Adalimumab

for treating inflammatory conditions

Technology Guidance from the MOH Drug Advisory Committee

Guidance recommendations

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

- ✓ Adalimumab biosimilar (Amgevita) 20 mg/0.4 ml prefilled syringe and 40 mg/0.8 ml prefilled autoinjector and syringe for treating the following inflammatory conditions in line with its registered indications in Singapore:
  - Adults with moderately to severely active rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, chronic plaque psoriasis, ulcerative colitis, Crohn's disease or hidradenitis suppurativa;
  - Adults with non-infectious intermediate, posterior and panuveitis;
  - Children aged 2 years or older with chronic non-infectious anterior uveitis or polyarticular juvenile idiopathic arthritis;
  - Children aged 4 years or older with severe chronic plaque psoriasis;
  - Children aged 6 years or older with moderately to severely active Crohn's disease or enthesitis-related arthritis; and
  - Children aged 12 years or older with moderate to severe hidradenitis suppurativa;
- ✓ The removal of adalimumab reference biologic (Humira) 40 mg/0.8 ml prefilled autoinjector from the Medication Assistance Fund (MAF) for all indications; and
- ✓ Not to list new formulations of Humira (20 mg/0.2 ml or 40 mg/0.4 ml prefilled syringe and pen) on SDL or MAF in view of unfavourable cost effectiveness compared with Amgevita at the price proposed by the manufacturer.

Subsidy status

Adalimumab biosimilar (Amgevita) 20 mg/0.4 ml prefilled syringe and 40 mg/0.8 ml prefilled autoinjector and syringe are recommended for inclusion on the MOH Standard Drug List (SDL) for the abovementioned indications from 1 September 2020. The MAF listing of Humira will cease on 1 March 2021.

SDL subsidy **does not** apply to any formulations or strengths of Humira.

Published on 1 September 2020

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 adalimumab biosimilar (Amgevita) and a new formulation (20 mg/0.2 ml and 40 mg/0.4 ml) of adalimumab reference biologic (Humira) for all registered indications. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for Amgevita and Humira 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.

Clinical need

2.1 A biosimilar is a biological therapeutic product with proven similar physicochemical characteristics, biological activity, safety and efficacy to the reference biological product. Amgevita is a biosimilar of adalimumab (a biological TNF inhibitor) and its reference biologic is Humira. The Committee acknowledged that Humira was already listed on the MAF for all registered indications except non-infectious uveitis (NIU) and paediatric chronic plaque psoriasis (PsO), which had not been previously assessed for subsidy consideration.

2.2 The Committee noted that international position statements from professional bodies for rheumatology and gastrointestinal disorders support the use of cheaper biosimilars when the prescribing decision is shared between the patient and the clinician, and patients are closely monitored for efficacy and safety outcomes.

2.3 Local clinical experts confirmed that they would prescribe adalimumab biosimilar if the clinical evidence showed that it was non-inferior to the reference biologic and it was more affordable for their patients. The Committee noted that the clinical experts were agreeable to only one brand of adalimumab being subsidised, provided that a 6-month overlap period for subsidy was put in place to allow

prescribing clinicians to assess any efficacy or safety differences when their patients switch products.

2.4 The Committee noted that uveitis is one of the leading causes of vision loss in Singapore, and there are currently no biologics subsidised for the treatment of NIU. Locally, adalimumab is prescribed for patients who have refractory NIU despite conventional immunomodulatory therapy, in line with international treatment guidelines. There are approximately 45 patients with NIU who would benefit from subsidy listing of adalimumab each year for this indication.

2.5 The Committee noted that there are fewer than 10 patients with paediatric PsO who require treatment with adalimumab annually in Singapore. Despite the small number of patients requiring adalimumab for NIU or paediatric PsO, the Committee agreed that extending subsidy of adalimumab to these additional indications will address the current therapeutic gap in the MOH List of Subsidised Drugs and provide affordable treatment to these patients with high clinical need.

Clinical effectiveness and safety

3.1 <u>New formulation of Humira (20 mg/0.2 ml and 40 mg/0.4 ml)</u>
The Committee noted that the new formulation of Humira was designed to reduce immediate injection site pain due to a smaller injection volume (reduced from 0.8 ml to 0.4 ml) and a different composition of inert ingredients. The HSA approved indications for the new formulation are the same as the original formulation.

3.2 The Committee noted limited randomised controlled trial (RCT) evidence which compared the new formulation of Humira with its current formulation (40 mg/0.8 ml) and acknowledged that one RCT showed no statistically significant differences between the two formulations for all clinical outcomes reported in rheumatoid arthritis. Findings also remained unchanged for patients who switched from the current to the new formulation. There was no RCT evidence available for other registered indications.

3.3 <u>Adalimumab biosimilar (Amgevita 20 mg/0.4 ml and 40 mg/0.8 ml)</u>
The Committee heard that the clinical development programme for Amgevita to show clinical equivalence to Humira was based on two Phase III RCTs in adults with moderate to severe rheumatoid arthritis (RA) and PsO. Studies for other approved indications were not available.

3.4 The Committee noted that the primary endpoints for the RA and PsO studies were within the predefined equivalence margins, demonstrating that Amgevita was therapeutically equivalent to Humira 40 mg/0.8 ml for both indications. They also noted that the immunogenicity and safety profiles were comparable between both products in each trial, and open label extension studies confirmed that switching from Humira to Amgevita did not appear to affect the safety or efficacy of treatment.

3.5 The Committee considered results from a Cochrane systematic review by Singh et al. (2009) that showed adalimumab and infliximab reference biologics were similar in terms of efficacy and safety in patients with RA. In view of previous evidence considered by the Committee in 2017 which confirmed that infliximab biosimilar (Remsima) and reference biologic (Remicade) were clinically comparable, and evidence (para 3.3) confirming that adalimumab biosimilar and reference biologic were also therapeutically equivalent, the Committee agreed that findings from the systematic review were also likely to be transferable to the biosimilars. Therefore, the Committee considered that Humira, Amgevita and Remsima were clinically comparable.

3.6 Review of new indications for subsidy consideration (NIU and paediatric PsO)
The Committee also reviewed available clinical evidence which showed that Humira significantly delayed time to treatment failure compared with placebo in children (SYCAMORE trial) and adults (VISUAL I and VISUAL II trials) with NIU. However, there was no clinically significant improvement in visual acuity versus placebo reported. While clinical evidence was based on the original Humira formulation, the Committee considered that results would also be applicable to the new Humira formulation and Amgevita.

3.7 The Committee noted that the long-term clinical relevance of the delay in treatment failure was unclear as the link between treatment failure and long-term ocular complications, such as blindness, was uncertain. However, on balance, they considered that subsidy for NIU could be considered reasonable in view of high clinical need and the relatively low number of patients who require adalimumab each year for this indication.

3.8 In view of the small number of patients with paediatric PsO who require treatment with adalimumab annually, the Committee did not consider that a review of the clinical evidence for this indication was required.

Cost effectiveness

4.1 The Committee agreed that a cost-minimisation analysis was appropriate to assess the cost effectiveness of Amgevita, in view of its comparable efficacy and safety with Humira and Remsima.

4.2 The Committee acknowledged that the price proposed by the manufacturer for Amgevita was substantially lower than the current prices for Humira and Remsima, and agreed that it represented a cost-effective treatment option for all registered indications.

4.3 At the price proposed by the manufacturer, the Committee considered that the new formulation of Humira (20mg/0.2ml and 40mg/0.4ml) was not cost-effective compared with Amgevita.

4.4 In view of the large price differential between Amgevita and Humira (current formulation, 40 mg/0.8 ml), the Committee considered that there was insufficient justification to retain Humira on the MAF.

Estimated annual technology cost

5.1 No additional annual cost impact to the government was estimated in the first year of listing Amgevita on the SDL due to estimated cost savings from patients initiating treatment with Amgevita instead of Humira, or switching from Humira to Amgevita. The Committee acknowledged that due to improved treatment affordability with Amgevita, the number of patients accessing adalimumab was likely to increase over time.

Additional considerations

6.1 The Committee acknowledged that therapeutic drug monitoring (TDM) is well-established in local clinical practice to guide treatment decisions for inflammatory bowel diseases, despite overseas HTA agencies (e.g. NICE in the UK) reporting that there is insufficient evidence to support routine TDM of anti-TNFα treatments. The Committee heard that the cost of the test is currently paid for by the manufacturer of Humira and that the manufacturer of Amgevita has agreed to also provide TDM for free if the biosimilar is subsidised.

Recommendations

7.1 Based on available evidence, the Committee recommended adalimumab biosimilar (Amgevita) 20 mg/0.4 ml prefilled syringe and 40 mg/0.8 ml prefilled autoinjector and syringe be listed on the SDL for treating all registered inflammatory conditions, given its favourable clinical and cost-effectiveness compared to the reference biologic (Humira).

7.2 Furthermore, the Committee did not recommend the new formulation of Humira (20 mg/0.2 ml and 40 mg/0.4 ml) for listing on SDL/MAF due to unfavourable cost effectiveness compared with Amgevita.

7.3 The Committee also recommended that adalimumab reference biologic (Humira 40 mg/0.8 ml) should be removed from the MAF for all indications in view of unfavourable cost-effectiveness compared with Amgevita. Clinicians should actively assess each patient's suitability for switching and provide relevant counsel to patients by taking into consideration the large price difference between Humira and Amgevita. The Committee advised that switching to Amgevita or to an alternative subsidised treatment should be done within six months, by 1 March 2021, before subsidy for Humira is completely withdrawn.

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. The guidance is based on the evidence available to the Committee as at 20 March 2020. 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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