

Pharmaceutical Benefits Scheme

Post-market Review of

Chronic Obstructive Pulmonary Disease Medicines

Executive Summary

Final Report
August 2017

Executive Summary

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Plain language summary

Background

In August 2015, the PBAC recommended a Post-market Review of chronic obstructive pulmonary disease (COPD) medicines (the Review), with the purpose of reviewing the use, safety, efficacy and cost-effectiveness of PBS-listed medicines for use in COPD. The Review was approved by the Minister for Health on 28 September 2015, and a Reference Group was established to provide independent expert clinical advice and consumer input. In line with the published Post-market Review Framework, there were a number of opportunities for stakeholder consultation and contribution to the Review.

Key Findings for each Term of Reference

- 1. Compare the prescribing restrictions for Pharmaceutical Benefits Scheme (PBS)-listed COPD medicines for consistency with the current clinical guidelines.*
 - The key clinical guidelines of relevance to Australian practice are the COPD-X Plan and the GOLD Strategy Report.
 - The current PBS prescribing rules and levels for dual bronchodilator combination (LAMA/LABA) and inhaled corticosteroid/bronchodilator combination (ICS/LABA) medicines do not align with the recommended medicine treatment pathway in the guidelines.
 - Many clinicians and patients are confused by the variety of available therapies and devices, which has the potential to cause inadvertent medicine duplication.
- 2. Review the clinical outcomes that are most important or clinically relevant to people with COPD and the extent to which these outcomes are included in the evidence previously provided to PBAC on the cost-effectiveness of these medicines.*
 - Reduced pulmonary symptoms, exacerbations and hospitalisations are the most important clinical outcomes for patients with COPD.
 - The main outcomes measured in clinical trials and considered by the PBAC are in line with the GOLD Strategy Report recommended approach of combining symptomatic assessment with a patient's lung function results and/or risk of exacerbations.
- 3. Review the evidence on the efficacy and safety of monotherapy and combinations of inhaled medicines for treatment of COPD that PBAC has not previously considered.*
 - The Review found that updated evidence on the efficacy and safety of COPD medicines was generally consistent with that previously considered by the PBAC.
 - No evidence was identified which supported triple therapy (inhaled corticosteroids plus a dual bronchodilator) as a more effective treatment than a dual bronchodilator combination medicine alone.

4. *Review the published literature on the safety of prolonged inhaled corticosteroid use in monotherapy and in combination with bronchodilators and/or muscarinic antagonists for COPD that PBAC has not previously considered.*
 - Some evidence indicated an increased risk of pneumonia with prolonged inhaled corticosteroid use. There is also some evidence of an increased risk of fracture, but this was not conclusive.
 - There are no other new significant safety concerns with inhaled corticosteroid use.

5. *Analyse the current utilisation of PBS-listed COPD medicines to identify the extent of co-prescribing and use that is inconsistent with clinical guidelines and/or PBS restrictions.*
 - Evidence suggests there is a high rate of initiation to inhaled corticosteroids/bronchodilator (ICS/LABA) combinations medicines, which is inconsistent with clinical guidelines.
 - There is evidence of widespread use of triple therapy already for COPD.

6. *Evaluate if the current utilisation of multiple therapies and the latest evidence relating to safety and efficacy justifies a review of cost-effectiveness for some or all medicines indicated for COPD.*
 - The Review did not identify any new evidence on the effectiveness of COPD medicines that would change previous PBAC decisions regarding their cost-effectiveness. Accordingly, no cost-effectiveness review was recommended at this time.
 - It was considered that improving use of inhaled medicines in accordance with current clinical guidelines would also improve the cost-effectiveness of therapies for COPD.

Outcomes

The PBAC considered this report in August 2017 and its recommendation to the Minister for Health can be found in the PBAC minutes published alongside this report.

Background and context

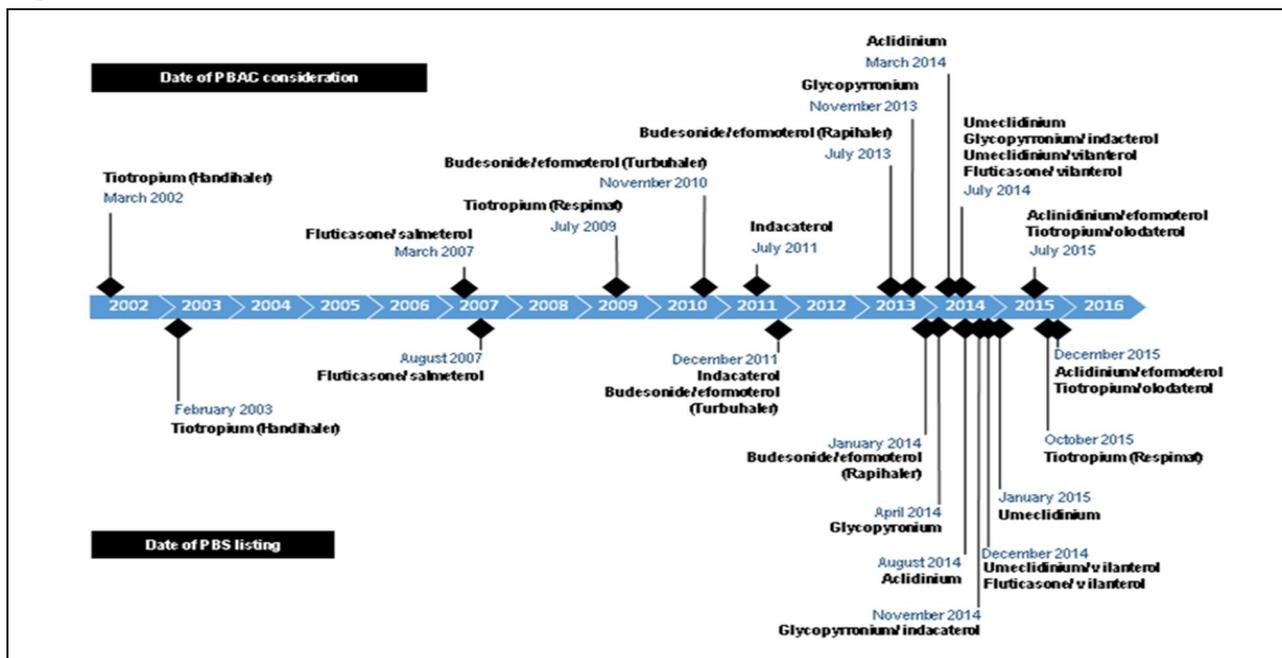
COPD is characterised by chronic inflammation of the lung tissue, and obstruction of the airways that cannot be fully reversed by medication. The symptoms of COPD are breathlessness, wheezing and chest tightness, and a chronic cough that produces mucus. Symptoms can be exacerbated by irritants such as infection or exposure to noxious particles or gases, most commonly cigarette smoke.

COPD is a major public health concern. The prevalence of COPD is estimated to be 4.9% in Australians, as indicated by self-reported emphysema and/or bronchitis (ABS, 2015). In 2012, 5,923 Australians were recorded as having died from COPD (4% of all deaths in Australia), making it the fifth leading cause of death.

There are three types of commonly used medications in COPD: long-acting muscarinic antagonists (LAMAs), long-acting beta-2 agonists (LABAs), and inhaled corticosteroids (ICSs). They are used to reduce the chronic symptoms of COPD and prevent acute exacerbations that can result in hospitalisation. Short-acting beta-2 agonists (SABAs) and short-acting muscarinic antagonists (SAMAs) may be used to provide short-term relief of breathlessness. People with COPD described their medicines as ‘improving breathing’ and ‘feeling the medicine open up/clear the lungs’ if they were working effectively (Kawata et al, 2014).

The first medicine specifically listed on the PBS for COPD only was tiotropium powder for oral inhalation (Spiriva®) in February 2003. Refer to Figure ES 1 for the details of the PBS listing of COPD medications.

Figure ES 1 Timeline of PBAC consideration of COPD medicines and date of PBS listing



In October 2013, the Drug Utilisation Sub-Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee (PBAC) reviewed the PBS utilisation of indacaterol for COPD. The review

identified co-administration of multiple LABA products in some patients, which was considered a significant quality use of medicines (QUM) issue.

In the context of considerable recent changes in COPD management, including the PBS listing of a number of new medicines, the purpose of the Post-market Review of COPD Medicines is to review the utilisation, safety, efficacy and cost-effectiveness of PBS-listed COPD medicines, and to address QUM concerns associated with the apparent use of multiple products. The Review is being conducted in accordance with the Post-Market Review Framework, which was developed following consultation with industry, and published in March 2015.

The draft Review Terms of Reference (ToR) were provided for public consultation between 16 October and 13 November 2015. The PBAC considered the draft Review ToR and comments from stakeholders at the December 2015 PBAC meeting. The Minister for Health approved the final ToR for the Review.

Review Terms of Reference (ToR)

1. Compare the prescribing restrictions for PBS-listed COPD medicines for consistency with the current clinical guidelines.
2. Review the clinical outcomes that are most important or clinically relevant to people with COPD and the extent to which these outcomes are included in the evidence previously provided to PBAC on the cost-effectiveness of these medicines.
3. Review the evidence on the efficacy and safety of monotherapy and combinations of LABA/LAMA, ICS/LABA and LAMA + ICS/LABA (separate items or fixed dose combinations) for treatment of COPD that PBAC has not previously considered.
4. Review the published literature on the safety of prolonged ICS use in monotherapy and in combination with LABA and/or LAMA for COPD that PBAC has not previously considered.
5. Analyse the current utilisation of PBS listed COPD medicines to identify the extent of co-prescribing and use that is inconsistent with clinical guidelines and/or PBS restrictions.
6. Evaluate if the current utilisation of multiple therapies and the latest evidence relating to safety and efficacy justifies a review of cost-effectiveness for some or all medicines indicated for COPD.

Methodological approach to the technical report

A Reference Group (RG) and HealthConsult Pty Ltd were involved in the preparation of this draft technical report for the COPD Review. Research questions relating to the ToR were developed to guide the review (refer to Background), and approved by the RG Chair. The ToR were addressed through specific reviews of evidence for medicines, guidelines, utilisation and COPD interventions (refer to Tables ES 1 and ES 2).

Table ES 1 Methodological approach to ToR 1, ToR 2, ToR 3 and ToR 4

Methodological approach	Criteria and time period
ToR 1: Compare the prescribing restrictions for PBS-listed COPD medicines for consistency with the current clinical guidelines	
A systematic search of relevant evidence-based guidelines from regulatory/funding/health technology assessment (HTA) bodies, guidelines databases and other relevant websites for the treatment of COPD.	The search was restricted to Australian and international guidelines published from 2011 to August 2016.
ToR 2: Review of clinically relevant outcomes	
Outcomes identified from the literature search of peer-reviewed publications, regulatory agencies, HTA and reimbursement agencies, guidelines and clinical studies were summarised.	Publications from 2010 to November 2016.
ToR 3: Review of LAMA and LABA efficacy and safety	
The peer-reviewed literature was systematically searched for clinical studies that evaluated the safety and effectiveness of LAMA and LABA monotherapy as well as combinations of LAMA, LABA and ICS at the doses and formulations listed on the PBS for the treatment of COPD. A hierarchical stepwise method was used to identify and select studies according to study design, as determined by the NHMRC Evidence Hierarchy for intervention questions.	The review focused on evidence that has not previously been considered by the PBAC until August 2016.
ToR 4: Review of safety of prolonged ICS use	
A systematic literature review was performed encompassing both the peer-reviewed literature and any additional evidence (published or unpublished) provided by the sponsors in their ToR public consultation submissions. The peer-reviewed literature was screened for clinical studies that consider the safety of prolonged ICS use in monotherapy and in combination with LAMA and/or LABA.	Evidence from 2010 to 8 September 2016.

Table ES 2 Methodological approach to ToR 5

Analysis	Data source	Methodological approach
ToR 5: Utilisation analysis of COPD medications		
1	Utilisation analysis of PBS/Repatriation PBS (RPBS) claims data	<ul style="list-style-type: none"> COPD and asthma PBS prescription and benefit analysis based on Department of Human Services date of processing data inclusive of 2006 to 2016 calendar years. COPD PBS patient record analysis based on de-identified data supplied by the Department of Health. Patients included in the analysis were aged 35 years and older and were those who initiated COPD therapy with a LAMA, LABA or LAMA/LABA fixed dose combination (FDC). Data file from November 2006 to October 2016. Patient initiations considered a consistent 2 year lookback.
2	MedicineInsight data analysis	<ul style="list-style-type: none"> NPS MedicineInsight data analysis which investigates the use of medicines by patients with COPD (with or without asthma). MedicineInsight data was drawn from 423 clinically relevant practice sites, 3,835 active GPs and 2,230,658 active patients, to 31 December 2016 inclusive.

Stakeholder consultation

Opportunities for stakeholder consultation throughout the COPD Review, included:

- Public consultation on the draft ToR (detailed above).
- Public submissions to the Review were open between 4 March and 22 April 2016. Except where requested otherwise, submissions are published on the Consultation website.
- A Stakeholder Forum was held by the Department of Health in Sydney on 21 March 2017. The Stakeholder Forum Summary is at Appendix F, and on the COPD Review website.
- The Lung Foundation Australia (LFA) was contracted to ascertain the views of COPD patients and carers on the Review ToR. The Report is at Appendix G.
- The draft COPD Review Report was available for public comment between 29 May and 13 June 2017.

Stakeholder views are included under the key findings for each ToR.

Key Review findings

ToR 1: Comparison of prescribing restrictions and clinical guidelines

Clinical guidelines in COPD

- The key clinical practice guidelines of relevance to Australian practice are the COPD-X Plan (2015/2016): Australian and New Zealand Guidelines for the Management of Chronic Obstructive Pulmonary Disease. There is also the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Strategy Report (2016): Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.
- The COPD-X guidelines have mild/moderate/severe COPD categories, primarily based on forced expiratory volume-one second (FEV₁) with associated symptoms and exacerbations. The COPD-X guidelines advocate a stepped algorithm for prescribing pharmacologic therapy for COPD, irrespective of disease severity, until adequate control has been reached.
- The most common treatment pathway for stable COPD following diagnosis is: step 1: SAMA or SABA; step 2: LAMA or LABA; step 3: LAMA/LABA; step 4: ICS/LABA (for patients with FEV₁ <50% predicted and ≥2 exacerbations in the previous year); step 5: various medications.
- Asthma-COPD overlap syndrome (ACOS) is generally treated by initiating an ICS, then adding a LABA or LAMA.

Inconsistencies between PBS-listed COPD medicines and clinical guidelines

- The LAMA/LABA FDCs have Authority Required (STREAMLINED) PBS restrictions, while dual therapy with ICS/LABA FDCs, which occur later in the treatment pathway, are a Restricted Benefit. The PBS Restricted Benefit listing for the ICS/LABA FDCs compared to the LAMA/LABA FDCs does not align with their place in therapy; that is, the desirability of delaying initiation of an ICS/LABA due to possible adverse effects.
- The LAMA/LABA FDCs have PBS restrictions that state that the patient must have been [already] stabilised on a LAMA and LABA, while the COPD-X guidelines state that LAMA/LABA FDCs are recommended for patients who remain symptomatic despite monotherapy with either LAMA or LABA alone.
- PBS restrictions do not require prescribers to review or confirm a patient's inhaler technique.
- Guidelines highlight that inappropriate combinations of agents should be avoided. The inappropriate combinations are not systematically addressed for all COPD medicines in their PBS restrictions.

Stakeholder views

- Consumer awareness about medications and treatment guidelines is limited.
- Consumers assume that PBS listings for COPD medicines are consistent with guidelines, and expect GPs and specialists to prescribe in accordance with guidelines.
- Consumers call for more support on inhaler techniques.
- The PBS requirement to stabilise patients on a LAMA and LABA separately, prior to LAMA/LABA initiation, causes increased costs and confusion for patients.
- Inconsistencies between the PBS restrictions and the COPD-X guidelines result in prescribers being directed away from evidence-based guidelines.
- A national standardised list of education materials for health professionals is required to improve overall adherence to COPD evidence-based guidelines and PBS restrictions.
- A number of QUM issues were highlighted:
 - The use of spirometry to confirm COPD diagnosis is low. Increased educational efforts and changes to the Medical Benefits Scheme (MBS) are required.
 - The increase in new COPD medicines, and various trade names, may be contributing to prescriber confusion and the prescribing of unsafe combinations.
 - Many health professionals are not confident or competent to confirm correct inhaler technique and may be confused about appropriate treatment for ACOS.
 - Need to include a PBS note for LABA/LAMA combinations: “Do not use in patients with a history of asthma without accompanying ICS”.
- The updated GOLD Strategy Report (2017) is an important additional reference.

ToR 2: Review of clinical outcomes

- The main outcomes published in the PBAC Public Summary Documents (PSDs) for COPD submissions since 2002 are FEV₁, St George’s Respiratory Questionnaire (SGRQ), exacerbations, rescue medication, and adverse events (AEs).
- The 2014 PSDs for glycopyrronium/indacaterol and umeclidinium/vilanterol (both LAMA/LABA combinations) reflect concern over the translation of FEV₁ into more clinically relevant measures of effect that were not reported in the submissions.
- The literature search for published articles on outcomes for COPD identified three industry-funded publications that support FEV₁ as a surrogate outcome that is weakly correlated with SGRQ and exacerbations. In contrast, two other industry-funded reviews found a poor correlation between FEV₁ and patient reported outcomes (PROs).
- The GOLD Strategy Report (2016) provides evidence of a weak correlation between FEV₁ and SGRQ. The document also presents evidence that there is an increase in risk of exacerbations, hospitalisation and death with worsening of airflow limitation. The document recommends an approach of combining symptomatic assessment with the patient’s spirometric classification and/or risk of exacerbations, which is consistent with the PBAC decision making based on FEV₁, SGRQ and exacerbations.

Stakeholder views

- The key outcome for consumers is to be able to ‘breathe’ and live as normal a life as possible.
- Some consumers have experienced side effects from medications. There is acceptance that side effects are part of the course, and that the benefits of medications outweigh the potential side effects.
- For many consumers, diagnosis was confirmed by spirometry by a specialist in hospital, often following a severe illness.
- The US Food and Drug Administration (FDA) requires a clinical outcome of FEV₁. Recent randomised controlled trials (RCTs) also assess other measures of efficacy, often via secondary endpoints, and this data is submitted to the Therapeutic Goods Administration (TGA) and PBAC for consideration.
- A recently published meta-regression analysis (approximately 120,000 patients) found that for every 100 mL change in pre-dose FEV₁, the HR decreased by 21% and the absolute exacerbation rate decreased by 0.06 per patient per year (Zyder et al, 2017).
- The GOLD Strategy Report (2017) ABCD (COPD patient assessment tool) uses respiratory symptoms and exacerbations alone to assign ABCD patient categories.
- COPD Assessment Test (CAT) is a questionnaire for people with COPD and is more reflective of PROs. The questionnaire is designed to measure the impact of COPD on a person's life, and how this changes over time.
- Longer term follow up in comparative COPD clinical trials is required to accurately assess the prevention of exacerbations, reduction in symptoms, HqoL and safety outcomes.

ToR 3: Review of efficacy and safety

The key findings from the systematic literature review identified new head-to-head trials as well as a summary of the trials that underpinned previous PBAC decision making. Importantly, all of the RCTs excluded patients with a history of asthma; thus, the evidence base presented here has limited applicability to patients with ACOS.

Monotherapy versus monotherapy in patients with COPD

Table ES 3 shows there appear to be no significant differences in efficacy between the PBS-listed LAMA monotherapies, which is consistent with previous PBAC recommendations. Furthermore, there were no noteworthy safety findings and all LAMA monotherapies were well tolerated.

Table ES 3 Summary of evidence for monotherapy versus monotherapy in patients with COPD

PBAC consideration	Head-to-head trials	Comparison	Summary of evidence
TIO (HandiHaler): LAMA vs SAMA			
March 2002	BI205.126A BI205.126B	TIO vs IPR	<ul style="list-style-type: none"> TIO was considered superior in efficacy and similar in safety to IPR.
New evidence	Not considered	TIO vs IPR	<ul style="list-style-type: none"> Comparison of TIO with IPR (i.e. a SAMA) is no longer considered to be clinically relevant.
TIO (Respimat): LAMA vs LAMA			
July 2009	BI205.249 BI205.250 BI205.291	TIO vs TIO ^a	<ul style="list-style-type: none"> TIO Respimat was comparable in efficacy and safety to TIO HandiHaler. The two formulations were cost-minimised.
New evidence	TIOSPIR Non-inferiority, double-blind Good quality N=17,135; 2-3 years	TIO vs TIO ^a	<ul style="list-style-type: none"> TIO Respimat appears non-inferior to TIO HandiHaler in terms of change from baseline in trough FEV₁. Two post hoc analyses also showed the treatments to be comparable based on mortality and exacerbation outcomes.
GLY (Seebri Breezhaler): LAMA vs LAMA			
November 2013	GLOW ₅ , GLOW ₂ SPARK SHINE A network analysis for add-on to LABA was also considered	GLY vs TIO	<ul style="list-style-type: none"> GLY was considered non-inferior in comparative effectiveness and similar in safety to TIO. GLY was cost-minimised to TIO. No head-to-head trials of GLY versus other LAMAs were considered by the PBAC at the time.
New evidence	NCT02236611 (unpublished) Non-inferiority, open-label Quality not assessed N=1,037; 12 weeks	GLY vs UME	<ul style="list-style-type: none"> UME appears non-inferior to GLY based on least squares mean change from baseline in trough FEV₁. No other head-to-head trials of GLY versus other LAMAs were identified.
ACL: LAMA vs LAMA			
March 2014	LAS-39 An indirect comparison via placebo as common comparator also considered	ACL vs TIO	<ul style="list-style-type: none"> ACL was considered non-inferior in term of comparative effectiveness and similar in safety to TIO and was cost-minimised. No head-to-head trials of ACL versus other LAMAs were considered by the PBAC at the time.
New evidence	Beier (2013) Superiority, double-blind, double-dummy Fair quality N=414; 6 weeks	ACL vs TIO	<ul style="list-style-type: none"> There were no significant differences between TIO and ACL in terms of efficacy or safety. Both TIO and ACL were associated with improvements from baseline in trough FEV₁ that met the MCID.
	Manoharan (2016) Superiority, open-label, cross-over Poor quality N=15; 2-3 weeks	ACL vs TIO	<ul style="list-style-type: none"> No difference was observed between TIO and ACL in terms of trough FEV₁ when used as triple therapy with ICS/LABA. No other head-to-head trials of ACL versus other LAMAs were identified.
UME: LAMA vs LAMA			
July 2014	No head-to-head trials Indirect comparison via placebo as common comparator	UME vs TIO	<ul style="list-style-type: none"> UME was considered non-inferior in terms of comparative effectiveness and of similar safety to TIO, and was cost-minimised. No head-to-head trials of UME versus other LAMAs were considered by the PBAC at the time.
New evidence	Feldman (2016) Non-inferiority, double-blind, double-dummy Good quality ^b N=1,017; 12 weeks	UME vs TIO	<ul style="list-style-type: none"> UME was superior to TIO based on trough FEV₁; however, there were no significant differences between UME and TIO based on other efficacy outcomes including TDI, SGRQ and CAT scores. UME non-inferior to TIO based on other efficacy outcomes including TDI, SGRQ and CAT scores.

PBAC consideration	Head-to-head trials	Comparison	Summary of evidence
	Donohue (2012) Dose-ranging study Double-blind, cross-over Fair quality N=176; 2 weeks	UME vs TIO	<ul style="list-style-type: none"> The results for the UME (blinded) and TIO (open-label) were not directly compared (UME and TIO were both compared with placebo). However, UME resulted in a numerically greater change in trough FEV₁ from baseline than TIO.
	See trial NCT02236611 (above)	UME vs GLY	<ul style="list-style-type: none"> UME appears non-inferior to GLY based on least squares mean change from baseline in trough FEV₁.

Abbreviations: ACL, aclidinium; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; FLU, fluticasone; GLY, glycopyrronium; ICS, inhaled corticosteroid; IND, indacaterol; IPR, ipratropium; LAMA, long-acting muscarinic antagonist; MCID, minimal clinically important difference; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; SAL, salmeterol; SAMA, short-acting muscarinic antagonist; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index; TIO, tiotropium; UME, umeclidinium.

a Respimat versus HandiHaler.

b Overall the study was deemed to be of good quality (see Appendix M); however, concerns have been raised about whether differences in the markings between TIO and placebo capsules may have impacted on the blinding of treatment assignment (discussed further in Section 3.4.1).

Monotherapy versus dual therapy in patients with COPD

There is evidence of a modest benefit in stepping up from LAMA monotherapy to LAMA/LABA dual therapy (see Table ES 4) in patients with COPD, with numerically reduced exacerbations observed. However, it should be noted that many of the studies summarised in Table ES 4 were only powered to detect a difference between LAMA/LABA dual therapy and placebo and not to detect differences between LAMA/LABA dual therapy and LAMA monotherapy. No studies were identified that examined the benefits of stepping up from LABA monotherapy to LAMA/LABA dual therapy.

The INSPIRE 2008 study aimed to compare LAMA monotherapy to ICS/LABA dual therapy (fluticasone/salmeterol versus tiotropium). Comparable healthcare utilisation exacerbations per year and a statistically significant lower risk of all-cause mortality in the ICS/LABA dual therapy group (fluticasone/salmeterol) were observed. Covelli (2016) compared LAMA monotherapy to ICS/LABA dual therapy (fluticasone/vilanterol versus tiotropium). No clinically meaningful difference in trough FEV₁ was observed across treatment groups. An increased rate of pneumonia and numerically fewer COPD exacerbations was observed in the ICS/LABA group.

No studies were identified that examined the benefits of stepping up from LABA monotherapy to ICS/LABA dual therapy. The INSTEAD 2014 study assessed the effect of switching patients who are at low risk of COPD exacerbations from fluticasone/salmeterol to indacaterol monotherapy. No clinically relevant differences between fluticasone/salmeterol and indacaterol for dyspnoea (Transition Dyspnoea Index: TDI), health status (SGRQ) and use of rescue medication were observed suggesting patients can be switched from ICS/LABA to indacaterol with no loss of efficacy and without triggering exacerbations.

These findings are generally consistent with previous PBAC decision making, where LAMA/LABA dual therapy was considered superior to LAMA monotherapy (July 2014), and ICS/LABA FDC was considered non-inferior to LAMA monotherapy (March 2007).

Table ES 4 Summary of new evidence for monotherapy versus dual therapy in patients with COPD

PBAC consideration	Head-to-head trials	Comparison	Summary of evidence
UME/VIL: LAMA/LABA vs LAMA or LABA			
New evidence	Maleki-Yazdi (2014) Superiority, double-blind, double-dummy Good quality N=905; 24 weeks	UME/VIL vs TIO	• UME/VIL resulted in statistically significant and clinically meaningful improvements in trough FEV ₁ compared with TIO monotherapy. The time to first on-treatment exacerbation also favoured UME/VIL. ^a
	Maltais (2014) Superiority, double-blind, cross-over Fair quality N=657; 12 weeks	UME/VIL vs UME	• The results for trough FEV ₁ numerically favoured UME/VIL over UME monotherapy; however, no statistical comparisons of these active treatments were conducted and it is unlikely that the study was adequately powered for this comparison.
GLY/IND: LAMA/LABA vs LAMA or LABA			
July 2014	SHINE, SPARK	GLY/IND vs GLY or IND	<ul style="list-style-type: none"> • For trough FEV₁, GLY/IND was statistically superior to its monocomponents but the difference did not exceed the accepted MCID.¹ • GLY/IND was cost-minimised to UME/VIL.
New evidence	BRIGHT Superiority, double-blind, cross-over Fair quality N=85; 3 weeks	GLY/IND vs TIO ^b	• GLY/IND was statistically superior to TIO based on trough FEV ₁ ; however the study was only powered to detect a difference between GLY/IND and PBO.
TIO/OLO: LAMA/LABA vs LAMA or LABA			
July 2015	TONADO 1 & 2 (Indirect comparison vs other FDCs via TIO monotherapy as common comparator)	TIO/OLO vs TIO or OLO	• For trough FEV ₁ , TIO/OLO was statistically superior to its monocomponents but the difference did not exceed the MCID.
New evidence	TONADO 1 & 2 ^c Superiority, double-blind Fair quality N=5,163; 52 weeks	TIO/OLO vs TIO	• TIO/OLO significantly improved lung function over TIO (Respimat) monotherapy in patients with GOLD 2 and 3-4 disease. There were no notable differences in lung function responses according to whether patients were naïve or experienced to LAMA or LABA therapy at baseline.
	OTEMTO 1 & 2 Superiority Double-blind Fair quality N=1,623; 12 weeks	TIO/OLO vs TIO	• Treatment with TIO/OLO resulted in numerically greater improvements in trough FEV ₁ compared with TIO (Respimat) monotherapy; however, it is unlikely that the observed differences would be considered clinically relevant. ^d
FLU/SAL: ICS/LABA vs LAMA			
March 2007	Trial 40036, plus two supportive trials (unpublished)	FLU/SAL vs TIO	• FLU/SAL was considered non-inferior to TIO on the basis of comparative efficacy and similar safety. FLU/SAL was cost-minimised to TIO.
New evidence	INSPIRE Superiority, double-blind, double-dummy Good quality N=1,323; 2 years	FLU/SAL vs TIO	• FLU/SAL and TIO were found to be comparable with respect to healthcare utilisation exacerbations per year; however, the risk of all-cause mortality was 52% lower in the FLU/SAL group, representing a statistically significant difference between the treatments.
	Sarac (2016) Superiority, open-label Poor quality N=44; 1 year	FLU/SAL vs TIO	• The mean number of exacerbations and number of severe exacerbations both numerically favoured FLU/SAL over TIO monotherapy; however, the differences were not statistically significant.
FLU/VIL: ICS/LABA vs LAMA			
New evidence	Covelli (2016) Superiority, double-blind, double-dummy Good quality N=623; 12 weeks	FLU/VIL vs TIO	• No statistically significant or clinically meaningful difference between FLU/VIL and TIO in terms of trough FEV ₁ . Safety results were comparable, with minor differences in rates of pneumonia and COPD exacerbations.

¹ Noted in March 2014 PSD for glycopyrronium/indacaterol FDC. The MCID was 100-140 mL.

PBAC consideration	Head-to-head trials	Comparison	Summary of evidence
IND: LABA vs LABA			
July 2011	No head-to-head trials Indirect comparison via TIO as common comparator	IND vs FLU/SAL	<ul style="list-style-type: none"> IND in combination with TIO was considered non-inferior in comparative effectiveness and similar in safety to FLU/SAL plus TIO by the PBAC. IND was cost-minimised to FLU/SAL.
New evidence	INDORSE Superiority, double-blind Good quality N=415; 52 weeks	IND 150 mcg vs IND 300 mcg	<ul style="list-style-type: none"> The two PBS-listed doses of indacaterol were associated with similar magnitudes of improvement from baseline in trough FEV₁ compared with placebo and were comparable in terms of risk of exacerbations.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; FLU, fluticasone; GLY, glycopyrronium; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IND, indacaterol; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; MCID, minimal clinically important difference; OLO, olodaterol; PBAC, Pharmaceutical Benefits Advisory Committee; PBO, placebo; SAL, salmeterol; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.

a Over half of the patients in each treatment arm were using ICS therapies at baseline and continued use of ICS throughout the study; thus, approximately half of the study participants were on triple therapy or dual (ICS + LAMA) therapy.

b Patients who were on ICS therapy at baseline were permitted to continue use of ICS; therefore, a subset of patients were on triple therapy, while others were on dual ICS + LAMA therapy during the treatment period.

c New evidence refers to a post hoc analysis based on disease severity and treatment intensity.

d The study was powered to detect differences between TIO/OLO and PBO, not TIO/OLO and TIO monotherapy.

Dual therapy versus dual therapy in patients with COPD

Only two RCTs were identified that compared two LAMA/LABA dual therapy combinations (umeclidium/vilanterol FDC versus tiotropium plus indacaterol) and (indacaterol/glycopyrronium FDC versus tiotropium plus eformoterol) as outlined in Table ES 5. Despite the limited body of evidence, the findings of that study were consistent with previous PBAC recommendations; that is, there appears to be no significant difference in efficacy (based on primary end points) or safety between PBS-listed LAMA/LABA FDCs.

Table ES 5 also summarises the key findings from several RCTs that examined the comparative efficacy and safety of LAMA/LABA and ICS/LABA FDCs. The FLAME trial is of particular interest as it enrolled patients with a history of at least one exacerbation in the previous 12 months requiring treatment. The FLAME trial demonstrated non-inferiority of glycopyrronium/indacaterol to fluticasone/salmeterol and, on a subsequent subgroup analysis, superiority of the LAMA/LABA FDC to the ICS/LABA FDC based on exacerbation and lung function outcomes.²

The ERG also considered the results of a recent Cochrane Review (Horita et al, 2017) published after the search period for the systematic review. The Cochrane review meta-analysed the results of 11 studies (n=9,839) that compared LAMA plus LABA to LABA plus ICS treatment, predominantly in patients with moderate to severe COPD without recent exacerbations.³ Horita (2017) found that compared to LABA plus ICS, LAMA plus LABA treatment was associated with greater improvements in FEV₁, fewer exacerbations, more frequent improvement in quality of life (measured by an increase in SGRQ of over four units), and lower risk of pneumonia.

² Note that a subgroup analysis of the FLAME RCT suggests that superiority (in terms of reducing exacerbations) is primarily driven by patients who had experienced only one exacerbation in the previous year. There was no statistically significant difference between the FDCs in patients who had experienced two or more exacerbations in the previous year.

³ The PBS restrictions for ICS/LABAs limit use for COPD treatment to patients with a history of two or more exacerbations in the previous year.

Table ES 5 Summary of new evidence for dual therapy versus dual therapy in patients with COPD

PBAC consideration	Head-to-head trials	Comparison	Summary of findings
GLY/IND: LAMA/LABA vs LAMA/LABA			
July 2014	BEACON An indirect comparison via TIO as common comparator also considered	GLY/IND vs GLY+IND	<ul style="list-style-type: none"> GLY/IND was cost-minimised to UME/VIL.
New evidence	QUANTIFY Non-inferiority, blinded, triple-dummy Good quality N=934; 26 weeks	IND/GLY vs TIO+EFO	<ul style="list-style-type: none"> IND/GYL was non inferiority to TIO+EFO based on SGRQ-C in patients had who moderate or severe risk of exacerbations (GOLD II and GOLD III). The non-inferiority margin was predefined as 4 units. IND/GLY showed a significantly increased pre-dose FEV₁ at week 26. Both treatments were well tolerated.
UME/VIL: LAMA/LABA vs LAMA/LABA			
July 2014	No head-to-head trials Indirect comparison via TIO as common comparator	UME/VIL vs TIO+IND	<ul style="list-style-type: none"> UME/VIL was cost-minimised to TIO+IND with an adjustment to account for efficacy being less than the sum of components.
New evidence	Kalberg (2016) Non-inferiority, double-blind, triple-dummy Good quality N=961; 12 weeks	UME/VIL vs TIO+IND	<ul style="list-style-type: none"> UME/VIL was non-inferior to TIO+IND in terms of trough FEV₁ in patients who were at high risk of exacerbations (over 60% of patients were classified as GOLD Group D; over 50% were receiving ICS at screening).
ACL/EFO: LAMA/LABA vs LAMA/LABA			
July 2015	No head-to-head trials Indirect comparison via placebo as common comparator	ACL/EFO vs GLY/IND ACL/EFO vs UME/VIL	<ul style="list-style-type: none"> ACL/EFO was considered non-inferior to GLY/IND and UME/VIL on the basis of comparative efficacy and safety. ACL/EFO was cost-minimised to GLY/IND and UME/VIL.
New evidence	No head-to-head trials	N/A	<ul style="list-style-type: none"> No new RCTs were identified that directly compared ACL/EFO with any PBS-listed single or dual therapies.
TIO/OLO: LAMA/LABA vs LAMA/LABA			
July 2015	No head-to-head trials Indirect comparison via TIO monotherapy as common comparator	TIO/OLO vs GLY/IND TIO/OLO vs UME/VIL	<ul style="list-style-type: none"> TIO/OLO was considered non-inferior to GLY/IND and UME/VIL on the basis of comparative efficacy and safety. TIO/OLO was cost-minimised to GLY/IND and UME/VIL.
BUD/EFO: ICS/LABA vs ICS/LABA			
November 2010	No head-to-head trials Indirect comparisons with both placebo and TIO as common comparators	BUD/EFO vs FLU/SAL	<ul style="list-style-type: none"> BUD/EFO was non-inferior in terms of comparative efficacy and similar safety to FLU/SAL, and was cost-minimised.
New evidence	No head-to-head trials	N/A	<ul style="list-style-type: none"> No new RCTs were identified that directly compared BUD/EFO with any PBS-listed single or dual therapies.
UME/VIL: LAMA/LABA vs ICS/LABA			
New evidence	Singh (2015a) Superiority, double-blind, double-dummy Good quality N=716; 12 weeks	UME/VIL vs FLU/SAL	<ul style="list-style-type: none"> UME/VIL was found to be statistically superior to FLU/SAL based on change from baseline in trough FEV₁ in patients with no history of exacerbations that required oral corticosteroids, antibiotics and/or hospitalisation in the previous year. However, the trial did not demonstrate any differences between the treatment groups with respect to symptom and quality of life outcomes.
GLY/IND: LAMA/LABA vs ICS/LABA			
New evidence	ILLUMINATE Superiority, double-blind, double-dummy Good quality N=523; 26 weeks	GLY/IND vs FLU/SAL	<ul style="list-style-type: none"> GLY/IND provided significantly better and clinically relevant improvements in trough FEV₁ over FLU/SAL in patients who had not experienced an exacerbation requiring treatment with antibiotics, systemic corticosteroids, or hospitalisation in the previous year.
	LANTERN Non-inferiority, double-blind, double-dummy Good quality N=744; 26 weeks	GLY/IND vs FLU/SAL	<ul style="list-style-type: none"> In patients with low risk of exacerbations, GLY/IND was shown to be non-inferior and, on a subsequent superiority analysis, superior to FLU/SAL on the basis of trough FEV₁ and was also associated with statistically significant improvements in time to first moderate or severe exacerbation. Several patient-reported outcomes were also assessed in the study, and failed to demonstrate a significant difference between treatments.

PBAC consideration	Head-to-head trials	Comparison	Summary of findings
	FLAME Non-inferiority, double-blind, double-dummy Good quality N=3,362; 52 weeks	GLY/IND vs FLU/SAL	<ul style="list-style-type: none"> In patients with a history of at least one exacerbation during the previous year, GLY/IND achieved non-inferiority to FLU/SAL on the basis of annual rate of COPD exacerbations. A subsequent superiority analysis showed that GLY/IND was consistently superior to FLU/SAL on the basis of exacerbations, lung function and health status outcomes.
TIO/OLO: LAMA/LABA vs ICS/LABA			
New evidence	ENERGITO Superiority, double-blind, cross-over Fair quality N=229; 6 weeks	TIO/OLO vs FLU/SAL	<ul style="list-style-type: none"> TIO/OLO was associated with statistically significant improvements in trough FEV₁ over FLU/SAL; however, the magnitude of the adjusted mean difference between the treatment arms (58 mL) is unlikely to represent a clinically meaningful difference.
ICS/LABA vs ICS/LABA			
July 2014	HZC113107	FLU/VIL vs FLU/SAL	<ul style="list-style-type: none"> No evidence was shown for triple therapy with FLU/VIL. FLU/VIL was considered non-inferior in terms of comparative effectiveness and safety to FLU/SAL. FLU/VIL was cost-minimised to FLU/SAL.

Abbreviations: ACL, aclidinium; BUD, budesonide; COPD, chronic obstructive pulmonary disease; EFO, eformoterol; FEV₁, forced expiratory volume in one second; FLU, fluticasone; GLY, glycopyrronium; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting beta-2 agonist; OLO, olodaterol; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; RCT, randomised controlled trial; SAL, salmeterol; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.

Dual therapy versus triple therapy in patients with COPD

Table ES 6 shows studies that investigated the benefit of adding a LAMA to ICS/LABA dual therapy which showed that the step up from dual to triple therapy results in statistically significant and clinically meaningful improvements in trough FEV₁. The PBAC has previously seen evidence from the GLISTEN trial that demonstrated that glycopyrronium plus fluticasone propionate/salmeterol is statistically superior to fluticasone propionate/salmeterol alone in terms of trough FEV₁ (November 2015 PSD for glycopyrronium).

Table ES 6 Summary of new evidence for dual therapy versus triple therapy in patients with COPD

PBAC consideration	Head-to-head trials	Comparison	Summary of findings
ICS/LABA + LAMA vs ICS/LABA			
July 2014	GLISTEN (2015)	GLY+ FLU/SAL vs FLU/SAL	<ul style="list-style-type: none"> Interim results presented to the PBAC from the study up to Week 12 indicated that triple therapy provided statistically significant improvements in trough FEV₁ compared to fluticasone/salmeterol alone.
New evidence	Siler (2015) Superiority, double-blind Good quality N=1,239; 12 weeks	FLU/VIL+PBO vs FLU/VIL+ UME	<ul style="list-style-type: none"> Triple therapy with FLU/VIL plus UME was associated with clinically meaningful improvements in trough FEV₁ compared with FLU/VIL (plus placebo).
	Sousa (2016) Superiority, double-blind Fair quality N=236; 12 weeks	ICS/LABA+ PBO vs ICS/LABA+ UME	<ul style="list-style-type: none"> The addition of UME to ICS/LABAs produced statistically significant and clinically meaningful improvements over dual therapy with ICS/LABA (plus placebo), based on trough FEV₁.

Abbreviations: FEV₁, forced expiratory volume in one second; FLU, fluticasone; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; PBAC, Pharmaceutical Benefits Advisory Committee; PBO, placebo; UME, umeclidinium; VIL, vilanterol.

No RCTs or large observational studies were identified that examined the comparative efficacy and safety of ICS + LAMA/LABA versus LAMA/LABA. A recent Cochrane review also failed to identify any ongoing or completed RCTs comparing the treatment of stable COPD with ICS plus combination LAMA/LABA inhalers against combination LAMA/LABA inhalers alone (Tan et al, 2016).

New inhaled ICS/LABA/LAMA FDCs, including fluticasone/vilanterol/umeclidinium, budesonide/formoterol/glycopyrronium and beclometasone/formoterol/glycopyrronium, are in Phase III of clinical development for COPD.

Stakeholder views

- The FLAME trial included patients with predominately a history of one exacerbation. Superiority of the LAMA/LABA compared to the ICS/LABA was not established in patients with a history of two or more exacerbations.
- The authors of the AFFIRM trial (recently published) claim that combined therapy with aclidinium/formoterol demonstrated superiority over salmeterol/fluticasone in peak FEV₁. Improvements in dyspnoea and symptom control were comparable between treatment groups.
- The GOLD Strategy Report (2017) recommends that where dual therapy is appropriate, LAMA/LABA is preferred to ICS/LABA. Many stakeholders considered that further evidence is required to establish the comparative effectiveness of ICS/LABA to LAMA/LABA therapies, and amend Australian clinical guidelines and PBS restrictions.
- Recent post-hoc analysis of the WISDOM study indicates that withdrawal of ICS from triple therapy (ICS/LAMA/LABA) increased the risk of exacerbations in a small group of patients with high eosinophil counts and history of two or more exacerbations.
- ICS monotherapy is not TGA indicated for COPD. Restricting PBS access to ICS/LABA to patients with asthma or combined asthma/COPD is problematic given the low use of spirometry and misdiagnosis of COPD.
- A culture change is already occurring and clinicians are prescribing LAMA/LABA in preference to ICS/LABA in COPD only patients to reduce the risk of pneumonia.

ToR 4: Review of the safety of prolonged ICS use

- Both meta-analyses and observational studies report increases in the risk of pneumonia of 40% to 70%.
- All-cause mortality was found to consistently favour ICS use in observational studies for both the general COPD population and those with pneumonia.
- There is some evidence for an intra-class difference for pneumonia risk between fluticasone and budesonide, favouring budesonide, but it is not conclusive.
- An ICS dose-response for pneumonia is apparent, but not conclusive.
- While the concept of a dose-response for pneumonia risk has biological plausibility and there is some supportive clinical evidence, this has not been demonstrated conclusively across all studies.
- RCTs and observational studies provide some evidence of an increased risk of fracture, but this was not conclusive.

Stakeholder views

- Predictors of individual patient risk of pneumonia include: age, severity of FEV₁ <50%, season, recent history of exacerbations, lower socio-economic status, current smokers, and those with worse dyspnoea.
- Patient requirement for ICS treatment and whether withdrawal is appropriate should be individually considered. Withdrawal of ICS treatment is not recommended for patients with ACOS and is potentially harmful.
- Diagnostic analysis of eosinophils may help with patient risk stratification. Retrospective evidence indicates that patients with higher eosinophil levels, but within normal levels, achieve greater clinical benefit from ICS treatment. Patients with levels within the low range of normal have a higher risk of pneumonia based on a post hoc analysis.
- Further evidence is also required prior to eosinophils being measured routinely in clinical practice and included in clinical guidelines.
- LAMA/LABA agents are likely to provide an effective, convenient and potentially safer alternative for persistently symptomatic COPD patients.
- A recent retrospective analysis of the UPLIFT trial claimed that ICS use was associated with an increase in respiratory adverse event rates and subgroup analysis showed that excess of morbidity in the ICS group appears to be associated with those receiving fluticasone propionate at randomisation.
- Longer-term studies are required to characterise the risk of pneumonia in patients treated with fluticasone.

ToR 5: Current utilisation of PBS-listed COPD medicines

Utilisation analysis of PBS/RPBS claims data

- The number of PBS/RPBS prescriptions for COPD/asthma medicines (LAMA, LABA and ICS) in the 2016 calendar year was approximately 5.2 million scripts based on claims processed. This number has increased by 70.5% compared to 2006.
- The total PBS/RPBS benefits paid for COPD/asthma medicines in the 2016 calendar year was \$299 million based on claims processed. This number has grown from \$215.2 million in 2006, which represents an increase in benefits paid of \$84.1 million or 39.1%.
- A COPD only cohort was identified from PBS unit record data based on: patients aged 35 years and above who initiated on medicines restricted to COPD only e.g. tiotropium, indacaterol or LAMA/LABA.
- The percentage of patients in the COPD cohort initiating to combinations outside COPD-X guidelines was 13.2% in 2010 and 25.7% in 2016. The percentage of use outside COPD-X guidelines is dominated by initiation to combinations of LABA/LAMA (15.4%) and ICS/LABA plus LAMA (8.3%).

MedicineInsight data analysis

- Of the 1.28 million current MedicineInsight patients aged 35 years and over included in the analysis, 3% were ever diagnosed with COPD only (n=38,650), and 1.6% with COPD plus asthma (n=20,546).
- In MedicineInsight data in 2016, 51,903 prescriptions for the medicines of interest were ordered for current patients with COPD only and 54,197 prescriptions for COPD plus asthma. For all COPD and COPD plus asthma patients, 41.6% had no prescriptions written for any SAMA, SABA, LAMA, LABA or ICS (including combinations) inhalers in 2016.
- Based on MedicineInsight data, for COPD only patients, 3.6% were at risk of unsafe duplicated therapy and 1.6% were on combinations of SAMA and LAMA. For patients with COPD plus asthma, 6.1% may be at risk of unsafe duplicated therapy and 3.2% were on combinations of SAMA and LAMA.
- Based on MedicineInsight data, between 1 July 2015 and 31 December 2016, of patients initiating COPD therapy, 45.9% were prescribed only one medicine of interest as initial therapy, 49.0% were prescribed dual therapy, and 4.5% triple therapy (excluding SABA). A significant amount of combination use of COPD medications was therefore observed to be outside clinical guidelines and PBS restrictions (53.5%).
- Among patients with COPD and COPD plus asthma, 38.1% (n=22,524) ever had a record of one or more spirometry tests.

Stakeholder views

- In the PBS data analysis, the exclusion of patients initiating therapy with ICS/LABA may significantly underestimate the COPD only population.
- The PBS data analysis did not consider samples, hospital initiations, or over-the-counter SABA use, which may lead to an overestimation of use outside guidelines and PBS restrictions.
- Analysis of SAMA, SABA and ICS/LABA patient utilisation, including initiations, is required to better understand the overall use of all COPD medications.
- The MedicineInsight analysis underestimates the utilisation of SABA medications (available over-the-counter) and should be interpreted with caution.
- International evidence was presented regarding the uncertainty in COPD patient identification. Concerns were expressed by a number of stakeholders as to whether healthcare utilisation databases are adequate to inform PBAC decision making.

ToR 6: Need for a review of cost-effectiveness

Utilisation

- From a cost and QUM perspective, the key concern identified by the Review is the growing proportion of patients initiating to dual or triple inhaled therapy of the COPD medicines in scope (a quarter of patients based on PBS/RPBS data). This is not recommended in the COPD-X guidelines, is not in line with the PBS restrictions, and the cost-effectiveness of this use is unknown.

- NPS MedicineInsight data indicates that around 3.9% of patients recorded with a diagnosis of COPD only, and 6.1% of patients recorded with a diagnosis of COPD plus asthma, may have duplicated therapy.

Efficacy and safety

- Previous PBAC decision making has considered medicines in the LAMA, LABA, ICS/LABA and LAMA/LABA classes to be of comparable efficacy and similar safety to other medicines within their class. Where available, new evidence generally supports these decisions and the previously determined price relativities.
- PBS-listed LAMAs, LABAs and ICS/LABAs were all considered by the PBAC to be of comparative efficacy and similar safety and were cost-minimised. Overall, new evidence regarding the comparative efficacy and safety of LAMAs and LABAs compared to ICS/LABA FDCs is inconclusive, but does not support a change to previous PBAC decision-making, which considered these therapies generally comparable. No new evidence was identified that would change the previously determined price relativities for these therapies.

[REDACTED]

- There is evidence to support a modest benefit of stepping up from LAMA monotherapy to LAMA/LABA dual therapy. Based on four studies identified in this review, the mean difference in trough FEV₁ between LAMA alone and LABA/LAMA ranged from 28 mL (Singh et al, 2015b) to 112 mL (Maleki-Yazdi et al, 2014). It is worth noting that the PBAC has previously considered the MCID for change in trough FEV₁ was in the range of 100 to 140 mL. No studies were identified that examined the benefits of stepping up from LABA monotherapy to LAMA/LABA dual therapy.
- Of the four RCTs identified that compared LAMA monotherapy to LAMA/LABA dual therapy, the following PROs were reported: SGRQ (3 studies), rescue medication (2 studies), time to first exacerbation (1 study), and physiological response to exercise during SMETT (1 study).
- The SGRQ results from the TONADO 1 and 2 studies have previously been considered by the PBAC (Ferguson et al, 2015). Singh (2015b and 2016) concluded of the OTEMTO study that treatment with tiotropium/olodaterol versus tiotropium led to improvements in lung function over tiotropium that “were translated into clinically significant improvements in symptoms and health-related quality of life”. Maleki-Yazdi (2014) showed that time to

first exacerbation favoured dual therapy over monotherapy with marginal statistical significance.

- Several RCTs were identified that examined the comparative efficacy and safety of LAMA/LABA and ICS/LABA FDCs. In general, these studies found LAMA/LABA FDCs provide superior efficacy and similar safety to ICS/LABA FDCs in COPD patients.
- No RCTs or large observational studies were identified that examined the comparative efficacy and safety of ICS plus LAMA/LABA versus LAMA/LABA. A recent Cochrane review also failed to identify any ongoing or completed RCTs comparing these treatments in stable COPD (Tan et al, 2016). Thus it is uncertain if triple therapy is cost-effective over dual therapy with LABA/LAMA.

Stakeholder views

- PBAC recommendations are required to be considered in the context of the available clinical evidence and best practice guidelines. A number of stakeholders provided additional recent published evidence, including updates to guidelines and further utilisation analyses (refer to ToR 1 to 5, and Appendix U).
- Refer to the Options section (below) for further information on stakeholder views.

COPD Review Options

Review Options 1-12 were included in the draft COPD Review Report that was provided for public consultation, and considered by the Economic Sub-Committee (ESC) and the Drug Utilisation Sub Committee (DUSC) of the PBAC in June 2017. Options 13-14 were added following the consultation process. The RG considered the public and sponsor comments, and DUSC and ESC advice to the PBAC, in July 2017, and commented on the following 14 options.

PBS Restriction Text

Option 1

Remove the requirement to stabilise patients on a LAMA and LABA separately, prior to initiation of LAMA/LABA FDC.

Current LABA/LAMA PBS restriction

Clinical criteria: Patient must have been stabilised on a combination of a long acting muscarinic antagonist and long acting beta-2 agonist.

Rationale

- The current restriction does not align with clinical guidelines, which state that combined therapy with LAMA/LABA should be available to patients who remain symptomatic despite treatment with a LAMA or LABA alone.
- The current requirement increases cost and confusion for consumers, who have to familiarise themselves with an additional device and medicine.

- The current process may also be confusing for clinicians and lead to unnecessary consultations. Following the change, clinicians could initiate a patient on LAMA monotherapy with the expectation of prescribing that same LAMA as part of a LAMA/LABA FDC at a later stage, without the current need to introduce (and then possibly discontinue) indacaterol as an intermediate step.

Suggested LABA/LAMA PBS restriction

- *Clinical criteria: Patient symptoms must be inadequately controlled by treatment with either a long acting muscarinic antagonist or long acting beta-2 agonist.*

Stakeholder views

- Stakeholders were generally supportive of this change.
- QUM concerns regarding the current PBS criteria included: inconsistency with clinical guidelines, delays in optimal treatment, prescriber and patient confusion from therapy changes, and challenges for patients with poor vision or manual dexterity in using the only available LABA monotherapy on the PBS.

RG comments

- The RG supported the removal of the current PBS requirement to stabilise patients on both individual monotherapy inhalers before commencing FDC LAMA/LABA.

Option 2

Add a PBS note regarding potentially unsafe medicine combinations to all LAMA, LABA and ICS/LABA products on the PBS, based on the notes currently used for LAMA/LABA products.

Current notes

LAMA/LABA FDCs:

Note: The treatment must not be used in combination with an ICS/LABA, or LAMA or LABA monotherapy.

Note: A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.

Note: A LABA includes olodaterol, indacaterol, salmeterol, eformoterol or vilanterol.

ICS/LABA FDCs:

Note: Patient must not be on a concomitant single agent long-acting beta-2 agonist.

LAMA and LABA monotherapy products: Nil notes.

Rationale

- The Review found that a small proportion of COPD patients are using potentially unsafe combinations, and highlighted that consistent advice is not provided across PBS products.
- Stakeholders considered that prescribing of unsafe combinations by the clinician or inadvertent polypharmacy is occurring due to a lack of understanding on behalf of the clinician or patient. Various trade names of respiratory inhaler products may be a point of confusion and the active ingredients may not be well understood.

Suggested notes

ICS/LABA FDCs:

Note: The treatment must not be used in combination with LABA monotherapy or LAMA/LABA combination therapy.

Note: A LABA includes olodaterol, indacaterol, salmeterol, eformoterol or vilanterol.

Note: A LAMA/LABA includes acclidinium/eformoterol, glycopyrronium/indacaterol, tiotropium/olodaterol, or umeclidinium/vilanterol.

LAMA/LABA FDCs:

Note: The treatment must not be used in combination with an ICS/LABA, LAMA, LABA, or SAMA.

Note: A LAMA includes tiotropium, glycopyrronium, acclidinium or umeclidinium.

Note: A LABA includes olodaterol, indacaterol, salmeterol, eformoterol or vilanterol.

Note: A SAMA includes ipratropium.

LAMA:

Note: The treatment must not be used in combination with a LAMA/LABA, or SAMA.

Note: A LAMA/LABA includes acclidinium/eformoterol, glycopyrronium/indacaterol, tiotropium/olodaterol, or umeclidinium/vilanterol.

Note: A SAMA includes ipratropium.

LABA:

Note: The treatment must not be used in combination with an ICS/LABA, or LAMA/LABA.

Note: A LAMA/LABA includes acclidinium/eformoterol, glycopyrronium/indacaterol, tiotropium/olodaterol, or umeclidinium/vilanterol.

Note: An ICS/LABA includes budesonide/eformoterol, fluticasone/salmeterol, or fluticasone/vilanterol.

Stakeholder views

- Stakeholders were generally supportive of this change.
- Stakeholders noted that ICS/LABA should not be used in combination with LAMA/LABA, which has been incorporated into the suggested notes text above.

RG comments

- The RG supported this option on the condition that the notes for all currently listed COPD medicines would be updated when similar COPD medicines are listed on the PBS.
- The RG considered that it was useful to include the generic names of the medicines in the restriction notes given the evidence of polypharmacy.

Option 3

Add a PBS note on checking device technique and adherence to all products listed for COPD treatment on the PBS.

Rationale

- The COPD-X guidelines highlight the importance of reviewing inhaler technique and adherence at each visit. PBS restrictions do not currently specify that clinicians must have reviewed adherence and inhaler technique before adding or changing treatments.
- Improved medication efficacy, safety and cost-effectiveness may be achieved from improved inhaler technique.
- An Australian study found that 50% to 83% of COPD patients made at least one error in inhaler technique.⁴
- Stakeholders indicated a need for greater support in inhaler technique. The different techniques required between devices can be complicated and confusing for patients and clinicians. While most patients received some initial instruction on device use, often from a pharmacist, some patients suggested that the GP practice nurse or respiratory nurse could provide this advice.

Suggested note

Note: Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before “stepping up” a patient’s medication regimen.

Stakeholder views

- Stakeholders were supportive of this option.
- Some stakeholders recommended inclusion of educational resource website links to the PBS restriction notes. A list of educational materials provided by stakeholders is at Appendix V.

RG comments

- The RG supported this option, and considered that checking device technique and adherence was part of standard clinical service. The RG noted that it would be unusual to reference educational websites or guidelines in a PBS restriction, and that there may be issues with maintaining the currency of the information if included.

⁴ SRIRAM, K. B. & PERCIVAL, M. 2016. Suboptimal inhaler medication adherence and incorrect technique are common among chronic obstructive pulmonary disease patients. *Chron Respir Dis*, 13, 13-22.

Option 4

Add a PBS note regarding the requirement to confirm COPD diagnosis with spirometry to all products listed for COPD treatment on the PBS.

Rationale

- The treatment algorithms for asthma, COPD and asthma-COPD overlap syndrome are different. The COPD-X guidelines state that accurate diagnosis of COPD, including the use of spirometry to confirm the presence of airflow obstruction, is needed to ensure appropriate treatment.
- Stakeholders and various data sources indicate that many Australian COPD patients do not have lung function testing within the first 12 months of therapy initiation.

Suggested note

Note: Diagnosis of COPD should include measurement of airflow obstruction using spirometry.

Stakeholder views

- Stakeholders were generally supportive of this change.
- One stakeholder recommended that the PBS note should include measurement of airflow obstruction using spirometry, with confirmation of post-bronchodilator airflow obstruction. A confirmatory spirometry reading was also recommended to determine eligibility for a change in COPD treatments.

RG comments

- The RG supported this option with the following revised wording:
Note: Diagnosis of COPD should include measurement of airflow obstruction using spirometry, with confirmation of post-bronchodilator airflow obstruction.

PBS Restriction Levels

Option 5

Increase the restriction level for ICS/LABAs listed on the PBS for the treatment of COPD to Authority Required (STREAMLINED).

The PBS restriction changes would apply only to ICS/LABA doses listed for both COPD and asthma treatment (refer to Background, Table B.1). Doses listed for the treatment of asthma only would continue to be Restricted Benefits.

Rationale

- The review found that both meta-analyses and observational studies of ICS/LABA use in COPD patients report increases in the risk of pneumonia of 40% to 80%. RCTs and observational studies also provide some evidence of an increased risk of fracture, but this was inconclusive.
- Makes the restriction level for ICS/LABAs and LAMA/LABAs the same, to encourage appropriate use of these medicines in line with guideline recommendations and to

improve the quality of care for COPD patients. NPS MedicineInsight data indicates that a large proportion of COPD patients without asthma commence ICS/LABA therapy.

- Would allow data collection on comparative use for COPD versus asthma, through use of a different streamlined code.
- Meets the criteria for Authority Required medicines.

Risks/disadvantages

- May be unpopular with prescribers.
- If spirometry is not undertaken to accurately determine diagnosis, some patients with ACOS may only receive LAMA/LABA treatment, which may be detrimental to their care.

Stakeholder views

- Some stakeholders supported this option, while others did not. Some considered that the PBS restriction level for LAMA/LABA and ICS/LABA FDCs should be consistent.
- A number of stakeholders were not supportive of Option 5 for the following reasons:
 - Patients should be assessed for disease severity and pneumonia risk, and receive individually tailored therapy.
 - Many patients gain symptomatic benefit from ICS/LABA treatment.
 - International and national evidence supports that COPD treatments are underutilised.
 - The real world evidence for ICS withdrawal is uncertain.
 - May reduce access to appropriate treatment for Asthma-COPD Overlap patients.
 - Increased prescriber administration burden.
 - Appropriate prescribing and use of ICS/LABAs may be achieved by increased access to educational activities for prescribers and patients.

RG comments

- The majority of RG members supported this option. The RG noted that the recent Post-market Review of Authority Required Medicines aimed to reduce the burden of authority restrictions on prescribers, but considered that a streamlined authority was not onerous on prescribers and that aligning the restriction levels for ICS/LABAs and LAMA/LABAs would encourage more appropriate prescribing.
- The RG recommended that a streamlined code also be included for Asthma-COPD Overlap, to improve awareness of the condition and allow data collection on medicines use for treatment.

Option 6

Increase the restriction level for ICS/LABAs and LAMA/LABAs listed on the PBS for the treatment of COPD to Authority Required (online).

Rationale

- As for Option 5.
- Sends a stronger and more auditable signal to prescribers that the patient should not commence therapy with a combination. Medicines utilisation data indicates that a

significant and growing proportion of COPD patients commence therapy with ICS/LABA and LAMA/LABA FDCs.

Risks/disadvantages

- As for Option 5.
- Online authority system is not yet complete.

Stakeholder views

- Stakeholders generally did not support this option, and considered the change may be problematic for prescribers/patients.

RG comments

- The RG did not support this option, as it was considered that too little information was currently available on the proposed online authority system.

Option 7

Reduce the restriction level for LAMA/LABAs to Restricted Benefit.

Rationale

- LAMA/LABAs are only listed for the treatment of COPD. Therefore, a streamlined code is unnecessary to collect indication data.

Risks/disadvantages

- May increase the proportion of patients initiating on a LAMA/LABA FDC, which is both a QUM and cost-effectiveness issue.
- Medicines utilisation data indicates that the proportion of COPD patients initiating therapy with LAMA/LABA FDCs is growing.
- From a cost perspective, LAMA/LABAs are priced over LAMA, LABA or ICS/LABA alone.

Stakeholder views

- The majority of stakeholders were supportive of this option.
- A less restrictive PBS listing for LAMA/LABA FDCs was considered to reduce barriers to patient access, improve QUM, and reduce administrative burden for prescribers.

RG comments

- The majority of RG members did not support this option, as they considered that a streamlined authority restriction level for LAMA/LABAs and ICS/LABAs (PBS-listed for COPD treatment) would encourage more appropriate prescribing of both medicine classes.

Cost-effectiveness

Option 8

Reconsider the cost-effectiveness of FDC inhalers for COPD.

Rationale

- There is evidence from both PBS data and MedicineInsight (prescriber data) of increasing use of FDC inhalers in first-line therapy. This use is not in line with the COPD-X guidelines.
- FDCs of both LABA/LAMA and ICS/LABA contribute to inappropriate use such as duplicated therapy, potentially causing harm and wastage.
- LAMA/LABAs are priced over LAMA, LABA and ICS/LABA alone. The cost-effectiveness of first-line use of LAMA/LABAs has not been considered by the PBAC.

Stakeholder views

- Pharmaceutical industry stakeholders were generally not supportive of this option, but other stakeholders were.
- Stakeholders opposed to this option gave the following reasons:
 - The PBAC has previously established and accepted the cost-effectiveness of these medicines through a robust evaluation process.
 - The Review findings are insufficient to warrant a cost-effectiveness review.
 - Inappropriate prescribing may be managed by education and QUM measures.
 - The price disparity in combination products resulting from individual component drugs not being listed on the PBS has been remedied by the 2017 Medicines Australia Agreement. Substantial savings will also result from this Agreement, due to future statutory price reductions to PBS-listed COPD medicines.
 - The Review's utilisation analysis overestimates the use of combination therapy that is outside of clinical guidelines and PBS restrictions.
 - COPD classes have different pharmacological properties, safety profiles and clinical places in therapy, and establishing price relativities across classes is not appropriate.

RG comments

- The RG considered that the Review had not identified any new, good quality evidence on the effectiveness of FDC inhalers not previously considered by the PBAC that would justify a review of their cost-effectiveness, noting that the Review did not consider the use of dual therapy for first-line treatment.
- The RG noted that the cost-effectiveness of dual therapy FDC inhalers may need to be re-considered if the PBAC received an application to list a triple therapy FDC inhaler for COPD treatment.

Non-PBS Recommendations

Option 9

PBAC to write to manufacturers regarding device use and medicine packaging issues raised by stakeholders during the Review.

Rationale

- Stakeholders suggested the addition of instructional video websites to packaging, and a referral to the Lung Foundation Australia for ongoing support with using devices.
- Problems determining when devices were empty and problems with removing tablets from foil packaging, were also raised.
- Stakeholders noted issues with accessing placebo inhalers on which to demonstrate device technique.

Stakeholder views

- Stakeholders were generally supportive of this option, and for additional support for consumers to ensure they correctly understand their medicines and how to use them.
- These issues would need to be discussed in the context of Therapeutic Goods Administration (TGA) regulations.

RG comments

- The RG supported this option.

Option 10

PBAC to write to, and engage, appropriate organisations to improve access to evidence-based educational materials and resources on COPD management for both health professionals and consumers.

Rationale

- Stakeholders requested improved access to educational resources, and development of a standardised national list of educational materials to avoid prescriber, pharmacist and patient confusion.
- May improve the quality of care for COPD patients, including improved diagnosis, adherence to guidelines, and inhaler technique.
- The LFA has an established suite of practical/online training options and resources covering topics such as inhaler device technique, COPD medicines and pulmonary rehabilitation. These are tailored to the specific audience and focused on up skilling of clinicians and optimising self-management for consumers.
- The NPS MedicineWise website also has a range of educational materials on COPD for GPs, pharmacists and nurses.

Stakeholder views

- Stakeholders were generally supportive of this option.

- A number of manufacturers stated they had developed educational resources that supported prescribing consistent with COPD-X guidelines and PBS restrictions.
- LFA and NPS MedicineWise educational activities were endorsed by a number of stakeholders, including materials to support correct inhaler technique (refer to Appendix V).

RG comments

- The RG supported this option. The RG considered that a wide range of quality educational resources was available, but that there was a need to improve access to and use of these resources.

Option 11

PBAC to request that the Pharmaceutical Benefits Division liaise with the Practice Incentives Programme (PIP) team in Health Services Division to highlight the relevant QUM findings from the Review.

Rationale

- Greater awareness of the Review's findings on QUM issues in COPD therapy may assist in linking general practice payments to quality improvements in the care of COPD patients. The new PIP Quality Improvement Incentive will be implemented from 1 May 2018.
- The medicines utilisation analysis identified issues with initiation of dual and triple therapy, and duplicated therapy. The Review has also highlighted the need for greater use of spirometry to ensure correct diagnosis and treatment, the importance of referring patients for pulmonary rehabilitation, and the importance of health care providers training patients in, and checking their, inhaler technique.

Stakeholder views

- Stakeholders were generally supportive of this option.
- Health professionals should be supported to: use spirometry to ensure correct diagnosis and treatment, appropriately refer patients for pulmonary rehabilitation, and regularly train and check patients' inhaler technique.
- The addition of MBS items for patient education on device technique was suggested.

RG comments

- The RG supported this option.

Option 12

PBAC to write to the MBS Review Taskforce to provide support for "Recommendation 1: Spirometry" in the *Report from the Thoracic Medicine Clinical Committee (August 2016)*.

Rationale

- The Review highlighted the need for greater utilisation of spirometry to confirm diagnosis of COPD and ensure appropriate treatment. The MBS Review proposes a number of

changes to spirometry items to encourage the use of spirometry in primary care to confirm COPD diagnosis.

Stakeholder views

- Stakeholders were generally supportive of this option.
- It was noted that the GOLD Strategy Report (2017) suggests that post-bronchodilator spirometry is adequate for diagnosis. However, the supporting clinical evidence does not consider asthma patients with significant bronchodilator reversibility.

RG comments

- The RG supported this option.

Option 13

PBAC to write to the TGA regarding the development of guidelines for naming, packaging and device design of inhalers.

Rationale

- Stakeholders considered that unclear naming and packaging, and differences in use between devices, was contributing to prescriber and patient confusion, incorrect use and therapy duplication. Clear identification of active ingredients and medicine class was considered important to reduce potentially unsafe use.

Risks/disadvantages

- As products are supplied internationally, it may be difficult for the TGA to influence naming, packaging and device design of COPD inhalers.

Stakeholder views

- This option was included after public consultation on the draft Review Report.

RG comments

- The RG supported this option.

Option 14

PBAC to liaise with the Medical Services Advisory Committee (MSAC) to convey the Reference Group's support for reimbursement of evidence-based pulmonary rehabilitation.

Rationale

- Pulmonary rehabilitation provides an opportunity to reinforce self-management principles including inhaler device technique.
- Increased use of evidence-based pulmonary rehabilitation programmes may reduce medicines usage.
- An application to the MSAC for reimbursement of pulmonary rehabilitation was deferred at the November 2016 meeting, and will likely be re-considered in November 2017.

- The LFA has recently released the Australia and New Zealand Pulmonary Rehabilitation Guidelines, which provides evidence-based recommendations for the practice of pulmonary rehabilitation specific to the Australian and New Zealand healthcare settings.

Stakeholder views

- This option was included after public consultation on the draft Review Report.

RG comments

- The RG supported this option. The RG agreed that evidence-based pulmonary rehabilitation programmes were a key and highly cost-effective component of COPD treatment, and should be considered for all patients prior to, or concurrent with, starting pharmacotherapy.