Technology Guidance

Ruxolitinib

for treating graft-versus-host disease

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Ruxolitinib 5 mg, 15 mg and 20 mg tablets for treating grades II to IV **acute** graft-versus-host disease (GVHD) in patients who have an inadequate response to corticosteroids.

Funding status

Ruxolitinib 5 mg, 15 mg and 20 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication from 1 August 2024.

MAF assistance **does not** apply to ruxolitinib for treating moderate to severe **chronic** GVHD in patients who have an inadequate response to corticosteroids.

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Factors considered to inform the recommendations for funding

Technology evaluation

1.1. At the March 2024 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of ruxolitinib for treating graft-versus-host disease (GVHD). The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions and patient experts from local patient and voluntary organisations. Clinical and economic evidence for ruxolitinib was considered in line with its 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 funding considerations.

Clinical need

2.1. Graft-versus-host disease (GVHD) is a complication of allogeneic haematopoietic stem cell transplant (alloHSCT) which occurs when the donor immune cells mount an immune response against the transplant recipient's tissues. GVHD is classified as acute or chronic based on the timing of onset and the pattern of organ involvement.

2.2. In Singapore, approximately 90 patients develop GVHD each year, with 60% of cases diagnosed as acute GVHD and the remaining as chronic GVHD. The Committee heard that acute GVHD often requires hospitalisation and is a major cause of short-term mortality after alloHSCT.

2.3. In local clinical practice, systemic corticosteroids are used as initial therapy for treating grades II to IV acute GVHD and moderate to severe chronic GVHD. This is in line with international clinical practice guidelines. The Committee heard that there is no standard treatment for patients who do not respond adequately to corticosteroids. They also heard that ruxolitinib is the preferred treatment option in patients who have inadequate response to corticosteroids, especially for acute GVHD where treatment alternatives were considered to have limited effectiveness.

2.4. The Committee noted that apart from ruxolitinib, other treatments or best available therapy (BAT) included mycophenolate mofetil (MMF), etanercept, infliximab, extracorporeal photopheresis (ECP) and anti-thymocyte globulin for acute GVHD and ECP, ibrutinib, MMF and sirolimus for chronic GVHD.

2.5. The Committee considered testimonials from two local patient experts about their lived experiences with GVHD. The Committee heard that GVHD had negatively impacted the patients' daily lives physically, mentally, and emotionally. Both patients were taking ruxolitinib, which they felt controlled their condition, was convenient to take, and could reduce their need for corticosteroids. However, the Committee noted that treatment benefits were slow to manifest, and ruxolitinib caused side effects such as decreased blood cell counts and increased cholesterol levels which required additional treatment. Overall, both patients considered that any new treatment for GVHD should be more effective in controlling symptoms faster, enable them to resume daily activities, and be more affordable than their current treatment.

Clinical effectiveness and safety

3.1. The Committee reviewed published clinical evidence from two open-label randomised controlled trials comparing ruxolitinib with BAT in patients with grades II to IV acute GVHD (REACH2) or moderate to severe chronic GVHD (REACH3), and who have an inadequate response to corticosteroids.

3.2. The Committee heard that ruxolitinib was associated with higher overall response rates (ORR) and longer median failure-free survival (FFS) for both indications. While there were no statistically significant improvements in overall survival (OS), the trials were not powered to detect a difference in OS, and patients in the BAT arm crossing over to receive ruxolitinib could have confounded results. Hence, the OS benefit of ruxolitinib compared with BAT remains uncertain.

3.3. The Committee noted that ruxolitinib was associated with higher overall adverse events (AEs) and treatment-related AEs compared with BAT across both trials. However, the Committee noted that the broad range of BATs and longer exposure duration of ruxolitinib may have exaggerated the incremental effect of AEs in the ruxolitinib arms.

3.4. Overall, the Committee considered that, compared with BAT, ruxolitinib may be considered superior in efficacy (based on ORR and FFS) and non-inferior in safety for treating grades II to IV acute GVHD or moderate to severe chronic GVHD in patients who have an inadequate response to corticosteroids. However, the Committee acknowledged the uncertainties regarding the generalisability of the clinical evidence to the local setting given the different composition of BAT used in REACH2 and REACH3 versus local practice.

Cost effectiveness

4.1. The Committee considered results from ACE's cost-effectiveness analyses comparing ruxolitinib with BAT for treating grades II to IV acute GVHD or moderate to severe chronic GVHD in patients who have an inadequate response to corticosteroids.

4.2. For acute GVHD, ruxolitinib was dominant over BAT (i.e. ruxolitinib resulted in more quality-adjusted life years [QALYs] gained at a lower cost).

4.3. For chronic GVHD, ruxolitinib was associated with a high base-case incremental cost-effectiveness ratio (ICER) of more than $365,000 per QALY gained compared with BAT. The Committee noted that time horizon, health state utility values, and cost of ruxolitinib were the key drivers of the model.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact to the public healthcare system was estimated to be less than SG$1 million in the first to fifth year of listing ruxolitinib on the MOH List of Subsidised Drugs for treating either acute GVHD or chronic GVHD in patients who have an inadequate response to corticosteroids.

Recommendations

6.1. Based on available evidence and given favourable clinical and cost-effectiveness and high clinical need to improve patient affordability, the Committee recommended ruxolitinib 5 mg, 15 mg and 20 mg tablets be listed on the Medication Assistance Fund for treating grades II to IV acute GVHD in patients who have an inadequate response to corticosteroids.

6.2. Based on available evidence, the Committee recommended not listing ruxolitinib on the MOH List of Subsidised Drugs for treating moderate to severe chronic GVHD in patients who have an inadequate response to corticosteroids. This decision was based on unfavourable cost-effectiveness at the price proposed by the company compared with alternative treatment options.

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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