Agenda item 15

Post-market Review of Chronic Obstructive Pulmonary Disease (COPD) Medicines

1 Purpose of Item

1.1 For the PBAC to consider the COPD Review report, and make recommendations to the Minister for Health regarding the PBS listings of COPD medicines and the Review options.

2 Background

2.1 In August 2015, the PBAC reviewed the Post-market Review work plan and recommended that a review of COPD medicines be prioritised for 2015-16. The Review was approved by the Minister for Health on 28 September 2015.

2.2 The Terms of Reference (ToR) for the COPD Review are:

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/long-acting muscarinic antagonists (LAMA), ICS/LABA and LAMA + ICS/LABA (separate items or fixed dose combinations) for the 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.

2.3 The Department commissioned an independent contractor (Health Consult) to undertake research to inform the Review's response to each ToR. The key findings for each ToR are contained in the Executive Summary of the COPD Review.

2.4 An independent Reference Group was established to guide the Review. The Reference Group provided advice on issues raised by stakeholders, considered the technical evidence provided in analyses/reports, and informed the development of the Report, including the Review options.

2.5 In line with the published Post-market Review Framework, there were a number of opportunities for stakeholder consultation including:

- the opportunity to comment on the Review ToR
- a public submission process addressing the ToR
- a stakeholder forum held in Sydney on 21 March 2017
- the opportunity to comment on the draft Report

Stakeholder views have been included throughout the Report, including in the Review options and key findings for each ToR.

2.6 12 options were provided in the draft Report for public comment, and a further two options were added as a result of the Drug Utilisation Sub Committee (DUSC) advice (options 13 and 14). The Reference Group considered the draft Report, public comments on the draft Report DUSC and ESC advices, and sponsor pre sub-committee responses, in July 2017.

2.7 For further information on the Review options, including the rationale for each option, stakeholder views and Reference Group comments, refer to the COPD Review's Executive Summary (pages 19-30).

3 Key findings of the COPD Review

The PBAC noted the key findings under the following six ToR.

3.1 *Compare the prescribing restrictions for PBS-listed COPD medicines for consistency with the current clinical guidelines.*

- The key clinical practice guidelines of relevance to Australian practice are the COPD-X Plan and the GOLD Strategy Report.

- The COPD Review found that the PBS restrictions for LAMA/LABA and ICS/LABA FDCs do not align with the recommended sequencing of medications in the 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 and this does not align with their place in therapy; that is, the desirability of delaying initiation of an ICS/LABA due to possible adverse effects.
- Currently the LAMA/LABA FDCs have PBS restrictions that state that the patient must have been [already] stabilised on both a LAMA and LABA before moving to LABA/LAMA FDC. Therefore COPD-X guidelines differ from the PBS restriction in that patients are not required to trial both monotherapy inhalers before changing to a LABA/LAMA FDC.
- PBS restrictions do not currently require prescribers to review or confirm a patient's inhaler technique which is strongly endorsed in the COPD-X Plan and GOLD Strategy Report.
- The Review also found there to be low recorded use of spirometry, and poor utilisation of available guidelines and educational materials.
- The Review also found evidence of widespread clinician and patient confusion over available therapies and devices and the potential for inadvertent utilisation of combination therapies such as ICS/LABA and LAMA/LABA or SAMA and LAMA.

3.2 *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.*

- The Review identified that whilst FEV_1 is widely used in a regulatory context, it is weakly correlated to relevant patient outcomes. Additionally the Review found evidence that spirometry is performed in less than 50% of patients.
- Stakeholders noted that reducing pulmonary symptoms, exacerbations and hospitalisations are also important clinical outcomes for patients with COPD.
- The main outcomes published in the PBAC Public Summary Documents for COPD submissions are FEV_1, St George's Respiratory Questionnaire (SGRQ), pulmonary exacerbations, rescue medications and adverse events. This is in line with the GOLD strategy report recommended approach of combining symptomatic assessment with the patient's spirometric classification and/or risk of exacerbations.

3.3 *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 the treatment of COPD that PBAC has not previously considered.*

3.3.1 Monotherapy versus monotherapy in patients with COPD

- 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.

3.3.2 Monotherapy versus dual therapy in patients with COPD

- The Review findings were 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).

3.3.3 Dual therapy versus dual therapy in patients with COPD

- Despite the limited body of evidence, there appears to be no significant difference in efficacy (based on primary end points) or safety between PBS-listed LAMA/LABA FDCs, which is consistent with previous PBAC recommendations.

3.3.4 Dual therapy versus triple therapy in patients with COPD

- The Review found several 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 FEV_1.
- A recent Cochrane review 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.
- New inhaled ICS/LABA/LAMA FDCs are in clinical development for COPD.

3.4 *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.*

- Meta-analyses and observational studies indicated a 40-70% increased risk of pneumonia with prolonged ICS use (which may possibly be drug specific and dose related, although this has not been established).
- Observational studies suggest that ICS are associated with a reduced risk in all-cause mortality.

- RCTs and observational studies provided some evidence of an increased risk of fracture, but this was not conclusive.
- There are no other new significant safety concerns with ICS.
- The PBAC noted that there is evidence of widespread use of triple therapy already (ICS with a LABA and/or a LAMA) for COPD.

3.5 *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.*

- The number of PBS/RPBS prescriptions for COPD/asthma medicines (LAMA, LABA and ICS) in the 2016 calendar year increased by 70.5% compared to 2006.
- Stakeholders raised concerns about the definition of the COPD only cohort that was identified from PBS unit record data. DUSC acknowledged the challenges in accurately capturing utilisation of PBS-listed medicines for COPD. DUSC considered that exclusion of patients initiating with ICS/LABA FDC was appropriate to obtain a COPD only cohort and that the PBS data analysis provided the more accurate assessment of PBS-listed COPD medicine use compared to the MedicineInsight data.
- Based on PBS/RPBS data, the percentage of patients in the COPD cohort initiating to combinations outside COPD-X guidelines increased from 13.2% in 2010 to 25.7% in 2016.
- Based on the MedicineInsight data, up to 53.5% of use of COPD medicines was observed to be outside clinical guidelines and PBS restrictions.
- The percentage of use outside the COPD-X guidelines is mainly driven by initiation to a LAMA/LABA and use of triple inhaled therapy.
- There were also significant quality use of medicines (QUM) issues found around duplicated medicines, sequencing of therapy and low recorded use of spirometry.

3.6 *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.*

- 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.

- Additional QUM issues include the low rate of recorded spirometry in diagnosis and poor inhaler device technique which is often not reviewed by clinicians.
- Previous PBAC decision making has considered medicines in the LAMA, LABA, ICS/LABA and LAMA/LABA classes to be of comparable efficacy and safety to other medicines within their class.
- Overall, new evidence regarding the comparative efficacy and safety in the LAMA, LABA, ICS/LABA and LAMA/LABA classes does not support a change to previous PBAC decision-making and previously determined price relativities.

4 PBAC outcome

4.1 Overall, the PBAC accepted the key findings presented in the COPD Review Report. The PBAC considered stakeholder submissions to the Review, the sponsors' pre-PBAC responses and ESC and DUSC advice in addition to the Report. The PBAC considered the 14 options presented in the Review and made the following comments.

4.2 *Option 1 - Remove the requirement to stabilise patients on a LAMA and LABA separately, prior to initiation of a LAMA/LABA fixed dose combination (FDC).*

The PBAC noted that requiring a patient to stabilise on both a LAMA and LABA separately before using a LAMA/LABA FDC was not consistent with the current guidelines and adds cost and confusion to patients due to the range of medicines and devices.

The current process may also be confusing for clinicians and lead to unnecessary consultations. Following the proposed 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.

The PBAC noted that this option was supported by the Reference Group and stakeholders.

PBAC Advice: The PBAC recommended removing the current PBS requirement in the LAMA/LABA restrictions to stabilise patients on both individual monotherapy inhalers before commencing a FDC LAMA/LABA.

4.3 *Option 2 - Add a PBS restriction 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.*

The PBAC noted that the risk of potentially prescribing unsafe combinations of medicines is exacerbated by the multitude of new medicines and devices available for the treatment of COPD.

The PBAC noted that the Reference Group 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. It was also considered useful to include the generic names of the medicines in the restriction notes given the evidence of polypharmacy.

The PBAC noted that this option was also generally supported by stakeholders.

PBAC Advice: The PBAC recommended the addition of a PBS restriction note to all LAMA, LABA and ICS/LABA products consistent with current LAMA/LABA products on the PBS.

4.4 *Option 3 - Add a PBS restriction note on checking device technique and adherence to all products listed for COPD treatment on the PBS.*

The PBAC noted that 50-83% of patients do not use their inhalers correctly and evidence supports the regular checking of device technique as an important and necessary aspect of COPD management. Improved medication efficacy, safety and cost-effectiveness may also be achieved from improved inhaler technique.

The PBAC noted that this option was supported by the Reference Group and approved by stakeholders.

PBAC Advice: The PBAC recommended adding a PBS restriction note on checking inhaler device technique to all products listed for COPD on the PBS.

4.5 Option 4 - Add a PBS restriction note regarding the requirement to confirm COPD diagnosis with spirometry to all products listed for COPD treatment on the PBS.

The treatment algorithms for asthma, asthma-COPD overlap syndrome and COPD 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. The PBAC noted that stakeholders and various data sources in the Review indicate that many Australian COPD patients do not have lung function testing within the first 12 months of therapy initiation.

The PBAC agreed that the addition of a PBS restriction note requiring diagnosis of COPD with spirometry would alert prescribers of its importance in clinical care.

PBAC Advice: The PBAC recommended adding a PBS restriction note to require prescribers to confirm COPD diagnosis with spirometry to all products listed for COPD treatment on the PBS.

4.6 *Option 5 - Increase the restriction level for ICS/LABAs listed on the PBS for the treatment of COPD to Authority Required (STREAMLINED).*

The PBAC discussed that increasing the restriction level on ICS/LABAs that are indicated for COPD and asthma would be appropriate. There is a concern that ICS use in COPD populations correlates to a 40-70% increase in the risk of pneumonia. RCTs and observational studies also provide some evidence of an increased risk of fracture, but this was inconclusive.

The PBAC noted that the MedicineInsight data suggests that there is a high rate of initiation to ICS/LABAs in COPD, which is inconsistent with clinical guidelines.

The PBAC noted that the ICS/LABA PBS item codes for COPD have dual listings for asthma. The PBAC discussed separating the item codes for COPD and asthma and only increasing the restriction level on the COPD item codes. The creation of a separate PBS listings for COPD with a higher restriction level (Streamlined) was considered likely to be ineffective in modifying prescribing habits to use ICS/LABAs in line with the guideline recommendations for COPD. The PBAC therefore supported increasing the restriction for high dose ICS/LABA item codes on the PBS that have dual listings for COPD and asthma. The PBAC considered that an Authority Required (STREAMLINED) listing for high dose ICS/LABAs in asthma would not be a burden on prescribers and would likely be a reminder that ICS/LABAs be used second line to other monotherapy preventers in patients with asthma.

The PBAC noted that the majority of the Reference Group supported this option.

PBAC Advice: The PBAC recommended increasing the PBS restriction level to Authority Required (STREAMLINED) for ICS/LABAs that have dual listings on the PBS for the treatment of COPD and asthma. Item codes affected: 8432T, 8519J, 10018G, 11124L and 8750M.

4.7 *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).*

The PBAC noted that this would send a stronger signal regarding the appropriate sequencing of therapy but that it had a low level of support from stakeholders and

the Reference Group.

The PBAC therefore did not recommend this option and discussed that it may be reconsidered in the future if the increase in restriction to Authority Required (STREAMLINED) for high dose ICS/LABAs is not effective.

PBAC Advice: The PBAC did not recommend increasing the restriction level for ICS/LABAs and LAMA/LABAs listed on the PBS for the treatment of COPD to Authority Required (online).

4.8 *Option 7 - Reduce the restriction level for LAMA/LABAs to Restricted Benefit.*

The PBAC discussed that the more significant issue is the increased and inappropriate commencement of COPD patients on a FDC inhaler. 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.

The PBAC noted that whilst this option was supported by stakeholders, it was not supported by the Reference Group. It was also noted that Option 5 helps to ensure the appropriate sequencing of LAMA/LABA FDC before ICS/LABA FDC and so Option 7 is not necessary to achieve this objective.

PBAC Advice: The PBAC did not recommend reducing the restriction level for LAMA/LABAs to Restricted Benefit.

4.9 *Option 8 – Reconsider the cost-effectiveness of FDC inhalers for COPD.*

The PBAC noted that there is increasing use of LAMA/LABA FDC inhalers in first-line therapy and that the cost-effectiveness of this had not yet been evaluated. The PBAC noted that the Review had not identified any new, good quality evidence on the effectiveness of FDC inhalers which has not previously been 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 PBAC agreed that a cost-effectiveness analysis of FDC inhalers for COPD was not warranted at this time regarding dual therapy and that PBAC would be required to consider the cost-effectiveness of triple therapy in the future due to impending submissions for triple FDC therapy.

PBAC Advice: The PBAC did not recommend reviewing the cost-effectiveness of current dual therapy FDC inhalers for COPD.

4.10 *Option 9 - PBAC to write to manufacturers regarding device use and medicine*

packaging issues raised by stakeholders during the Review.

The PBAC noted that stakeholders had suggested the addition of instructional video websites to packaging, and a referral to the Lung Foundation Australia for ongoing support with using devices. It also noted problems determining when devices were empty and issues with removing tablets from foil packaging.

The PBAC noted that the DUSC had discussed that the limited availability of placebo inhalers was an issue, and that sponsors should be encouraged to make more of these devices available, particularly to pharmacies. The PBAC discussed that sample devices were being supplied by manufacturers but they were mostly for FDCs and were not for monotherapy or placebo devices. The placebo devices were particularly useful for repeated demonstration of correct technique.

The PBAC noted that these issues would need to be discussed in the context of the Therapeutic Goods Administration (TGA) regulations.

The PBAC noted that these concerns were extensively discussed in sponsor pre-PBAC responses and that many sponsors did claim to provide placebo FDC devices to clinicians. However, placebo monotherapy devices appear to be infrequently supplied. Stakeholders and the Reference Group were supportive of this option.

PBAC Advice: The PBAC recommended the department write to manufacturers regarding device use and medicine packaging issues raised by stakeholders during the Review.

4.11 *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.*

The PBAC noted that there are a large number of helpful resources available from various sources including the Lung Foundation Australia 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 also has a range of educational materials on COPD for GPs, pharmacists and nurses. The PBAC noted that these existing resources were comprehensive and tailored to clinicians and patients and discussed the need to increase knowledge and use of these existing resources.

The PBAC noted that stakeholders were generally supportive of this option as was the Reference Group.

PBAC Advice: The PBAC recommended the Department write to appropriate organisations to and sponsors to help improve awareness and knowledge of the current evidence-based educational materials and resources on COPD management for both health professionals and consumers.

4.12 *Option 11 - PBAC to request that the Technology Assessment and Access Division liaise with the Practice Incentives Programme (PIP) team in Health Services Division to highlight the relevant QUM findings from the Review.*

The PBAC noted that 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 PBAC noted 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.

The PBAC noted that stakeholders were generally supportive of this option as was the Reference Group.

PBAC Advice: The PBAC recommended the department liaise with the PIP team in Health Services Division to highlight the relevant QUM findings from the Review.

4.13 *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).*

The PBAC noted that the Review highlighted the need for greater use 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.

The PBAC noted that the Reference Group and stakeholders supported this option.

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

4.14 *Option 13 - PBAC to write to the TGA regarding the development of guidelines for naming, packaging and device design of inhalers.*

The PBAC noted that stakeholders considered 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.

Whilst the PBAC was supportive of this option, it noted that the TGA may have limited ability to influence packaging and device design of COPD inhalers due to the international nature of the products.

The PBAC noted this option was supported by the Reference Group and stakeholders.

PBAC Advice: The PBAC recommended writing to the TGA regarding the development of guidelines for naming, packaging and device design of inhalers.

4.15 *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.*

The PBAC noted that pulmonary rehabilitation provides an opportunity to reinforce self-management principles including correct inhaler device technique. Further, the increased use of evidence-based pulmonary rehabilitation programmes may reduce medicines usage.

The PBAC noted that the Review did not address the evidence for cost-effectiveness of pulmonary rehabilitation and could therefore not offer advice to MSAC in considering the cost-effectiveness of this item.

The PBAC noted that stakeholders and the Reference Group were supportive of reimbursing pulmonary rehabilitation.

PBAC Advice: The PBAC recommended the department convey to the MSAC the Review findings, stakeholder input and the Reference Group's support for pulmonary rehabilitation as an effective therapy in the management of COPD.

4.16 The PBAC noted that the final COPD Review report and the PBAC recommendations would be provided to the Minister for Health for consideration, and if agreed, published on pbs.gov.au.