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

Department of Health
Sydney, 21 March 2017

This document is intended to provide a broad summary of the views expressed by stakeholders and only information provided at the Forum has been included. No attempt was made to reach consensus.

PURPOSE 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 aim of the Stakeholder Forum is to ensure that the final COPD Review Report includes the views of a wide range of stakeholders and that these views inform the discussions about future options. Representatives of peak bodies, consumer organisations, pharmaceutical sponsor companies, and individuals who provided a submission to the Review, were invited to participate in the Forum.

The Review is being conducted under the Australian Government's Post-market Review Program for Pharmaceutical Benefits Scheme (PBS) medicines. An Expert Reference Group has been established to provide independent expert clinical advice and consumer input to the Review. A summary of the stakeholder input received at the Forum will be included in the draft COPD Review Report to the Pharmaceutical Benefits Advisory Committee (PBAC). The PBAC is an independent, expert committee that makes recommendations to the Government on the subsidy of medicines on the PBS.

Prior to the meeting, attendees were provided with a background discussion paper that included information on the Review Terms of Reference (ToR), and identified key issues and questions for the Forum. A brief summary of the clinical evidence and COPD medicines utilisation was presented at this Forum. Focus questions were posed at the Forum to prompt discussion and there was also an opportunity for open discussion not related to the focus questions. Stakeholders were informed that the draft COPD Review Report is expected to be publically available for comment prior to consideration by the PBAC sub-committees in June 2017.

SUMMARY OF KEY DISCUSSION POINTS RAISED BY STAKEHOLDERS

- The increase in COPD medicines provides greater choice in management options for prescribers and patients. The Post-Market Review of COPD Medicines is timely to ensure clinical practices, guidelines, PBS restrictions and education resources are reflective of the new treatment paradigm.
- A patient centred, individualised approach to COPD treatment is required with accurate disease diagnosis. Choice of therapy needs to be considered in the context of: clinical evidence, consensus clinical guidelines, a stepwise approach to pharmacological treatment of COPD and the side effect profiles of medicine classes.
- COPD diagnosis and management is complex and measures should be adopted to reduce the use of inappropriate and unsafe combinations of COPD medicines.
- Improved quality and cost effective use of COPD medications can be achieved by alignment of PBS restrictions to consensus clinical guidelines, improved access to educational resources and system changes to prescribing software tools. PBS rules do not replace the need for guidelines,

and where possible they should be synchronous with guidelines to ensure clinicians can be concordant with best available evidence-based treatment.

SUMMARY OF STAKEHOLDER RESPONSES TO FOCUS QUESTIONS

ToR 1

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

Question 1.1: Is the current method of restriction of the ICS[1]/LABAs[2] and LAMA[3]/LABAs appropriate?

- The latest Australian and New Zealand (COPD-X) Guidelines and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Strategy Report recommend a stepwise approach to pharmacological treatment of COPD.
- The PBS restriction for subsidised access to LAMA/LABA fixed dose combinations (FDCs) is Authority Required (Streamlined) and for ICS/LABAs is a Restricted Benefit listing for people with moderate to severe COPD (and frequent exacerbations).
- Inconsistencies between the PBS restrictions and the COPD-X Guidelines are resulting in prescribers being directed away from evidence based guidelines, and prescriber confusion.
- The PBS Restricted Benefit listing for ICS/LABAs may inadvertently support earlier use of ICS in the COPD patient treatment algorithm that may not be clinically appropriate as outlined in the COPD-X Guidelines.
- Patients must be stabilised on both LAMA and LABA monotherapy (two separate devices) to be eligible for LAMA/LABA FDCs on the PBS. This requirement is inconsistent with the COPD-X Guidelines, which states that LAMA/LABA FDCs are available for patients who remain symptomatic despite monotherapy with either LAMA or LABA alone.
- The PBS requirement for patients to be stabilised on dual monotherapy devices prior to initiation of LAMA/LABA FDCs reduces optimal patient treatment. Unnecessary multiple medication changes increases device confusion and reduces patient compliance. Patient costs are also increased with the requirement for two dispensing fees.

Question 1.2: Is the Authority Required (Streamlined) restriction sufficient to discourage inappropriate prescribing of LAMA/LABA FDCs as first line therapy or in unsafe combinations?

- Early use of LAMA/LABA FDCs is occurring because only one LABA is currently available on the PBS as single drug inhaler.
- ICS monotherapy is not indicated by the Therapeutic Goods Administration (TGA) for COPD treatment. The appropriate use of SABA[4]/SAMA[5] in combination with LAMA/LABA should also be considered.
- Prescribing of unsafe combinations by the clinician or inadvertent poly pharmacy 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.
- The increase in new COPD medicines available through the PBS may also be adding to the confusion. It was recognised that more COPD treatment options is positive for patients and prescribers as it allows for more choice and tailored therapy.

[1] Inhaled corticosteroids
[2] Long-acting beta-2 agonist
[3] Long-acting muscarinic antagonist
[4] Short-acting beta2-agonist
[5] Short-acting muscarinic antagonist

- Education of prescribers and pharmacists is required to improve overall adherence to COPD evidence based guidelines and the PBS restrictions. NPS MedicineWise prescribing audits are also required.

Question 1.3: Is there a more clinically appropriate restriction for LAMA/LABA FDCs that would allow treatment for patients previously on LAMA or LABA monotherapy?

- Revision of the PBS restrictions for LAMA/LABA FDCs is required to ensure alignment with guidelines, including the COPD-X Guidelines.
- Symptomatic patients controlled with either LAMA or LABA monotherapy should be able to access step up therapy to a FDC without the requirement to be stabilised on two separate devices.

Question 1.4: Would there be value in reminding clinicians to confirm inhaler technique before changing or adding treatments? How could correct inhaler technique be incorporated into PBS restrictions? Are there sufficient placebo inhalers available for prescribers/health professionals to confirm patient's inhaler technique?

- Both the COPD-X Guidelines and GOLD Strategy Report highlight the importance of confirming inhaler technique and adherence at each visit to a clinician.
- Resources that guide clinicians and practitioners in having productive conversations with their patients may also be needed to ensure appropriate technique is confirmed.
- Improved patient efficacy, safety and cost-effectiveness may be achieved from improved inhaler technique.
- Studies have shown there is poor retention of inhaler technique over periods as short as 3 months – therefore technique confirmation and education needs to occur/reoccur frequently.
- Many health professionals are not confident or competent to confirm correct inhaler technique. All health professions including doctors, prescribers, nurses and pharmacists are responsible for ensuring correct patient inhaler technique.
- Placebo inhalers are helpful. Ideally doctors/prescribers/nurses/pharmacists should have their own set on which they can demonstrate inhaler technique to patients.
- Pharmacists also have an important education role, instructing correct technique using patients' own dispensed inhaler.
- A number of resources are available to improve inhaler technique and greater access to these materials is required for clinicians and patients. A standardised national list of educational materials is required to avoid prescriber, pharmacist and patient confusion.
- PBS restrictions for COPD medications do not currently specify that patients must have demonstrated adherence to correct inhaler technique before changing treatments. Adding a note to the PBS restrictions for prescribers to confirm inhaler technique may be helpful in reducing unnecessary use of dual or triple therapies.
- The addition of a linked educational resource within the PBS software may also be helpful to improve the quality use of COPD medications.
- Improved accountability and Medical Benefits Scheme (MBS) incentives for prescribers and pharmacists are required to facilitate behavioural change.

Question 1.5: Would the addition of a note in the PBS restrictions be helpful in highlighting inappropriate combinations of drug classes?

- Guidelines highlight that inappropriate combinations of agents should be avoided. For example, using a LABA in addition to an ICS/LABA or a LAMA/LABA FDC.
- The potential for prescribing inappropriate combinations of agents is not systematically addressed for all COPD medicines in their PBS restrictions. Some medicines have a note in their restriction (for example, ICS/LABA FDCs have the note 'Patient must not be on a concomitant single agent long-acting beta-2 agonist'), and some do not (for example, the LAMA/LABA FDCs). A note highlighting the inappropriate combination of drug classes may be an option.

- A comparative utilisation analysis of inappropriate drug class combinations could be conducted based on PBS note status to evaluate the effectiveness of the restriction change.
- Alerts and flags are recommended to be incorporated into dispensing/prescribing software systems to improve the visibility of drug interactions and duplicate drug prescribing.
- A number of patients attend multiple general practices and pharmacies. The increasing use of the My Health Record is expected to reduce the use of inappropriate combinations of COPD drug classes across the healthcare system.
- Samples are not generally recorded in dispensing/prescribing software systems or medical history records and therefore the risk of inappropriate prescribing cannot be entirely managed by systems.

Question 1.6: What information could be provided in the context of the PBS to assist doctors with correctly diagnosing COPD, asthma, and asthma-COPD overlap syndrome, in order to ensure appropriate prescribing?

- Approximately 20% of patients have asthma-COPD overlap syndrome. Correct diagnosis is important because the treatment algorithms for COPD, asthma and asthma-COPD overlap syndrome are different.
- Accurate diagnosis of COPD relies on clinical judgement based on a combination of symptoms, history, physical examination, and confirmation of the presence of airflow obstruction using spirometry.
- A large Australian population survey showed that most participants did not have lung function testing performed within 12 months of their initial prescription for chronic airways disease.
- Measures to expand the use of spirometry by prescribers in Australia are required.
- Significant evidence gaps have occurred because asthma-COPD overlap patients are excluded from Random Controlled Trials (RCTs).
- Asthma-COPD overlap syndrome is generally treated by initiating to an ICS, then adding a LABA or LAMA.
- Separate clinical guidelines are available for COPD and asthma. Clinicians may be confused about appropriate treatment for asthma-COPD overlap syndrome patients.
- LABA/LAMA PBS restrictions should be reworded to include the following note "Do not use in patients with a history of asthma without accompanying or prior use of an ICS". This note should also be included on the PBS website and prescribing software.
- Further development of real world evidence is required to develop a more contemporary and up to date guideline for asthma-COPD overlap syndrome. Additional educational resources and targeted advice are needed.
- It was suggested by a stakeholder that there is evidence that ICS/LABA use in patients with asthma-COPD overlap syndrome is more effective than LABA alone.

ToR 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.

Question 2.1: Do the outcomes that have been considered by PBAC reflect what is important to doctors and patients? Are there any other outcomes that should be highlighted for consideration?

- Patient symptoms including breathlessness are not well correlated with forced expiratory volume levels at 1 second (FEV_1 levels).
- The US Food and Drug Administration (FDA) requires a clinical outcome of FEV_1 and therefore RCT primary end points do not always include assessments of symptom load. RCTs also assess

other measures of efficacy via secondary endpoints and this data is also submitted to the TGA and PBAC for consideration.

- The objective of COPD assessment is to determine the level of air flow, impact on health status and risk of future events (exacerbations, hospitalisations, etc.).
- The consensus guidelines recommend an approach of combining symptomatic assessment with the patient's spirometric classification and/or risk of exacerbations, which is consistent with the above-mentioned PBAC decision-making based on FEV_1, St George's Respiratory Questionnaire (SGRQ) and exacerbations.
- The GOLD Strategy Report (2017) ABCD (COPD patient assessment tool) has been refined to include respiratory symptoms and exacerbations alone to assign ABCD patient categories.
- COPD Assessment Test (CAT) is a questionnaire for people with COPD and more reflective of patient relevant outcomes. The questionnaire is designed to measure the impact of COPD on a person's life, and how this changes over time.
- High Resolution Computerised Tomography (HRCT) is relevant to exclude patients with emphysema.

Question 2.2: Are there side effects from specific COPD medicines that impact negatively on patient's daily activities/quality of life?

- Both meta-analyses and observational studies report increases in the risk of pneumonia of up to 70% for patients treated with ICS. Patients at higher risk of pneumonia include patients that currently smoke, have a history of exacerbations and/or severe airflow limitation.

ToR 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 FDCs) for treatment of COPD that PBAC has not previously considered.

- Updates to the COPD-X Guidelines and GOLD Strategy Report were completed in the last 3 months of 2016, following the systematic literature search for the COPD Review (August 2016). In addition, the AFFIRM publication that compares an ICS/LABA and a LAMA/LABA was published in October 2016.

Question 3.1: Should anything be done to encourage clinicians to prescribe LAMA/LABAs in preference to ICS/LABAs in patients with moderate to severe COPD only and a history of frequent exacerbations with significant symptoms as per the guidelines?

- Several RCTs have examined the comparative efficacy and safety of LAMA/LABA and ICS/LABA FDCs.
- The FLAME trial (published 2016) demonstrated superiority of glycopyrronium/indacaterol (LAMA/LABA) to fluticasone propionate/salmeterol (ICS/LABA) on exacerbations, lung function and health status outcomes.
- 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.
- The recent updates to the GOLD Strategy Report (2017) indicate that, in patients at high risk of COPD exacerbations, LAMA/LABA is the preferred initiating treatment over ICS/LABA.
- A culture change is already occurring and clinicians are initiating patients to LAMA/LABA in preference to ICS/LABA to reduce the risk of pneumonia.
- Individualistic patient care is required in COPD management. The additional choice of new medicines allows tailored treatment based on patient symptoms, risk of exacerbations and co-morbidities.

- Further education of GPs is required to ensure the right diagnosis and treatment management plan. Spirometry should be used routinely and HRCT should be used to rule out emphysema.

Question 3.2: Should access to ICS/LABA through the PBS be restricted to: i) those whose symptoms/exacerbations are not adequately controlled with LAMA/LABA? ii) only those for whom a LAMA is inappropriate? Or iii) people with asthma or combined asthma/COPD only, noting ICS monotherapy is unrestricted and could be added to LABA/LAMA FDC.

- The current PBS restrictions for ICS/LABAs specify that suitable patients have a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy, and FEV_1 less than 50% of predicted normal prior to therapy. This is consistent with the current COPD-X guidelines.
- The PBS restrictions have evolved over time and hence inconsistencies have occurred. The review is an opportunity to realign the restrictions with the clinical evidence.
- The FLAME trial is a single study and further well designed RCTs are required prior to the PBS restrictions for ICS/LABAs being amended.
- 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.

ToR 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.

Question 4.1: What is the experience of prescribers and consumers with adverse events when taking ICS? How do prescribers balance the risks and benefits when using ICS?

- Both meta-analyses and observational studies report increases in the risk of pneumonia of up to 70% for patients treated with ICS.
- It is difficult to assess individual patient risk of pneumonia. Patient requirement for ICS treatment and whether withdrawal is appropriate should therefore be considered.
- There is some evidence for an intra-class difference between fluticasone and budesonide.
- An ICS dose response for pneumonia is apparent, but not conclusive. Most trials for fluticasone and budesonide were based on higher doses and therefore limited evidence is available for low/medium doses.
- Review of ICS clinical evidence, including dose response evidence and impact on lung function, is required.
- 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.
- Diagnostic analysis of eosinophils may be included in the guidelines in the future, but further evidence is required prior to being measured routinely in clinical practice.

ToR 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. 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.

- A preliminary utilisation analysis of COPD medications has been conducted from 1 April 2005 to 31 December 2015 (10 years and 9 months) based on PBS claims data. An updated utilisation analysis will be included in the draft COPD Report. Patients aged 35 years and older initiating COPD treatment from 1 April 2007 were included in the PBS data analysis. Patients initiating

ICS/LABA prior to LAMA or LABA medicines were excluded from the PBS data analysis to reduce the risk of patients with an asthma only diagnosis being included.

- Concerns were raised that the exclusion of the ICS/LABA initiations would significantly underestimate the COPD only population as many prescribers use ICS/LABA early in the treatment pathway of all respiratory conditions – partly because a diagnosis has not been initially confirmed and partly because ICS/LABA's have been available on the PBS for some years before the listing of monotherapy LABA's and FDC of LABA/LAMAs.
- Analysis of ICS/LABA patient utilisation including initiations is required to better understand the overall use of ICS/LABA medications for the treatment of COPD.
- The preliminary utilisation review of PBS-listed COPD medicines indicates that use inconsistent with the COPD-X Guidelines is low, but it is present and generally increasing.

Question 5.1: Are there any comments regarding the reasons for inappropriate prescribing? Is the number of new medicine combinations listed on the PBS for COPD an issue for prescribers and consumers?

- The use of ICS/LABA is a safety concern and therefore analysis of patient utilisation by diagnosis would be of value.
- Analysis of SABA and SAMA medications in combination with ICS/LABA and LAMA/LABA FDC would be beneficial.
- Alternative data sources including MedicineInsight and linked MBS/PBS data would be of value for the COPD utilisation review.

General issues

Question 6.1: Is there confusion among prescribers about which classes of medicine/s are contained in each product? To facilitate safe and appropriate prescribing, how could the nomenclature in the PBS restrictions be clarified? If possible, would stakeholders support identification of the class of medicine (e.g. LAMA, LABA or ICS) on the medicine packaging to reduce patient and prescriber confusion?

- System pressures result in GPs and pharmacists being time poor.
- Lack of understanding of terminology occurs due to lack of knowledge of drug names by medicine class and familiarity with brand names.
- Patient confusion on drug treatments often occurs due to inadequate education, poly pharmacy and medication burden associated with co-morbidities.
- A standardised national list of educational materials, that is widely accessed by prescribers, nurses, pharmacists and patients, will reduce medicine confusion.
- Identification of the class of medicine on the product packaging and device labels would reduce overall confusion. The colour of packaging and inhalers has always tried to communicate medicine class e.g. relievers blue and preventers red/brown. Patients and clinicians medication recall may be improved through consistent themes in the colour of inhalers.
- Manufacturers and the TGA were encouraged to collaborate to improve product packaging for COPD medications.

Question 6.2: There are several devices available that consumers and clinicians may favour (or avoid), and this may influence choice of medicine prescribed. Does device type influence choice of medicine prescribed?

- Device choice is not included in the scope of this Review.
- Choice of device should be considered by prescribers because different attributes may assist elderly patients with limited dexterity or vision.
- Prescriber education covering all devices is required.
- Individual patient expertise/preference should be considered and device changes should occur after correct device technique is established and after a consultation.