (measured by a median increase from baseline in 6-minute walking distance) and haemodynamic parameters compared with conventional therapy alone. Statistically significant improvements in survival and certain domains of quality of life measures were also observed. The Committee acknowledged that there were several limitations to the studies due to the relatively small number of patients recruited and possible lack of generalisability to the Singapore context.

3.2 To supplement the primary evidence base, several observational studies were considered which showed that long-term treatment with epoprostenol was associated with sustained improvements in exercise capacity and haemodynamic parameters. Epoprostenol was also shown to improve survival compared with historical controls. The Committee also reviewed data published from the French Pulmonary Hypertension Registry for patients diagnosed with idiopathic PAH between 2006 to 2010, and noted that one-year and three-year survival rates after starting epoprostenol were 84% and 69% respectively.

3.3 The Committee noted that there was limited evidence to evaluate the clinical effectiveness of epoprostenol as add-on therapy to oral PAH medications, but acknowledged that combination therapy is recommended in clinical guidelines and followed in local clinical practice for severe disease.

3.4 The Committee acknowledged that dose-related adverse events are common during initiation with epoprostenol and dose escalation due to the vasodilator effects of treatment. Adverse events associated with long-term use of epoprostenol include hypotension, bradycardia, headache, jaw pain, diarrhoea and nausea. The Committee considered that the safety profile of epoprostenol was well recognised and was comparable across all subgroups of patients with PAH.

Cost effectiveness

4.1 No published local cost-effectiveness studies of epoprostenol were identified. An evaluation reported by NICE (UK) indicated that epoprostenol plus best supportive care had an ICER of GBP277,000/QALY gained for WHO Class III PAH and GBP343,000/QALY gained for WHO Class IV PAH compared to best supportive care alone. The Committee noted that the ICERs reported in other overseas economic evaluations were also high and were sensitive to the price of epoprostenol assumed. In view of the small number of patients eligible for treatment, the Committee

concluded that epoprostenol was unlikely to be cost-effective in the local context at the current price.

4.2 The Committee heard that the manufacturer had offered a price discount contingent on an MAF listing in their value-based pricing proposal. They noted that the price offered by the manufacturer was comparable to or lower than list prices in Australia, New Zealand and England.

Estimated annual technology cost

5.1 The Committee noted that the annual cost impact was estimated to be between SG$500,000 to SG$1 million in the first year of listing epoprostenol on the MAF depending on the length of treatment assumed for each patient.

Recommendation

6.1 The Committee agreed that epoprostenol met all of the additional decision-making criteria considered for rare diseases (section 1.3).

6.2 Based on available evidence, the Committee recommended epoprostenol (Veletri) 1.5 mg powder for solution for infusion be listed on the MAF for treating PAH in patients with WHO Functional Class III–IV symptoms, in view of the high clinical need to provide financial assistance to patients with this condition, and acceptable clinical effectiveness and budget impact at the price proposed by the manufacturer.