Ivabradine

for the treatment of chronic stable angina and chronic heart failure

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Ivabradine 5mg and 7.5mg tablets for the treatment of chronic heart failure in patients:
  - with New York Heart Association (NYHA) class II to IV stable chronic heart failure with systolic dysfunction (LVEF of 35% or less);
  - who are in sinus rhythm with a heart rate of 75 bpm or more **and**
  - who are given concomitant standard medical management with maximum tolerated doses of beta blockers, angiotensin-converting enzyme inhibitors and aldosterone antagonists, unless contraindicated.

Subsidy status

Ivabradine 5mg and 7.5mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication.

MAF assistance **does not** apply to the use of ivabradine for chronic stable angina.

Published on 5 February 2018

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 ivabradine for chronic stable angina and chronic heart failure. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for ivabradine was considered in line with the 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
- 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 local expert advice that ivabradine is typically reserved as a third- or fourth-line agent for chronic stable angina when other treatment options have provided insufficient benefit or have not been well tolerated.

2.2 For chronic heart failure, ivabradine is usually considered as a third-line treatment option for people with left ventricular systolic dysfunction who are in sinus rhythm and are already receiving the target dose of beta blockers but are still unable to reach the target heart rate, or when beta blockers are not well tolerated. The Committee acknowledged that there are limited alternative third-line treatment options for these patients, and therefore considered that ivabradine addresses a moderate clinical need.

Clinical effectiveness and safety

Chronic stable angina

3.1 The Committee noted that the pivotal trials (BEAUTIFUL and SIGNIFY) did not explicitly include patients with chronic stable angina and there was no statistically significant difference between ivabradine and placebo for the primary composite outcome (including cardiovascular death) in the intention-to-treat populations.

3.2 The Committee further noted that in the SIGNIFY trial ivabradine led to an increased incidence of cardiovascular death or nonfatal myocardial infarction among patients who had Canadian Cardiovascular Society (CCS) scale class II or higher angina and was associated with an increased frequency of severe adverse events (including bradycardia and new-onset atrial fibrillation), compared to placebo.

3.3 On the basis of the limited clinical evidence supporting the use of ivabradine for chronic stable angina, the Committee agreed that further consideration of this indication for subsidy was not required. It acknowledged that paucity of evidence was also cited by the PBAC as the primary reason for not subsiding ivabradine for chronic stable angina in Australia.

3.4 Chronic heart failure

The Committee noted that clinical evidence supporting the use of ivabradine for chronic heart failure was limited to a single randomised controlled trial (SHIFT) and post-hoc subgroup analysis of patients with a resting heart rate of 75bpm or more (SHIFT-PRO). Although results suggested that ivabradine was associated with a statistically significant reduction in risk for the primary composite endpoint of cardiovascular death or hospitalisation for worsening heart failure, the results for the individual components of the composite measure were only statistically significant for heart failure hospitalisations, and not for cardiovascular death. The Committee agreed that frequency of hospitalisation was an important proxy measure of patients' health-related quality of life, and on balance considered that the available evidence supported the use of ivabradine for a subgroup of patients with high resting heart rates (≥75bpm).

Cost effectiveness

4.1 The Committee considered the cost-effectiveness of ivabradine for chronic heart failure based on published studies, and noted that there were no local economic evaluations available. Results from overseas economic analyses as part of the UK NICE appraisal showed that ivabradine plus standard care improved patient survival by approximately 3 months compared with standard care alone, and approximately 225 patients needed to be treated yearly to prevent 1 death due to heart failure.

4.2 The Committee noted that the incremental cost-effectiveness ratio (ICER) from this study ranged from £8K to £16K per QALY gained in different scenario analyses. The Committee concluded that at the price proposed by the manufacturer, ivabradine plus standard care was likely to represent a cost effective treatment option versus standard care alone for chronic heart failure in Singapore if used in line with strict clinical criteria.

Estimated annual technology cost

5.1 Following value-based pricing (VBP) discussions, the manufacturer offered a price discount for ivabradine which was contingent on achieving a listing on MAF.

5.2 The Committee estimated that around 470 people with chronic heart failure in Singapore would benefit from government assistance for ivabradine. The annual cost impact was estimated to be <$500,000 in the first year of listing on the MAF at the price proposed by the manufacturer.

5.3 The Committee advised that the price of ivabradine should be reviewed periodically if ivabradine use increases significantly following listing on MAF.

Recommendation

6.1 On the basis of acceptable clinical and cost-effectiveness, and moderate clinical need, the Committee recommended ivabradine 5mg and 7.5mg tablet for listing on the MAF for the treatment of chronic heart failure under specific clinical conditions.

6.2 The Committee did not recommend ivabradine for chronic stable angina, due to a paucity of robust evidence.