Technology Guidance

Emicizumab

prophylaxis for patients with haemophilia A

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended listing emicizumab on the Medication Assistance Fund (MAF) in line with its registered indication as prophylaxis for patients with haemophilia A with or without factor VIII inhibitors to prevent or reduce bleeding episodes, due to unfavourable cost-effectiveness compared with subsidised alternatives 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 emicizumab prophylaxis in patients with haemophilia A (congenital factor VIII deficiency) with or without factor VIII (FVIII) inhibitors to prevent and reduce bleeding episodes. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for emicizumab was considered in line with its registered indication.

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 there were 224 patients diagnosed with haemophilia A in Singapore in 2020. In local clinical practice, factor VIII replacement therapy is routinely used to manage bleeding episodes and prevent complications, however, up to 11% of patients can develop FVIII inhibitors and will require by-passing agents (BPAs) or alternative treatment options to manage their condition.

2.2. Locally, approximately 100 patients currently receive regular prophylaxis to prevent bleeding episodes, while the remaining patients receive on-demand (episodic) treatment. The Committee acknowledged that emicizumab is approved as prophylaxis for patients with or without FVIII inhibitors, however, its use in Singapore has been limited due to its high cost compared to alternative subsidised treatment options.

2.3. Patients without FVIII inhibitors

In line with clinical practice guidelines, regular FVIII prophylaxis is routinely used locally in patients with severe haemophilia A and in select patients with moderate haemophilia A without FVIII inhibitors who have recurrent joint bleeds. While plasma derived FVIII and standard half-life (SHL) recombinant FVIII (rFVIII) (Xyntha) products are already subsidised for these patients, the Committee acknowledged that emicizumab is a useful treatment option for some patients with difficult vascular access or who have recurrent bleeds while on FVIII prophylaxis.

2.4. Patients with FVIII inhibitors

Clinical experts confirmed that regular prophylaxis with emicizumab is considered standard of care in local clinical practice for patients with FVIII inhibitors. While FEIBA (a BPA) is already subsidised for patients who have FVIII inhibitors, the Committee acknowledged that it is only used as on-demand therapy for breakthrough bleeds and perioperative management, given its high cost; therefore, there was a clinical need to consider emicizumab for subsidy to improve treatment affordability and ensure appropriate care for patients who require prophylaxis.

Clinical effectiveness and safety

3.1. Patients without FVIII inhibitors

The Committee reviewed the available clinical evidence from a randomised controlled trial (RCT, HAVEN 3) which showed that regular prophylaxis with emicizumab was associated with a significant reduction in treated bleeds in patients with severe haemophilia A without FVIII inhibitors compared with no prophylaxis. Statistically significant differences in favour of emicizumab prophylaxis were also seen across other bleeding outcomes (overall bleeds, spontaneous bleeds, and joint bleeds).

3.2. The Committee acknowledged that there were no head-to-head trials comparing the efficacy and safety of emicizumab with FVIII prophylaxis and that indirect analyses considered by overseas reference HTA agencies, CADTH (Canada) and MSAC (Australia), were highly uncertain given the small number of trials included in the analyses, and the differences in study designs, patient populations and definitions of bleeding outcomes in the included trials. The Committee noted that MSAC (Australia) considered that the evidence was insufficient to support a clinical claim of superiority but accepted that emicizumab was non-inferior to FVIII prophylaxis.

3.3. The Committee considered that emicizumab was generally well tolerated in the trial and noted that patients in both treatment arms had comparable rates of Grade $\geq$3 adverse events, with no treatment emergent antibodies detected.

3.4. Based on the available evidence, the Committee considered that emicizumab had an acceptable safety profile and was non-inferior to FVIII prophylaxis in reducing bleeds in patients without FVIII inhibitors.

3.5. Patients with FVIII inhibitors

The Committee reviewed the available clinical evidence from an RCT (HAVEN 1) of patients with haemophilia A and FVIII inhibitors and acknowledged that regular prophylaxis with emicizumab was associated with a significant reduction in treated bleeds compared to on-demand treatment with a BPA.

3.6. The Committee considered that emicizumab was generally well tolerated in the trial but noted that thrombotic microangiopathy and thrombosis events were reported in patients who received multiple infusions of FEIBA concurrently for breakthrough bleeding. Treatment-emergent antidrug antibodies were not detected in patients who received emicizumab.

3.7. Based on the available evidence, the Committee considered that emicizumab had an acceptable safety profile and provided a clinically meaningful reduction in bleeds when compared to on-demand treatment with a BPA in patients with FVIII inhibitors.

Cost effectiveness

4.1. The manufacturer of emicizumab was invited to submit a value-based pricing (VBP) proposal for their product for subsidy consideration. In the absence of local cost effectiveness evaluations of emicizumab in patients with and without FVIII inhibitors, the Committee reviewed published economic analyses from overseas reference HTA agencies.

4.2. Patients without FVIII inhibitors

The Committee noted that results from economic analyses of emicizumab compared with regular FVIII prophylaxis for patients without FVIII inhibitors that were considered by CADTH (Canada) and MSAC (Australia) were highly uncertain. Given that emicizumab was considered to be clinically non-inferior to FVIII prophylaxis based on the available trials, the Committee agreed that emicizumab was unlikely to represent a cost-effective treatment option in Singapore as the annual cost of emicizumab prophylaxis per patient was significantly higher compared to FVIII prophylaxis at the price proposed by the manufacturer.

4.3. Patients with FVIII inhibitors

The Committee noted that the manufacturer proposed to increase the price of emicizumab if it was only recommended for subsidy for patients with FVIII inhibitors. Given the proposed price was higher than the current price at the public healthcare institutions and prices in overseas reference jurisdictions, the Committee considered that emicizumab was unlikely to be cost-effective in the local setting.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact in the first year of listing emicizumab on the MAF as prophylaxis for patients with haemophilia A (with and without FVIII inhibitors) was estimated to be between SG$1 million to less than SG$3 million based on local epidemiological estimates.

Recommendations

6.1. Based on the available evidence, the Committee recommended not listing emicizumab on the MAF as prophylaxis for patients with haemophilia A without FVIII inhibitors due to unfavourable cost-effectiveness compared with FVIII prophylaxis at the price proposed by the manufacturer.

6.2. Despite the clinical need and favourable clinical effectiveness of emicizumab compared to BPAs for managing bleeding in patients with haemophilia A with FVIII inhibitors, the Committee was unable to recommend emicizumab for listing on the MAF for this subgroup in view of unfavourable cost-effectiveness at the price proposed by the manufacturer.