Technology Guidance

Abrocitinib, baricitinib, upadacitinib and dupilumab

for treating atopic dermatitis

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Abrocitinib 50 mg, 100 mg and 200 mg film-coated tablets for treating moderate-to-severe atopic dermatitis in patients who have had an inadequate response, intolerance or contraindication to at least one systemic therapy such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil.

Funding status

Abrocitinib 50 mg, 100 mg and 200 mg film-coated tablets are recommended for inclusion on the MOH Medication Assistance Fund (MAF) for the abovementioned indication from 1 March 2024.

Abrocitinib should be used in line with additional clinical criteria for initial and continuing prescriptions for patients with moderate-to-severe atopic dermatitis.

MAF assistance **does not** apply to any formulations or strengths of baricitinib, upadacitinib or dupilumab for treating atopic dermatitis.

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Factors considered to inform the recommendations for funding

Technology evaluation

1.1. At the October 2023 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of Janus kinase (JAK) inhibitors (abrocitinib, baricitinib, upadacitinib) and dupilumab for treating atopic dermatitis (AD). 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. Published clinical and economic evidence for the drugs under evaluation was considered in line with their 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. The Committee acknowledged that in local practice, immunosuppressants available on the Standard Drug List (i.e. ciclosporin, methotrexate, azathioprine, mycophenolate mofetil) are usually considered first for patients with AD who had an inadequate response to topical treatments and phototherapy. However, there remains a clinical need for other treatment options, such as JAK inhibitors or dupilumab, for those patients who had an inadequate response, intolerance or contraindication to these immunosuppressants.

2.2. The Committee considered 61 testimonials from local patient experts and carers about their lived experiences with AD and the treatments they have received. The Committee acknowledged that people with moderate-to-severe AD experienced a negative impact on many aspects of their lives, including sleep, work, school and relationships. They heard that many of the respondents were receiving treatment with topical or oral steroids and felt that they worked well, were easy to use and had minimal side effects.

2.3. The Committee acknowledged that the patient experts who received the drugs under evaluation reported improvement in symptoms with minimal side effects. The average improvement in itch expected by respondents for a new treatment was 4.0 points on the peak pruritus numerical rating scale (PP-NRS4) to be considered acceptably effective. Overall, people with AD preferred daily oral tablets over bi-weekly self-injections. They also considered that any new treatments should be more affordable, able to reduce symptoms, decrease the occurrence of flares, and have manageable side effects.

Clinical effectiveness and safety

3.1. The Committee reviewed clinical evidence from nine randomised controlled trials (RCTs) on combination therapies, where the drugs under evaluation were added onto background topical treatment (corticosteroids and/or calcineurin inhibitors). The majority of the trials were placebo-controlled. Only JADE DARE and JADE COMPARE included active treatment arms (abrocitinib versus dupilumab). As no head-to-head trials directly compared the remaining interventions, a network meta-analysis (NMA) was conducted to assess the comparative clinical effectiveness between the interventions.

3.2. <u>All interventions versus placebo</u>
The Committee noted direct and indirect evidence that showed abrocitinib, baricitinib, upadacitinib and dupilumab were superior to placebo across all the efficacy outcomes: proportion of patients who achieve 75% and 50% reduction in Eczema Area Severity Index (EASI) score (EASI-75 and EASI-50), Investigator Global Assessment (IGA) response, Dermatology Life Quality Index (DLQI) response and mean change from baseline in DLQI score at week 16.

3.3. <u>Abrocitinib, upadacitinib and dupilumab versus baricitinib</u>
The Committee considered abrocitinib, upadacitinib and dupilumab to be superior in efficacy compared to baricitinib. This was based on indirect evidence which consistently favoured abrocitinib, upadacitinib and dupilumab over baricitinib, across all efficacy outcomes and timepoints measured .

3.4. <u>Abrocitinib and upadacitinib versus dupilumab</u>
The Committee heard that direct evidence from JADE COMPARE and JADE DARE showed that high-dose abrocitinib (200 mg) was associated with significantly better response rates in PP-NRS4 at week 2 and EASI-90 at week 4 and 16 compared with dupilumab. However, the results were not sustained at longer timepoints. A similar trend where between-group differences reduced over time was also seen with the other efficacy outcomes. The Committee noted no significant difference was observed between low-dose abrocitinib (100 mg) and dupilumab in PP-NRS4 at week 2.

3.5. The Committee heard that although indirect evidence showed high-dose upadacitinib

(30 mg) had statistically higher IGA response rates at week 16 compared with dupilumab, no significant differences were observed with other efficacy outcomes. The Committee agreed that it was uncertain if the difference in IGA response would be maintained at longer timepoints. They heard that the head-to-head RCT comparing upadacitinib monotherapy with dupilumab (HEADS UP) showed that the magnitude of the higher EASI-75 response rate for high-dose upadacitinib was reduced at timepoints beyond week 16. The Committee noted that indirect evidence showed no significant difference between low-dose upadacitinib (15 mg) and dupilumab across all efficacy outcomes at week 16, with some point estimates favouring upadacitinib and others favouring dupilumab.

3.6. Without consistent results across outcomes and timepoints measured, the superiority of one intervention over the other could not be demonstrated. Hence, the Committee considered high and low doses for both abrocitinib and upadacitinib were clinically comparable to dupilumab.

3.7. Abrocitinib versus upadacitinib

The Committee noted there were no head-to-head RCTs that compared abrocitinib and upadacitinib with each other for treating AD. The Committee heard that indirect evidence showed no significant difference between abrocitinib and upadacitinib across all efficacy outcomes at week 16, with some point estimates favouring abrocitinib and others favouring upadacitinib. The Committee also considered that abrocitinib and upadacitinib have similar mechanism of action and agreed it was reasonable to consider them as clinically comparable to each other.

3.8. Safety of JAK inhibitors and dupilumab

The Committee noted the adverse events reported were generally mild-to-moderate and rarely led to study withdrawal. JAK inhibitors were associated with a higher incidence of herpes simplex and herpes zoster infections, while dupilumab was associated with a higher incidence of injection site reactions and conjunctivitis.

3.9. The Committee also noted that some case series reported incidents of mycosis fungoides or lymphoid reactions in patients treated with dupilumab in real-world practice, although it was uncertain if it was associated with dupilumab use.

3.10. The Committee heard that JAK inhibitors for treating inflammatory conditions were under a regulatory review for a potential class effect of increased risk of major cardiovascular events, malignancy and thrombosis. HSA's review in 2022 concluded that the benefit-risk profile of JAK inhibitors for the treatment of inflammatory conditions in Singapore remains positive for their approved indications, where the use of JAK inhibitors is already limited to second-line or later therapy. For AD, the Committee also noted that NICE (UK) has recommended the positioning of JAK inhibitors after systemic immunosuppressants for treating moderate-to-severe AD, partly due to the potential adverse events associated with JAK inhibitors.

Cost effectiveness

4.1. The Committee agreed that a cost-minimisation approach was appropriate to assess the cost-effectiveness of abrocitinib, upadacitinib and dupilumab, given that they were considered clinically comparable to each other.

4.2. The Committee agreed that abrocitinib, which had the lowest treatment cost, was the most cost-effective option. The Committee also noted that the price of abrocitinib was comparable to prices in overseas reference jurisdictions, coupled with an adequate proposal to manage the uncertainty of the overall budget impact. Hence, the Committee agreed that abrocitinib was likely to be considered an acceptable use of healthcare resources in Singapore.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact to the public healthcare system was estimated to be between SG$5 million and SG$10 million in the first year of listing abrocitinib on the MOH List of Subsidised Drugs for moderate-to-severe AD.

Recommendations

6.1. Based on available evidence, the Committee recommended abrocitinib 50 mg, 100 mg and 200 mg be listed on the MAF for treating moderate-to-severe AD in patients who have had an inadequate response, intolerance or contraindication to at least one systemic therapy such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, in view of the clinical need and acceptable clinical- and cost-effectiveness compared with current treatment options.

6.2. The Committee recommended not listing baricitinib, dupilumab and upadacitinib on the MOH List of Subsidised Drugs, due to unacceptable clinical- or cost-effectiveness compared with abrocitinib.

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

Chief HTA Officer
Agency for Care Effectiveness
Email: ACE_HTA@moh.gov.sg