Ezetimibe and ezetimibe/simvastatin

for treating primary hypercholesterolaemia

Technology Guidance from the MOH Drug Advisory Committee

Guidance recommendations

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

- ✓ Ezetimibe 10 mg tablet for treating primary (heterozygous familial and non-familial) hypercholesterolaemia in adults as:
  - Add-on therapy to statins when the cholesterol concentration therapeutic target is not achieved at the maximum tolerated statin dose; or
  - Monotherapy as an alternative to statins for adults who are intolerant of, or contraindicated to, statin therapy.

Intolerance to statin therapy is defined as the occurrence of clinically significant adverse effects that are an unacceptable risk to the patient.

Subsidy status

Ezetimibe 10 mg tablet is recommended for inclusion on the MOH Standard Drug List (SDL) for the abovementioned indications.

SDL subsidy **does not** apply to ezetimibe/simvastatin 10/10 mg or 10/20 mg tablets.

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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 ezetimibe and ezetimibe/simvastatin for primary (heterozygous familial and non-familial) hypercholesterolaemia. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from public healthcare institutions. Published clinical and economic evidence for both drugs 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 noted that statins are routinely prescribed as first-line treatment for primary hypercholesterolaemia in local clinical practice in line with local and international clinical practice guidelines. Although dose escalation of statins is trialled to maximum tolerated doses to achieve control of cholesterol concentrations in line with therapeutic targets, many patients have residual cardiovascular risk that requires the addition of other lipid-modifying strategies, such as ezetimibe. The Committee acknowledged comments from clinical experts suggesting a greater need to subsidise ezetimibe over ezetimibe/simvastatin to enable use as monotherapy or as add-on therapy to other statins.

Clinical effectiveness and safety

3.1 The Committee discussed the clinical effectiveness of ezetimibe add-on therapy from published clinical trials and noted ezetimibe plus statin therapy significantly lowered low-density lipoprotein cholesterol (LDL-C) levels compared with statin monotherapy, doubling statin doses, or switching to a more potent statin; however, ezetimibe was considered clinically comparable to statin doses intensified by at least three-fold.

3.2 They further acknowledged results from the large IMPROVE-IT trial of 18,144 patients with stabilised acute coronary syndrome, where ezetimibe plus simvastatin significantly reduced the primary composite endpoint of death from cardiovascular causes, major coronary event, or non-fatal stroke, compared with simvastatin alone at a median follow-up of six years (HR 0.936; 95%CI 0.89 to 0.99; p=0.016). The Committee agreed there was uncertainty surrounding the effect of ezetimibe on mortality benefits, noting no significant difference in all-cause mortality, cardiovascular mortality, or cerebrovascular events were reported in a recent meta-analysis (Fei 2018) that included IMPROVE-IT and other small randomised controlled trials.

3.3 The Committee considered the clinical effectiveness of ezetimibe monotherapy for adults who are contraindicated to, or intolerant of statin therapy. They noted results from clinical trials demonstrating ezetimibe monotherapy leads to statistically significant improvements in LDL and total cholesterol concentrations compared with placebo. The Committee agreed although the trials were generally conducted in patients tolerant of statins, there was no biologically plausible reason why the results could not be generalised to patients with statin intolerance or who are contraindicated to statins.

3.4 The Committee acknowledged that ezetimibe was well tolerated by patients in the clinical trials and was found to have a similar adverse event profile to the comparators (statin therapy or placebo).

Cost-effectiveness

4.1 In the absence of local cost-effectiveness studies, the Committee acknowledged overseas published analyses which showed that in patients with cardiovascular disease risk, adding ezetimibe to statin therapy was a cost-effective use of healthcare resources in their local contexts when LDL-C targets were not achieved despite maximum statin doses or when patients were intolerant of statins. The Committee noted that with the availability of generic formulations in Singapore, ezetimibe was likely to be at least as cost-effective in local practice when used as part of similar treatment strategies.

Estimated annual technology cost

5.1 Value-based pricing discussions were not conducted with the manufacturer due to the availability of generic formulations. The Committee estimated around 9,800 people with primary hypercholesterolaemia in Singapore would benefit from government subsidy for generic ezetimibe. The annual cost impact was estimated to be less than SG$500,000 in the first year of listing on the SDL.

5.2 The Committee cautioned that listing ezetimibe on the SDL without any clinical criteria to govern use may lead to inappropriate prescribing, and advised that the uptake of ezetimibe should be carefully monitored by MOH.

Recommendation

6.1 Based on available evidence, the Committee recommended ezetimibe 10 mg tablet be listed on the SDL in line with its registered indication for treating primary (heterozygous familial and non-familial) hypercholesterolaemia, given its favourable clinical and cost-effectiveness compared to comparators when used as add-on therapy to statins, or as monotherapy in adults who are intolerant of, or contraindicated to, statin therapy.