Febuxostat

for treating chronic hyperuricaemia in adults with gout

Technology Guidance from the MOH Drug Advisory Committee

Guidance recommendations

The Ministry of Health's Drug Advisory Committee has not recommended listing febuxostat on the Medication Assistance Fund (MAF) for treating chronic hyperuricaemia in adults with gout because of unacceptable cost-effectiveness compared with alternative treatments at the price proposed by the manufacturer.

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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 febuxostat for chronic hyperuricaemia in adults with gout. The Agency for Care Effectiveness conducted the evaluation in consultation with the MOH Gout Expert Working Group comprising senior healthcare professionals from public healthcare institutions. Published clinical and economic evidence for febuxostat was considered in line with the registered indication, and for a subgroup of patients with gout and moderate to severe renal impairment (chronic kidney disease (CKD) Stage 3b and above) who are unsuitable for alternative urate-lowering treatment options.

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 heard that in local clinical practice, allopurinol is given first-line to most patients who receive urate-lowering therapy for gout; however, a small proportion of patients may experience rare serious adverse events, such as Severe Cutaneous Adverse Reactions (SCAR) including Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). The Committee acknowledged that there is a genetic association between SCAR and the presence of the HLA-B*58:01 allele; however, the coexistence of other immunological factors may also play a role in the development of SCAR. In local practice, genotyping for HLA-B*58:01 prior to starting a patient on allopurinol is not routinely recommended in view of the test's low positive predictive value. Instead, patients are carefully monitored for adverse reactions for up to 12 weeks after starting treatment. Febuxostat is generally only used last-line after allopurinol and probenecid due to its high cost relative to alternative treatments. In local practice, it is typically administered at a maintenance dose of 80 mg.

2.2 The Committee noted patients with moderate to severe renal impairment have fewer treatment options for gout, since they can only receive low-dose allopurinol (up to 300 mg) and are unsuitable for probenecid. For these patients, febuxostat is considered a suitable alternative treatment.

Clinical effectiveness and safety

3.1 The Committee discussed the clinical effectiveness of febuxostat 80 mg reported in published randomised controlled trials (RCTs) and meta-analyses, in addition to pooled results from a network meta-analysis (NMA) performed by ACE. They noted the primary outcome in most trials was a surrogate endpoint (target serum uric acid (sUA) level), and there was limited data available connecting it to outcomes which have a direct clinical impact on patients with gout. The Committee noted that first-line treatment of hyperuricaemia with febuxostat 80 mg resulted in a higher proportion of patients reaching a target sUA level <6.0 mg/dL (<360 µmol/L) compared to either allopurinol 300mg or placebo in the individual RCTs and NMA. The Committee also noted limited clinical data was available to support using febuxostat beyond first-line treatment.

3.2 Results for patient-related outcomes (such as acute gout flares, tophus resolution, and quality-of-life) were not significantly different for febuxostat versus allopurinol in the individual trials. Indirect analysis or NMA for patient-related outcomes were not conducted because of variations in outcome measures between trials and lack of data.

3.3 In patients with moderate to severe renal impairment, studies demonstrated febuxostat 80 mg was more effective than low-dose allopurinol (200 mg) or placebo in lowering sUA to <6.0 mg/dL.

3.4 Adverse events were generally consistent across the different treatment arms in the trials. However, the Committee noted all-cause mortality and CV mortality were higher for patients receiving febuxostat compared to allopurinol in a large RCT, for patients with gout and major cardiovascular (CV) disease. Statistical significance was not reached for the primary composite endpoint of CV death, nonfatal MI, nonfatal stroke, or unstable angina in the trial.

Cost-effectiveness

4.1 The manufacturer submitted a price discount for subsidy consideration through the value-based pricing process which was used to inform ACE's economic evaluation of febuxostat.

4.2 The Committee considered cost-effectiveness analyses of various urate-lowering pharmacotherapy strategies, with and without prior HLA-B*58:01 genotyping, in two gout populations—symptomatic patients with sUA above 8 mg/dL (480 µmol/L; "general gout population") and patients with moderate to severe renal impairment. Results indicated that in the general gout population, strategies where febuxostat was used first-line were dominated (that is, lower QALYs gained and higher costs) by first-line allopurinol (standard of care). For second-line febuxostat treatment after allopurinol, the base case incremental cost-effectiveness ratio (ICER) was >SG$105,000 per QALY gained. When febuxostat was modelled as a third-line treatment strategy (allopurinol → probenecid → febuxostat), the base case ICER was <SG$15,000 per QALY gained. Results were sensitive to the magnitude of treatment effect, utility weights, and cost of febuxostat.

4.3 The Committee noted that HLA-B*58:01 genotyping before treatment selection was not cost-effective for any scenarios modelled (dominated by non-genotyping strategies).

4.4 In the subgroup of patients with gout and moderate to severe renal impairment, first-line allopurinol followed by second-line febuxostat versus allopurinol alone produced a base case ICER in the range SG$15,000 to SG$45,000 per QALY gained. First-line febuxostat was dominated by allopurinol.

4.5 The Committee concluded that febuxostat did not represent a cost-effective use of healthcare resources for the general gout population at the price proposed by the manufacturer when used as a first-line or second-line treatment option. Although the base-case ICER was more favourable when febuxostat was used third-line for the general gout population, or second-line for patients with renal impairment, the Committee acknowledged the analyses were informed by limited clinical data and were uncertain.

4.6 The Committee noted comments from local clinical experts that patients with moderate to severe renal impairment could still be managed with low-dose allopurinol with careful dose titration over two to three months instead of febuxostat to mitigate the risk of SCAR, and concluded that there was low need to routinely subsidise febuxostat for this subgroup.

Estimated annual technology cost

5.1 The Committee estimated around 600 patients with gout would benefit from government assistance if febuxostat was listed on the MAF. The annual cost impact was estimated to be between SG$500,000 to <SG$1 million in the first year of listing.

5.2 If an MAF listing for febuxostat was restricted to patients with moderate to severe renal impairment who require urate lowering therapy for gout, approximately 142 people in Singapore would benefit from government assistance. The annual cost impact was estimated to be below SG$500,000 in the first year of listing on the MAF for this subgroup.

Recommendation

6.1 Based on available evidence, the Committee recommended not listing febuxostat on the MAF because of unacceptable cost-effectiveness compared with alternative urate-lowering treatment options at the price proposed by the manufacturer.