Benralizumab, mepolizumab and omalizumab

for treating severe asthma

Technology Guidance from the MOH Drug Advisory Committee

Guidance recommendations

The Ministry of Health's Drug Advisory Committee has not recommended listing:

- Benralizumab and mepolizumab on the Medication Assistance Fund (MAF) for treating severe eosinophilic asthma; and
- Omalizumab on the MAF for treating severe allergic asthma

due to unacceptable cost-effectiveness at the prices proposed by the manufacturers.

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 following technology evaluations in October 2019:

a) **Benralizumab** for treating adults and **mepolizumab** for treating adults and adolescents (≥12 years of age) with severe eosinophilic asthma, in line with their registered indications; and

b) **Omalizumab** for treating adults and adolescents (≥12 years of age) with severe allergic asthma, in line with its registered indication.

The Agency for Care Effectiveness conducted the evaluations in consultation with clinical experts from 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; 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.

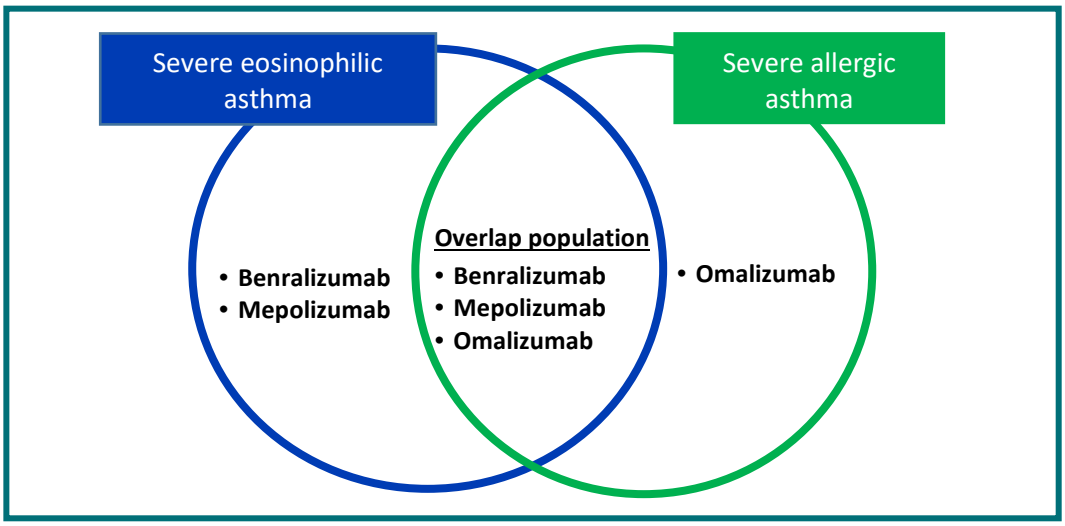
1.4 Following a negative subsidy decision in October 2019 due to unacceptable cost-effectiveness, the manufacturers of all products were invited to submit revised price proposals, which the Committee considered in March 2020.

Clinical need

2.1 The Committee acknowledged that local practice is well-aligned with international clinical guidelines for treating severe asthma. Patients with uncontrolled severe asthma despite use of standard of care controller therapy may receive add-on biologic therapy (including mepolizumab, benralizumab or omalizumab). Standard of care controller therapy is defined as high-dose inhaled corticosteroids (ICS) plus long-acting inhaled beta$_2$-agonist (LABA) with or without other controllers.

2.2 Benralizumab or mepolizumab, known as anti-interleukin-5 (anti-IL-5) agents, are typically considered for patients with severe eosinophilic asthma, while omalizumab (anti-immunoglobulin E agent) is considered for patients with severe allergic asthma. Patients with severe asthma who have both positive allergic biomarkers and high blood eosinophil count ("overlap population") may be treated with any one of the three biologics (Figure 1).

Figure 1. Biologic treatment options among patients with severe asthma



Clinical effectiveness and safety

3.1 The Committee agreed that placebo was the appropriate comparator for benralizumab, mepolizumab and omalizumab. For patients with severe eosinophilic asthma, benralizumab and mepolizumab were also compared with each other. For the overlap population with both positive allergic biomarkers and high blood eosinophil count, all three biologics were compared with each other.

3.2 The Committee noted that because there was no single randomised controlled trial (RCT) comparing all the relevant comparators, network meta-analyses (NMA) were conducted by ACE for patients with severe eosinophilic asthma as well as the overlap population, to inform the clinical evidence base.

3.3 ***Treating patients with severe eosinophilic asthma***

The Committee reviewed the evidence from four clinical studies of benralizumab as add-on therapy (SIROCCO, CALIMA, ZONDA, BORA), and seven clinical studies of mepolizumab as add-on therapy (MENSA, MUSCA, DREAM, SIRIUS, COSMOS, COLUMBA, COSMEX) in patients with severe eosinophilic asthma.

3.4 Results of two RCTs of benralizumab (SIROCCO, CALIMA) and three RCTs of mepolizumab (MENSA, MUSCA, DREAM) were included in an NMA to indirectly compare the two anti-IL5 agents with each other.

3.5 *Biologics vs placebo*

The Committee heard that direct evidence showed that reductions in the rates of clinically significant exacerbations for benralizumab and mepolizumab compared with placebo were statistically significant. Mepolizumab was also associated with a statistically significant reduction in the rate of exacerbations requiring an emergency department (ED) visit or hospitalisation compared with placebo. Benralizumab showed a statistically significant reduction in the rate of exacerbations requiring an ED visit or hospitalisation compared with placebo in the SIROCCO trial, but not in the CALIMA trial.

3.6 Benralizumab and mepolizumab use also led to significant reductions in maintenance oral corticosteroid (OCS) dose while maintaining asthma control among patients who were receiving high dose ICS-LABA and maintenance OCS.

3.7 Mean changes from baseline in forced expiratory volume in 1 second (FEV_1), Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) scores were not clinically significant for both benralizumab and mepolizumab compared with placebo. Mepolizumab was associated with an improvement in St George's Respiratory Questionnaire (SGRQ; quality of life) scores when compared to placebo. SGRQ results were not available for benralizumab.

3.8 *Biologic vs biologic (benralizumab vs mepolizumab)*

The Committee noted that indirect evidence (from NMAs) showed no significant differences between benralizumab and mepolizumab for most outcomes considered (any clinically significant exacerbation, any exacerbation requiring hospitalisation or ED visit, mean change in pre-bronchodilator FEV_1, mean change in AQLQ score, any adverse events).

3.9 ***Treating patients with severe allergic asthma***

The Committee reviewed the evidence from five clinical studies of omalizumab as add-on therapy in patients with severe allergic asthma. The studies included two double-blind RCTs (EXTRA and INNOVATE), two open-label RCTs (EXALT and QUALITX), and a meta-analysis by MacDonald et al 2019.

3.10 The results of the studies showed that omalizumab was effective in reducing incidence rates of asthma exacerbations, hospitalisations and total emergency visits due to exacerbations, when compared to placebo or standard of care controller therapy. Omalizumab also led to an improvement in patients' asthma control and quality of life.

3.11 In addition, the Committee reviewed the evidence from two published studies which investigated the clinical effectiveness of omalizumab according to blood eosinophil count in patients with severe allergic asthma. The studies included a retrospective, observational, real-world study (STELLAIR) and subgroup analyses of the EXTRA double-blind RCT. On the basis of the available evidence, the Committee considered that the clinical effectiveness and safety profiles of omalizumab were comparable among patients with low and high eosinophil counts.

3.12 ***Treating the overlap population***

Biologic vs biologic (benralizumab vs mepolizumab vs omalizumab)

For the indirect comparison of all three biologics against one another in the overlap population, results of two RCTs of benralizumab (SIROCCO, CALIMA), three RCTs of mepolizumab (MENSA, MUSCA, DREAM), and subgroup analyses of patients with severe allergic asthma and high blood eosinophil count in two RCTs of omalizumab (EXTRA and INNOVATE) were included in an NMA. The Committee noted that results from the NMA showed no significant differences among all three biologics for most outcomes considered (any clinically significant exacerbation, mean change in AQLQ, any adverse events).

3.13 ***Safety***

Overall, the Committee agreed that all three biologics were well-tolerated during the trials, and rates of adverse events were similar. They acknowledged that no new safety concerns had emerged with longer term extension studies for mepolizumab and benralizumab. Long-term observational data for omalizumab reported that it had a well-tolerated safety profile consistent with pivotal trial findings, with a small risk of anaphylaxis (0.1 to 0.2%).

3.14 ***Clinical conclusion***

In patients with severe eosinophilic asthma, the Committee agreed that both benralizumab and mepolizumab as add-on therapies were effective in reducing the rate of clinically significant exacerbations when compared with placebo. Both benralizumab and mepolizumab were also shown to be associated with significant OCS-sparing effects. In patients with severe allergic asthma, the Committee agreed that omalizumab as add-on therapy was effective in improving asthma control when compared to placebo or standard of care controller therapy.

3.15 Due to the heterogeneity of the evidence base, the Committee agreed that a clear recommendation on the superiority of one biologic over another for the treatment of severe asthma could not be concluded with certainty. Benralizumab and mepolizumab were considered to be clinically comparable in patients with severe eosinophilic asthma, and all three biologics were considered to be clinically comparable in the overlap population.

Cost effectiveness

4.1 ***Treating patients with severe eosinophilic asthma (including overlap population)***

Cost-effectiveness of biologic vs placebo

The Committee considered results from ACE's cost-effectiveness analysis which compared the biologics as add-on therapy to standard of care with standard of care alone. At the prices proposed by the manufacturers initially in 2019 and as part of their revised value-based pricing proposals in 2020, the biologics were associated with considerably high base-case ICERs of more than SG$105,000 per QALY gained compared with placebo. The ICERs were sensitive to the estimated proportion of exacerbations requiring ICU hospitalisation and the utility weights of non-exacerbation health states, however, even when parameters were varied in sensitivity analyses, none of the ICERs were considered an acceptable use of healthcare resources.

4.2 Scenario analyses which restricted the use of biologics to a more severe subgroup of patients (who experienced three exacerbations in the past year) resulted in lower ICERs, but they still remained above SG$105,000 per QALY gained.

4.3 ***Treating patients with severe allergic asthma***

A cost-effectiveness analysis was not performed by ACE to assess omalizumab for treating severe allergic asthma in view of the few patients who require treatment annually and the relatively low financial impact associated with omalizumab use. In the absence of published local studies, the Committee considered published overseas evaluations of the cost-effectiveness of omalizumab as add-on therapy to standard of care compared with standard of care alone in patients with severe allergic asthma.

4.4 Conclusions regarding the cost-effectiveness of omalizumab in different overseas settings varied, and in most instances, omalizumab was only considered cost-effective following confidential price discounts from the manufacturer. The Committee acknowledged the limitations of the available studies and the uncertainty in the analyses, but considered that the results were likely to be generalisable to Singapore's context.

4.5 Given that omalizumab was not considered to be cost-effective in the overlap population, and its clinical effectiveness and safety profiles were comparable among patients with low and high eosinophil counts, the Committee concluded that omalizumab was unlikely to be cost-effective for treating severe allergic asthma at the proposed price.

Estimated annual technology cost

5.1 The Committee noted that the annual cost impact was estimated to be:

- between SG$500,000 to less than SG$1 million in the first year of listing benralizumab or mepolizumab on the MAF for treating severe eosinophilic asthma; and
- less than SG$500,000 in the first year of listing omalizumab on the MAF for treating severe allergic asthma.

Recommendation

6.1 Based on available evidence, the Committee recommended not listing:

- Benralizumab and mepolizumab on the MAF for treating severe eosinophilic asthma; and
- Omalizumab on the MAF for treating severe allergic asthma

due to unacceptable cost-effectiveness at the prices proposed by the manufacturers.

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 7 October 2019 and 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

Principal Head (HTA)
Agency for Care Effectiveness
Email: ACE_HTA@moh.gov.sg