

Long-acting muscarinic antagonist (LAMA) monotherapy and combination therapy with long-acting beta₂ agonists (LAMA/LABA) *for the treatment of chronic obstructive pulmonary disease*

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Umeclidinium 62.5mcg inhalation powder for the:
 - Maintenance treatment of patients diagnosed by spirometry with chronic obstructive pulmonary disease (Group B or C) who have breathlessness.
- ✓ Umeclidinium/vilanterol 62.5/25mcg inhalation powder for the:
 - Maintenance treatment of patients diagnosed by spirometry with chronic obstructive pulmonary disease (Group B or C) who have frequent exacerbations (at least 2 per year or at least 1 leading to hospitalisation per year) and/or persistent breathlessness despite treatment with LAMA monotherapy.
 - Maintenance treatment of patients diagnosed by spirometry with chronic obstructive pulmonary disease (Group D) with persistent symptoms and frequent exacerbations.

Definitions of Group B, C and D are listed in the [Annex](#).

Subsidy status

Umeclidinium 62.5mcg inhalation powder and umeclidinium/vilanterol 62.5/25mcg inhalation powder are recommended for inclusion on the MOH Standard Drug List (SDL) for the abovementioned indications.

SDL subsidies do not apply to the following:

- Other LAMAs (glycopyrronium, tiotropium or aclidinium)
- Other LAMA/LABAs (indacaterol/glycopyrronium, tiotropium/olodaterol or aclidinium/formoterol)

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 long-acting muscarinic antagonists (LAMAs; glycopyrronium, tiotropium and umeclidinium) monotherapy and combination therapy with long-acting beta₂ agonists (LAMA/LABAs; indacaterol/glycopyrronium, tiotropium/olodaterol and umeclidinium/vilanterol) for maintenance treatment of stable chronic obstructive pulmonary disease (COPD). The Agency for Care Effectiveness conducted the evaluation in consultation with the MOH COPD Expert Working Group comprising senior healthcare professionals from the public healthcare institutions. The use of any LAMA or LAMA/LABA combination for the treatment of asthma was outside the scope of this evaluation.
- 1.2 By request of the manufacturer, aclidinium (LAMA) and aclidinium/formoterol (LAMA/LABA) were not included in the evaluation.
- 1.3 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
- 1.4 Additional factors, including social and value judgments, may also inform the Committee’s subsidy considerations.

Clinical need

- 2.1 International clinical practice guidelines such as GOLD 2017 recommend LAMAs as first-line therapy for patients with COPD. For patients with persistent symptoms (Group B), step-up to a LAMA/LABA is recommended. For patients with frequent exacerbations (Group C or D), step-up to a LAMA/LABA (preferred) or ICS/LABA is recommended. Inhaled corticosteroid (ICS) monotherapy is not recommended.
- 2.2 The Committee acknowledged that local clinical practice was largely aligned with the GOLD guidelines. However, due to high treatment costs for LAMA and LAMA/LABA, a proportion of patients were inappropriately prescribed with alternative subsidised therapy, such as ICS monotherapy or ICS/LABA. Therefore, the Committee agreed that listing a LAMA and LAMA/LABA on SDL was needed to encourage more appropriate use of COPD drugs. In addition, the Committee heard that there was no clinical need for LABA monotherapy based on local experts' advice.

Clinical effectiveness and safety

- 3.1 The Committee agreed that short-acting muscarinic antagonists (SAMA: ipratropium) were the appropriate comparator for the LAMA class, and LAMA monotherapy (e.g. tiotropium) and ICS/LABA were the appropriate comparators for the LAMA/LABAs. Agents within the LAMA class and the LAMA/LABA class were also compared with each other.
- 3.2 The Committee noted that because there was no single RCT comparing all the relevant comparators, a network meta-analysis (NMA) was conducted by ACE to inform the clinical evidence base. A summary of the results is presented in Table 1.
- 3.3 ***LAMA versus SAMA (ipratropium)***
The Committee noted that the available evidence suggested that all LAMAs were superior to ipratropium in improving lung function (forced expiratory volume in 1 second; FEV₁) and symptom control (Transition Dyspnoea Index; TDI). There was only one study comparing a LAMA (tiotropium) to ipratropium, and results showed a significant reduction in moderate to severe exacerbations in the LAMA arm. There were no significant differences in health-related quality of life measurements and adverse events. The Committee concluded that all LAMAs were clinically superior to SAMA.

3.4 ***LAMA versus LAMA***

The Committee noted that there were no clinically significant differences between the LAMAs for all outcomes investigated and agreed that all LAMAs were clinically comparable.

3.5 ***LAMA/LABA versus LAMA/LABA***

The Committee noted that there were no clinically significant differences between the LAMA/LABAs for all outcomes and agreed that all LAMA/LABAs were clinically comparable.

3.6 ***LAMA/LABA versus LAMA (tiotropium)***

The Committee noted that there was some evidence to suggest that all LAMA/LABAs were superior to tiotropium (18mcg) in improving lung function, symptom control and health-related quality of life, and reducing exacerbations. There were no significant differences in adverse event rates. The Committee concluded that all LAMA/LABAs were clinically superior to LAMA.

3.7 ***LAMA/LABA versus ICS/LABA***

The Committee noted that there was some evidence to show that all LAMA/LABAs were superior to ICS/LABA in improving lung function and reducing exacerbations. While there were no statistically significant differences in symptoms and health-related quality of life outcomes, the point estimate favoured LAMA/LABA. However, when all the LAMA/LABAs were pooled as a class, a Cochrane review (2017) suggested a significantly higher number of patients achieved an improved SGRQ (quality of life) score with LAMA/LABAs compared to those on ICS/LABA. LAMA/LABA was also shown to have a reduced risk of pneumonia when compared to ICS/LABA. The Committee concluded that all LAMA/LABAs were clinically superior to ICS/LABA.

Table 1 Summary of clinical results

Comparison	FEV ₁	Exacerbations	Dyspnoea	Quality of life	Adverse events	Overall
LAMA versus SAMA (ipratropium)	LAMA superior (statistically significant higher FEV ₁)	No difference	LAMA superior (clinical and statistical differences)	No difference	No difference	LAMAs were clinically superior to SAMA
LAMA versus LAMA	No clinically significant difference	No difference	No difference	No difference	No difference	All LAMAs were clinically comparable to one another
LAMA/LABA versus LAMA/LABA	No statistically significant differences	No difference	No difference	No difference	No difference	All LAMA/LABAs were clinically comparable to one another
LAMA/LABA versus LAMA (tiotropium)	LAMA/LABA superior (statistically significant higher FEV ₁ for almost all comparisons)	Possible LAMA/LABA superior (occasional statistically significant differences)	Probable LAMA/LABA superior (some clinically significant differences)	Possible LAMA/LABA superior (statistical and clinical differences)	No difference	LAMA/LABAs were clinically superior to LAMA
LAMA/LABA versus ICS/LABA	LAMA/LABA superior (statistically significant higher FEV ₁)	Probable LAMA/LABA superior (occasional statistically significant difference)	No difference	No difference	No difference overall. Increase in pneumonia for ICS/LABA	LAMA/LABAs were clinically superior to ICS/LABA

Cost effectiveness

4.1 ***Cost-effectiveness of LAMAs versus SAMA***

The Committee noted that the cost-effectiveness analysis conducted for LAMA versus SAMA showed that LAMA was dominant over ipratropium (i.e. LAMAs resulted in more quality adjusted life years gained at a lower cost).

4.2 ***Cost-minimisation among the LAMAs and LAMA/LABAs***

Given all 3 LAMAs and 3 LAMA/LABAs were considered clinically comparable within their classes, the Committee agreed a cost-minimisation approach was appropriate to select the lowest priced LAMA and LAMA/LABA for subsidy consideration. It noted that the manufacturer of umeclidinium and umeclidinium/vilanterol had offered the lowest price as part of their value-based pricing proposal (VBP). As a result, the Committee did not recommend the other 2 LAMAs (glycopyrronium and tiotropium) and LAMA/LABAs (indacaterol/glycopyrronium and tiotropium/olodaterol) for subsidy at that time given their higher cost prices compared with umeclidinium and umeclidinium/vilanterol.

4.3 ***Cost-effectiveness of LAMA/LABAs versus LAMAs or ICS/LABAs***

Given that LAMA/LABAs are considered to have a better efficacy and/or safety profile compared to LAMAs or ICS/LABAs, and are available at no higher costs following VBP proposals, the Committee agreed that cost-effectiveness analyses were not required given LAMA/LABAs were dominant over LAMAs or ICS/LABAs.

4.4 The Committee acknowledged that the proposed prices for both umeclidinium and umeclidinium/vilanterol were significantly lower than for ICS/LABA agents which are already listed on SDL.

Estimated annual technology cost

5.1 The Committee estimated that around 6100 people with COPD in Singapore would benefit from government assistance for umeclidinium and umeclidinium/vilanterol if they are listed on SDL. The annual cost impact was estimated to be less than \$1 million in the first year of listing on SDL.

Additional considerations

- 6.1 The Committee agreed that listing umeclidinium and umeclidinium/vilanterol on SDL would encourage the appropriate use of COPD drugs in line with clinical guidelines, with a potential shift from inferior ICS/LABA or ICS regimens to LAMA or LAMA/LABA.
- 6.2 The Committee heard that there may be initial resistance from clinicians and patients switching from their current treatment to umeclidinium or umeclidinium/vilanterol, as these drugs have only recently become available in Singapore and patients are not familiar with how to administer them. However, they agreed that this resistance was likely to be short-lived due to the cost savings patients would have from switching to a more affordable agent.

Recommendation

- 7.1 On the basis of the evidence available, the Committee recommended umeclidinium 62.5mcg inhalation powder and umeclidinium/vilanterol 62.5/25mcg inhalation powder for listing on the SDL for the maintenance treatment of COPD, due to acceptable clinical and cost-effectiveness, and a high clinical need for these treatments to ensure appropriate patient care.

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.

Find out more about ACE at www.ace-hta.gov.sg/about

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ANNEX

COPD assessment framework

Group B: ≤ 1 exacerbations requiring outpatient treatment; **AND** a COPD Assessment Test (CAT) score of ≥ 10 .

Group C: ≥ 2 exacerbations requiring outpatient treatment or ≥ 1 exacerbation leading to hospitalisation; **AND** a CAT score of ≤ 9 .

Group D: ≥ 2 exacerbations requiring outpatient treatment or ≥ 1 exacerbation leading to hospitalisation; **AND** a CAT score of ≥ 10 .