Technology Guidance

Biologics and Janus kinase inhibitors

after conventional disease modifying antirheumatic drugs for treating rheumatoid arthritis

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Baricitinib 2 mg and 4 mg tablets for treating adults with moderately to severely active rheumatoid arthritis;
- ✓ Tofacitinib 5 mg tablet for treating adults with moderately to severely active rheumatoid arthritis; and
- ✓ Rituximab biosimilar (Truxima) 500 mg concentrate for infusion for treating adults with severely active rheumatoid arthritis

in line with their registered indications.

Subsidy status

Baricitinib 2 mg and 4 mg tablets and tofacitinib 5 mg tablet are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication.

Baricitinib and tofacitinib should be used in line with the clinical criteria in the MAF checklist for initial and continuing prescriptions for patients with rheumatoid arthritis.

Rituximab biosimilar (Truxima) 500 mg concentrate for infusion is recommended for inclusion on the MOH Standard Drug List (SDL) for the abovementioned indication.

SDL subsidy and MAF assistance **does not** apply to any formulations or strengths of tocilizumab, rituximab reference biologic (MabThera) or other rituximab biosimilars (such as Rixathon).

Updated: 1 July 2022

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 biologics (tocilizumab, rituximab biosimilar (Truxima) and rituximab reference biologic (MabThera)) and Janus kinase (JAK) inhibitors (baricitinib and tofacitinib) for treating rheumatoid arthritis (RA) in August 2020. The Agency for Care Effectiveness conducted the evaluation in consultation with the MOH Rheumatoid Arthritis Expert Working Group comprising senior healthcare professionals from public healthcare institutions. Published clinical and economic evidence for all drugs 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 subsidy considerations.

1.4. In March 2022, the Committee considered an evaluation of tofacitinib for ulcerative colitis (UC) which included a revised pricing proposal for subsidy consideration covering use for UC and RA.

Clinical need

2.1. The Committee noted that RA is the most common autoimmune inflammatory arthritis, affecting ~56,000 people in Singapore. Multiple treatment options, with different mechanisms of action, are needed to control disease progression and manage symptoms.

2.2. In local clinical practice, four drug classes are typically used to treat patients with moderate to severe active RA, who have had an inadequate response to methotrexate and other conventional disease modifying antirheumatic drugs (DMARDs), including tumour necrosis factor alpha (anti-TNFα) inhibitors, interleukin-6 inhibitors, JAK inhibitors, and anti-CD20 agents, in line with international clinical guidelines.

2.3. While anti-TNFα inhibitors (adalimumab biosimilar (Amgevita), infliximab biosimilar (Remsima and Ixifi) and golimumab) are already subsidised for treating RA, the Committee agreed that there was a clinical need to improve the affordability of alternative biologic treatment options for patients to help them control symptoms and reduce disability.

2.4. A biosimilar is a biological therapeutic product with proven similar physicochemical characteristics, biological activity, safety and efficacy to the reference biological product. Truxima is a biosimilar of rituximab (a biological anti-CD20 agent) and its reference biologic is MabThera. The Committee acknowledged that MabThera IV was already listed on the MAF for non-Hodgkin's lymphoma, but its use in RA had not been previously assessed for subsidy consideration. The Committee heard that local clinical experts would prescribe a rituximab biosimilar if the clinical evidence showed that it was non-inferior to the reference biologic and it was more affordable for their patients.

2.5. The Committee noted that another rituximab biosimilar (Rixathon) was available in Singapore, however, it had not been approved by the Health Sciences Authority (HSA) for use in RA, therefore, it was outside the scope of the evaluation. Similarly, the subcutaneous formulation of MabThera, which is not subsidised, was also not considered as part of the evaluation.

Clinical effectiveness and safety

3.1. Tofacitinib for moderate to severe RA

The Committee acknowledged that available evidence showed that tofacitinib was non-inferior to adalimumab in achieving an American College of Rheumatology 50% response rate (ACR50) at week 24. Tofacitinib was comparable with adalimumab for other efficacy and safety outcomes. The Committee acknowledged that an ACR50 response had been accepted by the PBAC (Australia) as a reasonable treatment target for previous RA evaluations.

3.2. Baricitinib for moderate to severe RA

The Committee reviewed the available evidence which compared baricitinib with adalimumab, both in combination with methotrexate, and noted that the ACR50 response at week 24 was not statistically significantly different between the two treatments. Although significantly more patients receiving baricitinib achieved ACR20 and ACR70 responses at week 24 compared with adalimumab, the Committee noted that the absolute differences were small and were unlikely to be clinically meaningful. Baricitinib was considered comparable with adalimumab for other efficacy and safety outcomes measured in published studies.

3.3. Tocilizumab for moderate to severe RA

No randomised controlled trials (RCTs) comparing tocilizumab with adalimumab in combination with methotrexate were identified. The Committee reviewed the available evidence which compared tocilizumab monotherapy with adalimumab monotherapy and noted that tocilizumab was superior to adalimumab in terms of efficacy, and had a comparable safety profile in patients for whom methotrexate is contraindicated.

3.4. The Committee noted that these results had limited generalisability to local context as fewer than 30% of patients in Singapore use anti-TNFα monotherapy as it is less effective than when combined with methotrexate. The Committee acknowledged that the subcutaneous dosage form for tocilizumab was non-inferior to the intravenous formulation in terms of efficacy and safety when used concurrently with methotrexate.

3.5. Rituximab for severe RA

Three double blind RCTs were identified which compared MabThera with methotrexate versus placebo with methotrexate in patients with severe RA. The Committee acknowledged that MabThera with methotrexate had superior efficacy and comparable safety versus background methotrexate alone.

3.6. The Committee heard that the clinical development programme for rituximab biosimilar (Truxima) to show clinical equivalence to MabThera was based on a Phase III study in adults with active RA. The Committee noted that the primary endpoint was within the bioequivalence margin, demonstrating that Truxima was therapeutically equivalent to MabThera. They also noted that the immunogenicity and safety profiles were comparable between Truxima and MabThera, and open label extension studies confirmed that switching from MabThera to Truxima did not lead to any safety issues.

3.7. Clinical conclusions

The Committee considered results from a published network meta-analysis by Fakhouri et al. (2020) that showed baricitinib, tofacitinib, tocilizumab, rituximab and anti-TNFα inhibitors had similar efficacy, as measured by ACR50 response, when used in combination with methotrexate in patients with moderate to severe RA. Overall, the Committee considered baricitinib, tofacitinib, tocilizumab, rituximab and anti-TNFα inhibitors to be clinically comparable.

Cost effectiveness

4.1. No local economic evaluations were identified. The Committee heard that baricitinib, tofacitinib, tocilizumab and rituximab were considered cost effective by overseas reference HTA agencies, predominantly in patients with severe RA. However, they noted that the drug costs used in the economic models were not published and therefore, it was unknown whether the prices were comparable to those in Singapore and if the cost-effectiveness results were generalisable.

4.2. The Committee agreed that a cost-minimisation approach was appropriate to assess the cost effectiveness of these drugs, in view of their comparable efficacy and safety with anti-TNFα inhibitors.

4.3. All manufacturers were invited to submit value-based pricing (VBP) proposals for subsidy consideration of their products. At the prices proposed by the manufacturers in 2020, the cost of baricitinib was higher than Amgevita (listed on SDL) and lower than golimumab (listed on MAF), tofacitinib and tocilizumab. Therefore, the Committee agreed that baricitinib represented a cost-effective treatment option for MAF listing for patients with moderate to severe active RA.

4.4. The Committee acknowledged that the cost of Truxima was lower than MabThera and similar to Amgevita. Results remained consistent when the re-treatment interval for Truxima was reduced from yearly to twice a year. Therefore, the Committee agreed that Truxima also represented a cost-effective treatment option for SDL listing for patients with severe active RA.

4.5. At the prices proposed by the manufacturers in 2020, the Committee considered that tofacitinib and tocilizumab were not cost effective compared with baricitinib, Truxima, golimumab and Amgevita.

4.6. Following a revised pricing proposal in 2022, the Committee agreed that an MAF listing for tofacitinib was also appropriate as it represented a cost-effective treatment option for patients with moderately to severely active RA at the revised price.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact in the first year of listing on SDL or MAF for treating RA was estimated to be:

- Baricitinib and tofacitinib (MAF): less than SG$1 million
- Truxima (SDL): less than SG$1 million

5.2. The Committee acknowledged that due to improved treatment affordability once baricitinib, tofacitinib and Truxima are subsidised, the number of patients receiving treatment was likely to increase over time.

Recommendations

6.1. Based on available evidence presented in August 2020, the Committee recommended rituximab biosimilar (Truxima) 500 mg concentrate for infusion be listed on the SDL for treating RA in line with its registered indication, in view of its therapeutic similarity and favourable cost effectiveness compared with the reference biologic (MabThera).

6.2. The Committee recommended baricitinib 2 mg and 4 mg tablets be listed on the MAF for treating moderate to severe active RA, given their favourable clinical and cost-effectiveness compared with other biologics.

6.3. In March 2022, the Committee also recommended tofacitinib 5 mg tablet be listed on the MAF in line with the same clinical criteria as baricitinib, following a revised pricing proposal from the manufacturer.

VERSION HISTORY

Guidance on biologics and Janus kinase inhibitors after conventional disease modifying antirheumatic drugs for treating rheumatoid arthritis

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

Publication of guidance

Date of Publication	18 Jan 2021

Guidance updated to include MAF listing of tofacitinib 5 mg tablet for treating moderately to severely active rheumatoid arthritis

Date of Publication	1 July 2022

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 subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 19 August 2020 and 18 March 2022. It 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.

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