Mycophenolate

for treating active lupus nephritis

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- Mycophenolate mofetil 250 mg capsule and 500 mg tablet for the induction and maintenance treatment of active lupus nephritis in patients who have biopsy-proven Class III, IV, V, or combinations of lupus nephritis based on International Society of Nephrology/Renal Pathology Society (ISN/RPS) criteria.

A renal biopsy should be performed as far as possible to confirm active lupus nephritis before starting treatment. If a renal biopsy is not possible, the following clinical criteria should be used to diagnose active lupus nephritis:

- Significant proteinuria of ≥1g per 24 hours; or
- Proteinuria ≥0.5g per 24 hours plus haematuria defined as ≥5 red blood cells per high power field; or
- Proteinuria ≥0.5g per 24 hours plus cellular casts.

Subsidy status

Mycophenolate mofetil 250 mg capsule and 500 mg tablet are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication.

MAF subsidy does not apply to mycophenolate mofetil for non-renal systemic lupus erythematosus, or to mycophenolate sodium for any indications.

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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 mycophenolate mofetil (MMF) and mycophenolate sodium (EC-MPS) for common off-label indications, including lupus nephritis, non-renal systemic lupus erythematosus, IgA nephropathy, myasthenia gravis, and neuromyelitis optica. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from the public healthcare institutions.

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
- 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 subsidy consideration for off-label use of HSA-registered drugs was permissible if all these conditions were met:

- There is sufficient evidence available to assess the safety, efficacy, and cost-effectiveness of the off-label use of the drug
- The off-label use of the drug is the current standard of care in local clinical practice and also in line with international best practice
- There is a lack of affordable and cost-effective treatment alternatives to the off-label drug.

2.2 Local clinical experts confirmed that the majority of current non-transplant (off-label) mycophenolate use was for renal, rheumatology, or neurology indications, with the most common conditions being lupus nephritis, non-renal systemic lupus erythematosus, IgA nephropathy, myasthenia gravis, and neuromyelitis optica. The Committee agreed that out of the five indications identified, there was only sufficient clinical evidence to evaluate mycophenolate for lupus nephritis.
2.3 The Committee noted that oral mycophenolate was used routinely as first-line induction and maintenance treatment for Class III to V lupus nephritis in local practice, in line with international guidelines, and this use was endorsed by a consensus statement from the College of Physicians, Singapore. Clinicians confirmed that patients who are of child-bearing age, have high risk of infections, are at risk of potential drug interactions with other therapies, or have had an inadequate response or intolerance to other therapies would benefit from using mycophenolate compared to alternative treatments because of its superior side-effect profile.

2.4 The Committee acknowledged that clinicians typically consider MMF and EC-MPS to be clinically comparable but usually initiate MMF therapy because of its lower cost, and only switch patients to EC-MPS if they develop gastrointestinal side effects or cannot tolerate MMF.

2.5 The Committee agreed with the clinicians that there was sufficient clinical need to consider subsidising mycophenolate for patients with lupus nephritis.

Clinical effectiveness and safety

3.1 The Committee agreed that cyclophosphamide and azathioprine were the appropriate comparators to mycophenolate for the induction and maintenance treatment of lupus nephritis respectively.

3.2 Published clinical evidence demonstrated no statistically significant difference in mortality or renal outcomes between MMF and cyclophosphamide for induction therapy. However, MMF was associated with significantly lower risk of alopecia, leucopenia, and ovarian failure, but a higher risk of diarrhoea. For maintenance therapy, MMF was associated with a statistically significantly lower risk of renal relapse and leucopenia when compared with azathioprine.

3.3 The Committee noted that there were no published head-to-head randomised controlled trials (RCTs) comparing the efficacy or safety of EC-MPS and MMF for lupus nephritis. However, they acknowledged published RCT evidence in solid organ transplants comparing EC-MPS with MMF showed no statistically significant differences in safety or efficacy outcomes between both salts.

3.4 Based on available evidence, the Committee considered EC-MPS and MMF were clinically comparable.
Cost effectiveness

4.1 The Committee agreed a cost-minimisation analysis was appropriate to assess the cost effectiveness of MMF and EC-MPS, given their comparable efficacy and safety.

4.2 Manufacturers of MMF and EC-MPS were invited to submit a value-based pricing proposal for consideration. The Committee concluded that at the prices proposed by the manufacturers, generic MMF resulted in the lowest cost to the system and was considered an acceptable use of healthcare resources. EC-MPS resulted in the highest cost to the system.

Estimated annual technology cost

5.1 The Committee noted around 300 people with lupus nephritis in Singapore would benefit from government assistance for mycophenolate. The annual cost impact was estimated to be less than $500K in the first year of listing MMF on the MAF.

Additional considerations

6.1 The Committee noted that local clinicians surveyed were agreeable to using generic mycophenolate for lupus nephritis. However, they acknowledged that the generic formulation was only available in the 500 mg strength, and the tablet was not divisible. The Committee therefore agreed that subsidy for MMF should not be limited to the generic formulation only, given the clinical need for the 250 mg capsule for dose titration.

Recommendation

7.1 Based on available evidence, the Committee recommended mycophenolate mofetil 250 mg capsule and 500 mg tablet be listed on the MAF for active lupus nephritis, given acceptable clinical and cost effectiveness, and high clinical need for this treatment. MMF should be used for active lupus nephritis in line with specific clinical criteria, as defined in the consensus statement on the use of MMF in systemic lupus erythematosus from the College of Physicians, Singapore.

7.2 Without sufficient clinical evidence to justify using MMF for non-renal systemic lupus erythematosus, the Committee concluded that it should not be listed on the MAF for this indication.
About the Agency

The Agency for Care Effectiveness (ACE) is the national health technology assessment agency in Singapore residing within the Ministry of Health. It conducts evaluations to inform the subsidy of treatments, and produces guidance on the appropriate use of treatments for public hospitals and institutions in Singapore. When using the guidance, the responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

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