Rifaximin

for reducing recurrent episodes of overt hepatic encephalopathy

Technology Guidance from the MOH Drug Advisory Committee

Guidance recommendations

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

- ✓ Rifaximin 550 mg tablet as add-on therapy to lactulose for reducing recurrent episodes of overt hepatic encephalopathy.

Subsidy status

Rifaximin 550 mg tablet is recommended for inclusion on the MOH Standard Drug List (SDL) for the abovementioned indication.

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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 rifaximin as add-on therapy to lactulose for reducing recurrent episodes of overt hepatic encephalopathy. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from public healthcare institutions. Published clinical and economic evidence for rifaximin was considered in line with the 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 noted that in local clinical practice, rifaximin is used as add-on therapy to lactulose for preventing hepatic encephalopathy (HE) in line with its registered indication and international clinical guidelines. Locally, it is estimated that 30 to 75% of patients receiving lactulose will experience breakthrough HE and eventually require rifaximin.

Clinical effectiveness and safety

3.1 The Committee discussed results from the pivotal RFHE3001 trial which demonstrated that rifaximin significantly reduced the risk of overt HE and HE-related hospitalisations versus placebo in patients receiving lactulose; however, because of the short six-month trial duration, there was no evidence to confirm if rifaximin was effective in reducing subsequent events.

3.2 Additional results from an open-label, follow-up study (RFHE3002) showed long-term treatment (up to 24 months) with rifaximin continued to reduce the rate of HE-related and all-cause hospitalisations. However, there was no evidence to demonstrate the impact of treatment on improving quality of life for any Chronic Liver Disease Questionnaire (CLDQ) domains.

3.3 The Committee noted no apparent differences in the incidence of adverse events between rifaximin and placebo groups in the trials.

Cost-effectiveness

4.1 The Committee acknowledged that other HTA agencies, including NICE (UK), PBAC (Australia), and PHARMAC (New Zealand) have previously recommended reimbursing rifaximin as a cost-effective treatment in their local contexts; however, in most instances, results were uncertain and marginally cost-effective—at the upper end of an acceptable ICER range—and decisions were driven by the high unmet medical need for a subsidised treatment option in a population with limited alternatives. The Committee considered these overseas findings were generalisable to Singapore's context, noting the local price of rifaximin was comparable to overseas prices used in the analyses.

4.2 The Committee reviewed unpublished data from the NUH gastroenterology team, which indicated that the base-case ICER for rifaximin as add-on therapy to lactulose compared to lactulose alone was in the range of SG$15,000 to <SG$45,000 per QALY gained. The Committee noted the ICER was highly sensitive to assumed quality of life improvements for patients receiving rifaximin, and could be up to 10-fold higher than the base case estimate in sensitivity analyses. In addition, the validity and robustness of the model could not be verified as only limited details were provided by NUH.

4.3 On balance, the Committee concluded rifaximin was likely to reduce the duration of hospitalisation and associated resources and costs for treating hepatic encephalopathy compared to lactulose alone; and therefore would represent a cost-effective treatment option in the local context for patients with high clinical need.

Estimated annual technology cost

5.1 Through the value-based pricing process, the manufacturer offered a price discount for rifaximin contingent on an SDL listing. The Committee estimated around 180 people in Singapore would benefit from government subsidy for rifaximin. The annual cost impact was estimated to be between SG$500,000 to <SG$1 million in the first year of listing on the SDL. The Committee acknowledged that the risk of use beyond the registered indication was low and agreed an SDL listing for rifaximin was appropriate.

Recommendation

6.1 Based on available evidence, the Committee recommended rifaximin 500 mg tablet be listed on the SDL as add-on therapy to lactulose for reducing recurrent episodes of overt hepatic encephalopathy, given favourable clinical effectiveness, acceptable cost-effectiveness and high clinical need to provide a subsidised treatment option to ensure appropriate care for patients.