Astra Zeneca Submission to the Post Market Review of COPD Medicines

COPD Review Background

The stated 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 quality use of medicines concerns associated with the apparent use of multiple products. This submission from AstraZeneca provides information for PBAC's consideration under the Review Terms of Reference.

Summary of Key Points

The clinical criteria in the PBS restrictions for LABA/ICS treatments are different and more restrictive than the criteria that apply to other COPD treatments (LAMAs, LABAs, LAMA/LABAs). According to COPD-X Guidelines, when FEV_1 is <50% predicted and there have been 2 or more exacerbations in the previous 12 months, ICS/LABA combination therapy can be commenced. ICS/LABA combination therapy has different positioning in the clinical treatment algorithm to other COPD treatments. The PBS restrictions for COPD medicines and the COPD-X Guidelines are broadly aligned for the management of stable COPD. AstraZeneca suggests no changes to the PBS restrictions or notes for COPD medicines are required to improve the quality use of these medicines.

In the interest of improving quality use of medicines AstraZeneca and Medical Director prescribing software have worked together and identified that Medical Director have some software irregularities with flag warnings ('pop-up' warnings) which appear when a doctor tries to prescribe a new COPD medicine. The flags appear when there is doubling up of the same **molecule** with a single agent product or a combination product, however they do not currently appear if there is doubling up of **different molecules within the same class.** Medical Director have advised AstraZeneca that these issues will be rectified in the next available patches and updates to Medical Director.

AstraZeneca recommends caution in interpretation of analyses based on Medicare Australia PBS claims data, which may have serious limitations in differentiating between asthma and COPD use as there is no link to diagnosis. In addition, asthma-COPD overlap syndrome (ACOS) is well known and accounts for approximately 15-25% of obstructive airway diseases. ACOS patients experience worse outcomes compared to patients with asthma or COPD alone.

Early diagnosis of COPD may well be hindered by the ready availability of short-acting bronchodilator treatments such as SABAs over the counter in Australia, enabling mild COPD patients to self-manage symptoms without proper diagnosis and management in primary care. Although they are in-scope medicines for this review, the extent of utilisation of these medicines is likely to be significantly underestimated on the basis of Medicare Australia PBS claims. This deficiency with Medicare Australia script based data may give the impression that patients are initiating bronchodilator therapy with LABA/ICS fixed dose combinations (or LAMAs or LABAs), when in fact SABAs are being used to initiate bronchodilator therapy.

Reliable comparison of frequency of exacerbations and prevention of exacerbations requires clinical trial durations that are significantly longer than 6 weeks. However, these important outcomes have not been frequently compared in the evidence previously considered by PBAC, because longer term trials including these outcomes were not

available. These outcomes are both highly relevant to the patient experience with COPD, and are also important drivers of health care resource utilisation, including primary care and specialist physician attendances, emergency room attendance and hospitalisations for COPD.

On the outcome of COPD exacerbations, AstraZeneca would like to emphasise the NH&MRC Level 1 evidence for Symbicort (budesonide/eformoterol) and Symbicort used in combination with a LAMA (tiotropium), demonstrated in the recently published systematic review and network meta-analysis by Tricco and coworkers (Tricco 2015). The odds ratios for moderate to severe exacerbations for patients who had experienced an exacerbation in the last year for both Symbicort (budesonide/eformoterol) alone versus placebo [OR 0.64 (95%CI 0.45, 0.91)] and Symbicort used in combination with a LAMA (tiotropium) versus placebo [OR 0.23 (95%CI 0.14, 0.40)] were among the most effective and statistically significant treatment differences demonstrated for this important outcome measure.

AstraZeneca considers the practice of withdrawing ICS from patients stabilised on ICS/LABA/LAMA triple therapy in the WISDOM trial (Magnussen et al 2014) may not be appropriate for the more severe patients receiving ICS/LABA/LAMA on the PBS.

It appears that ICS-containing treatments increase the risk of pneumonia compared to placebo in COPD patients. Although the management of pneumonia has important health care resource utilisation consequences, the increases in risk compared to placebo are small and it is clear from several large outcomes trials that patients can be managed without significantly impacting mortality compared to placebo. ICS/LABA treatments remain an important treatment option for COPD patients where the benefits, particularly for reduction in the frequency of COPD exacerbations, significantly outweigh the risk.

Liberal rules for patient compliance in data analysis from the Medicare Australia claims database are recommended as poor compliance with COPD treatments may be observed even for this highly symptomatic disease. Compliance issues can confound analyses of initiations to therapy, and caution is recommended.
AstraZeneca has noted some seasonality associated with the use of Symbicort 400/12 in COPD based on its own analysis of Medicare Australia claims data and other proprietary databases. The seasonality in COPD is not as marked as for asthma, but does exist and should not be interpreted as an indicator of inappropriate use.

Review Terms of Reference

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

   The PBS restrictions for COPD medicines and the COPD-X Guidelines are broadly aligned for the management of stable COPD. AstraZeneca suggests no changes to the PBS restrictions or notes for COPD medicines are required to improve the quality use of these medicines.

   The prescribing restrictions for PBS-listed COPD Medicines are summarised in **Attachment 1.** The four long acting muscarinic antagonists (LAMAs) Spiriva Handihaler 18 mcg (tiotropium), Seebri Breezhaler 50 mcg (glycopyrronium), Bretaris Genuair 322 mcg (aclidinium) and Incruse Ellipta 62.5 mcg (umeclidinium) are all PBS listed with Restricted benefit for COPD. Spiriva Respimat 2.5 mcg (tiotropium) has a more detailed Restricted benefit for long-term maintenance treatment of bronchospasm and dyspnoea associated with COPD.

   There is only one long acting beta-2-agonist (LABA), Onbrez 150 or 300 mcg (indacaterol) which is PBS listed with Restricted benefit for COPD. There is also a note in the listing that indacaterol should not be used for asthma.

   There are currently four PBS-listed LAMA/LABA fixed dose combination brands for COPD: Ultibro Breezhaler 110/50 mcg (glycopyrronium/indacaterol); Anoro Ellipta 62.5/25 mcg (umeclidinium/vilanterol); Spiolto Respimat 2.5/2.5 mcg (tiotropium/olodaterol) and Brimica Genuair 340/12 mcg (aclidinium/eformoterol). All of these products have the same Authority required (Streamlined) PBS restriction. The restrictions for these COPD medicines also specify patients must have been stabilised on a combination of a LAMA and a LABA. Other notes in the restrictions indicate the products are not PBS-subsidised for asthma, are not indicated for the initiation of bronchodilator therapy in COPD, and must not be used in combination with an inhaled corticosteroid (ICS)/LABA fixed dose combination, or LAMA or LABA monotherapy.

   There are three PBS listed ICS/LABA fixed dose combination brands for COPD: Symbicort [Turbohaler 400/12 (budesonide/eformoterol) and Rapihaler 200/6 (budesonide/ eformoterol)]; Seretide [Accuhaler 500/50 (fluticasone/salmeterol) and MDI 250/25 (fluticasone/salmeterol)]; and Breo Ellipta 100/25 (fluticasone/vilanterol). All of these treatments are also PBS listed for asthma, and the asthma listings were in place for several years prior to the COPD listings. The Restricted benefit listings for COPD are all the same and have the requirement for the forced expiratory volume in one second (FEV_1) to be less than 50% predicted, a history of repeated exacerbations with significant symptoms despite regular beta-2-agonist bronchodilator therapy, and symptomatic treatment. The restrictions note that patients must not be on a concomitant single agent LABA, and ICS/LABAs are not indicated for the initiation of bronchodilator treatment in COPD. These clinical criteria are different and more restrictive than the criteria that apply to other COPD treatments (LAMAs, LAMA/LABAs).

   The current COPD-X Guidelines produced by Lung Foundation Australia are summarised in **Attachment 2** “Stepwise Management of Stable COPD” and “Guide to Addition of Therapies”. According to the COPD-X Guidelines, the aim of pharmacological treatment may be to treat symptoms, prevent deterioration (decreasing exacerbations or reducing decline in quality of life) or do both. These Guidelines recommend a stepwise approach for

management of stable COPD, irrespective of disease severity, until adequate control has been achieved. Short-acting beta-2-agonist (SABAs) or short-acting muscarinic antagonists (SAMAs) can be used from mild to severe disease. LAMAs and/or LABAs are recommended for symptom relief from mild to severe disease, and may also help to prevent exacerbations. There is not clear guidance on when a single long-acting bronchodilator becomes inadequate and combination bronchodilators are required; use of combination LAMA and LABA is recommended even from mild disease. When FEV_1 is <50% predicted and there have been 2 or more exacerbations in the previous 12 months ICS/LABA combination therapy can be commenced. ICS/LABA combination therapy is recommended in moderate to severe disease, which is different positioning in the clinical treatment algorithm to other COPD treatments.

There are a large number of therapies now available for COPD and the Lung Foundation of Australia has also included a "Guide to the Addition of Therapies" in order to minimise inappropriate combination therapy use. To summarise, LABAs can be used with LAMAs, LAMAs can be used with LABAs or ICS/LABAs, and ICS/LABAs can be used with LAMAs. LABA/LAMA combinations should NOT be used with LABAs or LAMAs or ICS/LABAs.

Quality Use of Medicine Issues

The DUSC review of indacaterol for COPD conducted in 2013 after the first 12 months on the PBS noted a significant amount of co-administration of COPD medicines is occurring, and the co-administration of multiple LABA products was a significant quality use of medicines issue. The recent increase in the number of LABA/LAMA combination treatments PBS listed for COPD may also increase risk of inappropriate co-administration of multiple LABA or LAMA containing medicines and may be identified as an ongoing issue in the utilisation studies to be conducted for the COPD Review.

Minimising inappropriate combination therapy use is reflected in the current Restrictions and Notes controlling PBS prescription of medicines for COPD. In addition, the National Prescribing Service (NPS) Medicine Wise have issued a number of RADAR documents (NPS 2014, 2015) for COPD medicines that have clarified appropriate and inappropriate combination therapy use for COPD.

To investigate further ways that quality use of COPD medicines could be improved, AstraZeneca has contacted Medical Director prescribing software and has verified that there is a flag ('pop-up' warning) which appears when a doctor tries to prescribe Symbicort (eformoterol/budesonide) to a patient using Oxis (eformoterol). The flag warning indicates the patient is already on the molecule and is a prompt to discontinue the new or previous treatment. Similarly if a patient using Spiriva Handihaler (tiotropium) is prescribed Spiolto Respimat (tiotropium/olodaterol) the flag pops up to warn the prescriber. Apparently the warning flag convention currently applies for doubling up of the same **molecule** with a single agent product or a combination product. However AstraZeneca discovered the flag currently does not apply if there is doubling up of **different molecules within the same class.** For example, it would not appear if a LABA/LAMA like Ultibro (indacaterol/ glycopyrronium) was prescribed for a patient already on a LAMA like Spiriva (tiotropium). The flag also doesn't appear for fixed dose combinations where the component class may be the same but not the molecules. For example, there is no flag for prescribing the ICS/LABA Symbicort (budesonide/eformoterol) for a patient already on the LAMA/LABA Ultibro (indacaterol/ glycopyrronium), and no flag for prescribing Symbicort (budesonide/eformoterol) for a patient already on Breo Ellipta (fluticasone/vilanterol). Medical Director has confirmed that there are

some gaps in their class coding and ineffective screening of multi-ingredient products which have led to these irregularities in flag warnings. In the interest of improving quality use of ICS/LABA medicines for COPD AstraZeneca has worked with Medical Director to ensure warning flags appear when there is doubling up of different molecules within the same class. Medical Director have advised AstraZeneca that these issues will be rectified in the May 2016 Medical Director update and forthcoming 3.16b patch.

AstraZeneca has also verified that none of the currently available brands of dispensing software used in pharmacy provide warning flags for dispensing doubling up of molecules for the same patient or doubling up of different molecules within the same class for the same patient. AstraZeneca suggests that Department of Health staff could work with pharmacy prescribing software vendors to obtain warning flags at the time of dispensing a PBS medicine as another check point for inappropriate prescribing.

To improve quality use of medicines and reduce inappropriate prescribing such as doubling up of LABA containing products AstraZeneca has previously run educational meetings for pharmacists conducting Home Medicine Reviews (HMR). These meetings were considered very successful and greatly appreciated by the pharmacists and patients participating in the HMR service. Given the increased number of LABA-containing products now available on the PBS for COPD, AstraZeneca would be prepared to run another series of similar educational meetings for HMR pharmacists. AstraZeneca would also be willing to collaborate with the Department of Health, clinical organisations and other sponsors to deliver other education programs to improve quality use of medicines for COPD patients.

Under-diagnosis of patients with mild stable COPD

The stepwise approach to management of stable COPD works well when patients obtain an early diagnosis of COPD with mild disease when they can be managed with short-acting bronchodilators and a single long-acting bronchodilator. With regular primary care monitoring treatments are revised and stepped up as required with the declining lung function, worsening symptoms and the more frequent exacerbations which characterise this degenerative disease. A practical difficulty is a significant proportion of patients are not diagnosed until they have moderate or even severe disease when declining lung function, worsening symptoms, and more regular exacerbations drive them to seek health care in the primary care setting or in hospital emergency rooms. These patients may already be suitable candidates for short-acting bronchodilators and multiple long-acting bronchodilator treatments. Early diagnosis may well be hindered by the ready availability of short-acting bronchodilator treatments such as SABAs over the counter in Australia, enabling mild COPD patients to self-manage symptoms without proper diagnosis and management in primary care.

Asthma-COPD Overlap Syndrome (ACOS)

The clinical features and pathophysiology of COPD can overlap with asthma, as most COPD patients have at least some degree of reversibility of airflow limitation after use of beta-2-agonist. Asthma-COPD overlap syndrome (ACOS) is well known (GINA/GOLD 2014, Marsh 2008, Louie 2013) and accounts for approximately 15-25% of obstructive airway diseases. ACOS patients experience worse outcomes compared to patients with asthma or COPD alone. Patients with ACOS have multiple risk factors including smoking and atopy, are generally younger than most patients with COPD and experience acute exacerbations with higher frequency and greater severity than most patients with COPD alone. ACOS does complicate analysis of the utilisation of medicines such as ICS/LABAs which can be used for

both COPD and asthma, or either disease alone. Caution is recommended if using simple methods such as an age-based demarcation alone for asthma and COPD usage within the COPD Review.

Other higher risk COPD populations

Exacerbations of COPD requiring hospital admission occur across all stages of airflow limitation and are a significant prognostic factor of reduced survival across all COPD stages. Recent studies have shown that patients with COPD at a high risk for hospitalisation can be identified by their past history for similar events and other factors including the severity of airflow limitation, poor health status, age, presence of emphysema, and leucocytosis (Mullerova et al 2015). Despite the increased availability of new treatments for COPD, there remains an unmet need for new treatments for COPD patients at higher risk of hospitalisations.

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.

COPD clinical trial outcomes frequently include the lung function spirometry tests trough FEV_1, $FEV_{\text{Area under curve (AUC)/time}}$, and forced vital capacity (FVC). These tests are routinely performed pre- and post-beta-2-agonist treatment as the lack of, or incomplete, reversibility in airway function post-beta-2-agonist treatment in COPD is a characteristic that contributes to the differential diagnosis of COPD and asthma. Patients notice symptomatic declining lung function (dyspnoea, cough) however spirometry is more sensitive and is able to detect deteriorations in lung function which may not yet be symptomatic. There are more directly patient relevant outcome measures such as respiratory-specific quality of life symptom scores [St George Respiratory Questionnaire (SGRQ), Total Dyspnoea Index (TDI)]. Most importantly, the outcome measures of frequency of exacerbations or prevention of exacerbations have substantial patient impact and also significantly impact health care resource utilisation. COPD clinical trials usually report treatment emergent and/or drug-related adverse events. Only a small number of cardiovascular and all-cause mortality outcome trials have been conducted for COPD.

Economic evaluation is inherently comparative and so the evidence that is presented to PBAC in submissions is often restricted to trials that enable direct comparisons or, more frequently, indirect comparisons to other therapies via a common comparator such as placebo. This may also create a practical limitation of the comparative evidence available for decision-making to a narrow range of clinical outcomes, for example, the available evidence may only enable robust comparisons of trough FEV_1, and safety data from short term trials. A review of the Public Summary Documents for recent PBS listings of inhaled therapies for COPD indicates that many of these listings were based on a limited range of clinical outcomes from short term clinical trials, and seldom included comparisons of the important and patient relevant outcome of COPD exacerbations, for the reasons described below (refer **Attachment 3**).

Reliable comparison of frequency of exacerbations and prevention of exacerbations requires clinical trial durations that are significantly longer than 6 weeks. However these important outcomes have not been frequently compared in the evidence previously considered by PBAC because longer term trials including these outcomes were not available. These outcomes are both highly relevant to the patient experience with COPD, and are also important drivers of health care resource utilisation, including primary care and specialist

physician attendances, emergency room attendance and hospitalisations for COPD. In the context of this review of COPD medicines the PBAC should consider the larger body of comparative evidence, including real world evidence, on the frequency of exacerbations and prevention of exacerbations now available since many COPD medicines were listed on the PBS.

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.**

COPD Exacerbations

On the outcome of COPD exacerbations, AstraZeneca would like to emphasise the NH&MRC Level 1 evidence for Symbicort (budesonide/eformoterol) and Symbicort used in combination with a LAMA (tiotropium), demonstrated in the recently published systematic review and meta-analysis by Tricco and coworkers (Tricco 2015). The systematic review for this network meta-analysis (NMA) was conducted in late 2013.

This NMA presented the odds ratios for moderate to severe exacerbations for patients who had experienced an exacerbation in the last year from 20 randomised placebo-controlled trials (refer [redacted]). This data shows that the results for both Symbicort (budesonide/eformoterol) alone versus placebo [OR 0.64 (95%CI 0.45, 0.91)] and Symbicort used in combination with a LAMA (tiotropium) versus placebo [OR 0.23 (95%CI 0.14, 0.40)] were among the most effective and statistically significant treatment differences demonstrated for this important outcome measure.

[redacted]

The long-term real-world evidence from the PATHOS study (Larsson 2013) recently showed that COPD patients treated with budesonide/formoterol are significantly less likely to suffer from COPD-related exacerbations and are significantly less likely to be hospitalised for COPD than those treated with fluticasone/salmeterol. Budesonide/formoterol reduced the annual rate of moderate to severe exacerbations by 26% compared to fluticasone/salmeterol (0.80 vs. 1.09 per patient-year; p<0.0001). Budesonide/formoterol also reduced rates of COPD-related hospitalisation by 29% (0.15 versus 0.21 per patient-year; p<0.0001) with hospital days due to COPD exacerbation 34% fewer (0.63 vs. 0.95 per patient-year; p<0.0001) compared with fluticasone/salmeterol.

St George Respiratory Questionnaire (SGRQ)

The Cochrane Airways Group has also conducted a recent NMA on long-acting inhaled therapy for COPD (Kew et al 2014). However, only two outcomes [SGRQ and trough FEV_1] were considered and data was pooled by class of treatment (LABA, LAMA, ICS, ICS/LABA, placebo). The SGRQ total score change from baseline in 6 months (based on 25 randomised controlled trials) were analysed. Combination LABA/ICS was the highest ranked intervention by this measure with a mean improvement over placebo of -3.89 units (95% CI -4.70, -2.97) at 6 months and -3.60 units (95% CI -4.63, -2.34) at 12 months. The accepted minimal clinically important difference for the SGRQ score is 10 units. Nevertheless, any improvements in quality of life over time are meaningful outcomes for COPD patients given the natural history of COPD, which is known to be a degenerative condition.

Trough FEV_1

Trough FEV_1 data for COPD have frequently been presented to PBAC as the pivotal efficacy outcome measure based on short term studies of 12 weeks duration. The Kew 2014 meta-analysis presented data from 31 studies with results for 6 and 12 months treatment. As for SGRQ, combination LABA/ICS was the highest ranked class, with a mean improvement over placebo of 133 mL at 6 months (95% CI 100.6, 164) and slightly less at 12 months, 100 mL (95% CI 55.5, 140 mL).

Stepping down ICS and time to the first moderate/severe exacerbation

The WISDOM trial (Magnussen et al 2014) considered the impact of stepping down the ICS dose on the time to the first moderate/severe exacerbation during the twelve month study period. The patients on this study were stabilised during a 6 week run-in period on triple therapy with tiotropium plus salmeterol/fluticasone, then randomised 1:1 to continue the same triple therapy regimen or continue to receive tiotropium and salmeterol with a three-step reduction in fluticasone dose every 6 weeks, ultimately to placebo for fluticasone. The study found that glucocorticoid withdrawal compared to glucocorticoid continuation did not appear to impact the time to the first moderate or severe exacerbation [HR 1.06 (95% CI 0.94, 1.19)]. This primary endpoint is less sensitive than the overall exacerbation rate at identifying the responsive subset (with recurring events) that may benefit most from ICS therapy. There are significant concerns with this study and its conclusions, raised in several letters to the Editor (Cosio et al 2015, Singanayagam et al 2015, Brightling et al 2015) following publication. The patients randomised to the study were at least 40 years old, current (>10 pack-years) or former smokers and had a diagnosis of severe or very severe COPD, defined as FEV1<50% predicted and forced vital capacity (FVC) <70% after bronchodilation. The patients required a history of at least one exacerbation in the 12 months prior to screening. 30% of patients were not receiving ICS at the time of enrolment

in the trial (Reilly 2014). This is quite different to the PBS population eligible for ICS/LABA treatment, which requires a history of repeated exacerbations with significant symptoms despite regular beta-2-agonist bronchodilator therapy. Consequently the PBS population of ICS/LABA patients appears to be a more severe group than those included in the WISDOM trial. The WISDOM trial primary endpoint was time to first moderate to severe exacerbation and did not investigate the impact of withdrawal of glucocorticoids on the overall frequency of exacerbations over a long period of treatment. Those that were withdrawn from ICS had a significant decline in lung function at 18 and 52 weeks (Magnussen 2014). AstraZeneca considers the practice of withdrawing ICS from patients stabilised on ICS/LABA/LAMA triple therapy may not be appropriate for the more severe patients receiving ICS/LABA/LAMA on the PBS. This is supported by a recent post-hoc analysis of the WISDOM trial (Watz et al 2016) which showed patients with higher eosinophil levels were at significantly higher risk of severe exacerbations 9 months after withdrawal of ICS.

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.**

ICS/LABA use and risk of pneumonia

The Tricco 2015 NMA also considered the outcome of pneumonia occurrence, based on evidence from 54 randomised controlled trials. This NMA identified 24 treatment comparisons with statistically significant differences in risk of pneumonia, including two treatments (fluticasone alone and fluticasone/salmeterol) that increased risk of pneumonia versus placebo. The NMA also considered the published evidence on mortality. The mortality analysis was conducted on 88 randomised controlled trials and showed that fluticasone/salmeterol was more effective at reducing mortality than placebo, formoterol and fluticasone alone.

In late 2015 a very large outcomes trial (16,485 patients) sponsored by GSK released topline results (GSK Media Release November 2015) comparing the ICS/LABA Breo Ellipta (fluticasone/vilanterol) to placebo in COPD patients with moderate airflow limitation (FEV1 50-70% predicted) and a history or increased risk of cardiovascular disease. The primary endpoint of the trial was the all-cause mortality risk, which was only 12.2% lower in the fluticasone/vilanterol 100/25 mcg group compared to the placebo group, and did not show a statistically significant difference (p=0.137).

Budesonide is a less potent ICS compared to fluticasone and consequently the low incidence of drug-related pneumonia observed in randomised controlled trials of budesonide/eformoterol to date is pharmacologically plausible.

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has recently reviewed the known risk of pneumonia with ICS-containing medicines when used to treat chronic obstructive pulmonary disease (COPD). The PRAC review confirmed *"that COPD patients treated with inhaled corticosteroids are at increased risk of pneumonia; however the Committee's view is that the benefits of inhaled corticosteroids continue to outweigh their risks. The PRAC also looked whether there were any differences in the risk of pneumonia between these products, and did not find conclusive evidence of such difference. Pneumonia remains a common side effect for all of them."*

It appears that ICS-containing treatments increase the risk of pneumonia compared to placebo. Although the management of pneumonia has important health care resource

utilisation consequences, the increases in risk compared to placebo are small and it is clear from several large outcomes trials that patients can be managed without significantly impacting mortality or cardiovascular mortality compared to placebo. ICS/LABA treatments remain an important treatment option for COPD patients where the benefits, particularly for reduction in the frequency of COPD exacerbations, significantly outweigh the risk.

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.**

   Comments under Terms of Reference 5 and 6 are considered together under Terms of Reference 6.

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.**

   AstraZeneca recommends caution in interpretation of analyses based on Medicare Australia PBS claims data, which may have serious limitations in differentiating between asthma and COPD use as there is no link to diagnosis. The very recent PBS listing dates for some COPD medicines included in the scope of this COPD Review means Medicare Australia utilisation data of less than 24 months duration will be used. The uncertainty associated with such limited data could impact some treatments (LABA/LAMA combinations in particular) and may misrepresent longer term use.

   SABAs are inexpensive and can be readily purchased over the counter in Australia. Although they are in-scope medicines for this review the extent of utilisation of these medicines is likely to be significantly underestimated on the basis of Medicare Australia PBS claims. This deficiency with Medicare Australia script based data may give the appearance that patients are initiating bronchodilator therapy with LABA/ICS fixed dose combinations (or LAMAs or LABAs), when SABAs are in fact being used appropriately to initiate bronchodilator therapy.

   In the 2013 DUSC review of Symbicort 400/12 in COPD, utilisation was higher than expected from the PBAC submission. The DUSC suggested this was possibly due to increased awareness/diagnosis of COPD and arrival of new agents in the COPD market. There was a trend towards more initiations in winter compared to summer, and the DUSC suggested that this may indicate some use outside COPD, for example respiratory tract infections and cough.

   Utilisation analyses conducted by AstraZeneca suggests there has been overall growth in the COPD market which could be attributed to improvements in diagnosis, patient management and the increased number of therapeutic options available for COPD patients. Liberal rules for patient compliance in data analysis are recommended as poor compliance with COPD treatments is frequently observed even for this highly symptomatic disease. Compliance issues can confound analyses of initiations to therapy, and caution is recommended.

   AstraZeneca has also noted some seasonality associated with the use of Symbicort 400/12 in COPD based on analysis of Medicare Australia claims data and other proprietary databases. The seasonality in COPD is not as marked as for asthma, but does exist and should not be interpreted as an indicator of inappropriate use. The DUSC should be aware

that cough is an established symptom of both COPD and asthma and some seasonality in utilisation should be expected, in particular for patients who are sensitive to the cold air more common in winter months. To be eligible for ICS/LABA treatment patients must be symptomatic, and these treatments are more likely to be prescribed for COPD patients for whom cough is a symptom. In addition, both COPD and asthma patients suffer from exacerbations, and antibiotic treatments may be prescribed in association with COPD treatment for management of infections if they develop during exacerbations. Use of ICS/LABA medicines outside COPD for respiratory infections is not expected to be significant since there are more suitable, fast-acting and readily accessible treatments such as SABAs which can provide temporary symptom relief.

References

Brightling CE, Pavord ID, Bafadhel M. Inhaled glucocorticoids and COPD exacerbations. *N. Engl. J. Med.,* 2015; 372(1):93.

Cosio M, Baraldo S, Saetta M. Inhaled glucocorticoids and COPD exacerbations. *N. Engl. J. Med.,* 2015; 372(1):92.

Global Initiative for Asthma (GINA)/Global Initiative for Chronic Obstructive Lung Disease (GOLD) Diagnosis of Diseases of Chronic Airflow Limitation:Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS). http://www.goldcopd.org/uploads/users/files/AsthmaCOPDOverlap.pdf

GSK Media Release 08 September 2015 “GSK and Theravance announce results from the SUMMIT COPD CV Survival Study” (http://www.gsk.com)

Kew KM, Dias S and Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2014 Issue 3 Art. No CD010844 DOI:10.1002/14651858.

Larsson K, Janson C, Lisspers K, Jørgensen L, et al Combination of budesonide/formoterol more effective than fluticasone/salmeterol in preventing exacerbations in chronic obstructive pulmonary disease: the PATHOS study. *J Intern Med.* 2013 Jun; 273(6):584-94.

Louie S, Zeki AA, Schivo M, Chan AL, Yoneda KY, Avdalovic M, Morrissey BM, Albertson TE. The asthma-chronic obstructive pulmonary disease overlap syndrome: pharmacotherapeutic considerations. *Expert Rev Clin Pharmacol.* 2013 Mar; 6(2):197-219.

Magnussen H, Disse B, Rodrigues-Roisin R, Kirsten A, *et al.* Withdrawal of Inhaled Glucocorticosteroids and Exacerbations of COPD. *N. Engl. J. Med.* 2014; 371:1285-94.

Marsh SE, Travers, J, Weatherall M, Williams MV, Aldington S, Shirtcliffe PM, Hansell AL, Nowitz MR, McNaughton AA, Soriano JB and Beasley RW. Proportional classifications of COPD phenotypes. *Thorax* 2008, 63:761-7.

Mullerova H, Maselli DJ, Locantore N, Vestbo J, et al. Hospitalised exacerbations of COPD: Risk factors and Outcomes in the ECLIPSE cohort. *Chest* 2015; 147(4):999-1007.

NPS MedicineWise. New fixed-dose combination bronchodilators for COPD NPS RADAR (December 2015). (accessed 29 March 2016)

NPS MedicineWise. Indacaterol with glycopyrronium (Ultibro Breezhaler) for chronic obstructive pulmonary disease. NPS RADAR (December 2014). 2014. (accessed 29 March 2016).

Reilly JJ. Stepping down therapy in COPD. *N. Engl. J. Med.* 2014; 371(14):1340-41.

Singanayagam A, Johnston SL, Mallia P. Inhaled glucocorticoids and COPD exacerbations. *N. Engl. J. Med.* 2015; 372(1):92-93.

Tricco AC, Strifler L, Veroniki A-A, Yadzi F, *et al.* Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis. *BMJ Open* 2015; 5:e009183.

Watz H, Tetzlaff K, Woulters EFM, Kirsten A, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir. Med*. 2016 Published online April 7 DOI 10.1016 S2213-2600(16)00100-4.

Attachment 1 COPD Medicines Current PBS Restrictions

Generic name	Brand Name	Company	Current PBS restriction(s)
LAMAs			
Tiotropium	Spiriva Respimat 2.5mcg Spiriva Handihaler 18 mcg	Boehringer Ingelheim	*Restricted benefit* *Bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease. Treatment Phase: Long-term maintenance treatment* *Restricted benefit* *Chronic obstructive pulmonary disease*
Glycopyrronium	Seebri Breezhaler 50mcg	Novartis	The following medications all have the same controls on prescribing: *Restricted benefit* *Chronic obstructive pulmonary disease*
Aclidinium	Bretaris Genuair 322 mcg	A.Menarini	
Umeclidinium	Incruse Ellipta 62.5mcg	GSK	
LABAs			
Indacaterol	Onbrez 150 and 300 mcg	Novartis	*Restricted benefit* *Chronic obstructive pulmonary disease* *Note: Indacaterol is not PBS-subsidised for the treatment of asthma*
Eformoterol	Oxis	AstraZeneca	Asthma only
Salmeterol	Serevent	GSK	Asthma only
LAMA/LABAs			
Glycopyrronium/ indacaterol	Ultibro Breezhaler 110/50mcg	Novartis	The following medications all have the same controls on prescribing: *Authority required (STREAMLINED)* *Chronic obstructive pulmonary disease (COPD)* *Clinical criteria: Patient must have been stabilised on a combination of a long acting muscarinic antagonist and long acting beta-2 agonist.* *Notes:*
Umeclidinium/ vilanterol	Anoro Ellipta 62.5/25mcg	GSK	
Tiotropium/ olodaterol	Spiolto Respimat 2.5/2.5mcg	Boehringer Ingelheim	

Aclidinium/ eformoterol	Brimica Genuair 340/12mcg	A.Menarini	*This product is not PBS-subsidised for the treatment of asthma.* *This product is not indicated for the initiation of bronchodilator therapy in COPD.* *The treatment must not be used in combination with an ICS/LABA, or LAMA or LABA monotherapy.* *A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.* *A LABA includes olodaterol, indacaterol, salmeterol, eformoterol or vilanterol.*
ICS/LABAs			
Fluticasone propionate/ eformoterol	Flutiform 50/5mcg 125/5mcg 250/10mcg	Mundipharma	 Asthma only Asthma only Asthma only
Budesonide/ eformoterol	Symbicort Turbohaler 100/6mcg 200/6mcg 400/12mcg	AstraZeneca	 Asthma only Asthma only *Restricted Benefit (also PBS listed for asthma)* *Chronic obstructive pulmonary disease (COPD)* *Patient must have a forced expiratory volume in 1 second (FEV1) less than 50% of predicted normal prior to therapy,* *Patient must have a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy,* *The treatment must be for symptomatic treatment.* *Notes:* *Patient must not be on a concomitant single agent long-acting beta-2 agonist.* *This product is not indicated for the initiation of bronchodilator therapy in*

	Symbicort Rapihaler (2 packs) 50/3mcg 100/3mcg 200/6mcg		*COPD.* Asthma only Asthma only *Restricted Benefit (also PBS listed for asthma)* *Chronic obstructive pulmonary disease (COPD)* *Clinical criteria:* *Patient must have a forced expiratory volume in 1 second (FEV1) less than 50% of predicted normal prior to therapy,* *Patient must have a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy,* *The treatment must be for symptomatic treatment.* *Notes:* *Patient must not be on a concomitant single agent long-acting beta-2 agonist.* *This product is not indicated for the initiation of bronchodilator therapy in COPD.*
Fluticasone propionate/ salmeterol	Seretide Accuhaler (60 puffs) 100/50mcg 250/50mcg 500/50mcg	GSK	Asthma only Asthma only *Restricted Benefit (also PBS listed for asthma)* *Chronic obstructive pulmonary disease (COPD)* *Clinical criteria:* *Patient must have a forced expiratory volume in 1 second (FEV1) less than 50% of predicted normal prior to therapy,* *Patient must have a history of repeated exacerbations with significant*

	Seretide MDI (120 puffs) 50/25mcg 125/50mcg 250/50mcg		*symptoms despite regular beta-2 agonist bronchodilator therapy,* *The treatment must be for symptomatic treatment.* *Notes:* *Patient must not be on a concomitant single agent long-acting beta-2 agonist.* *This product is not indicated for the initiation of bronchodilator therapy in COPD.* Asthma only Asthma only *Restricted Benefit (also PBS listed for asthma)* *Chronic obstructive pulmonary disease (COPD)* *Clinical criteria:* *Patient must have a forced expiratory volume in 1 second (FEV1) less than 50% of predicted normal prior to therapy,* *Patient must have a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy,* *The treatment must be for symptomatic treatment.* *Notes:* *Patient must not be on a concomitant single agent long-acting beta-2 agonist.* *This product is not indicated for the initiation of bronchodilator therapy in COPD.*
Fluticasone furoate/ vilanterol	Breo Ellipta 100/25	GSK	*Restricted Benefit (also PBS listed for asthma)* *Chronic obstructive pulmonary disease (COPD)* *Clinical criteria:* *Patient must have a forced expiratory volume in 1 second (FEV1) less*

	200/25		*than 50% of predicted normal prior to therapy,* *Patient must have a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy,* *The treatment must be for symptomatic treatment.* *Notes:* *Patient must not be on a concomitant single agent long-acting beta-2 agonist.* *This product is not indicated for the initiation of bronchodilator therapy in COPD.* Asthma only

Attachment 2 Stepwise Management of Stable COPD

Stepwise Management of Stable COPD

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	MILD	MODERATE	SEVERE
Typical Symptoms	• few symptoms • breathless on moderate exertion • recurrent chest infections • little or no effect on daily activities	• increasing dyspnoea • breathless walking on level ground • increasing limitation of daily activities • cough and sputum production • exacerbations requiring oral corticosteroids and/or antibiotics	• dyspnoea on minimal exertion • daily activities severely curtailed • experiencing regular sputum production • chronic cough • exacerbations of increasing frequency and severity
Lung Function	**FEV_1 ≈ 60-80% predicted**	**FEV_1 ≈ 40 -59% predicted**	**FEV_1 < 40% predicted**

Non-Pharmacological Interventions

Management of stable COPD should centre around supporting smoking patients to quit. Encouraging physical activity and maintenance of a normal weight range are also important. Pulmonary rehabilitation is recommended in symptomatic patients.

RISK REDUCTION Check smoking status, support smoking cessation, recommend annual influenza and pneumococcal vaccine according to immunisation handbook

OPTIMISE FUNCTION Encourage physical activity, review nutrition, provide education, develop GP management plan and initiate regular review

CONSIDER CO-MORBIDITIES especially osteoporosis, coronary disease, lung cancer, anxiety and depression

REFER TO PULMONARY REHABILITATION and consider psychosocial needs, agree written action plan

Consider oxygen therapy, surgery, palliative care and advanced care directives

Pharmacological Interventions

The aim of pharmacological treatment may be to treat symptoms (e.g. breathlessness) or to prevent deterioration (either by decreasing exacerbations or by reducing decline in quality of life) or both. A stepwise approach is recommended, irrespective of disease severity, until adequate control has been achieved.

CHECK DEVICE USAGE TECHNIQUE AND ADHERENCE AT EACH VISIT - Up to 90% of patients don't use devices correctly

SHORT-ACTING RELIEVER MEDICATION: Short-acting $beta_2$-agonist (SABA) or short-acting muscarinic antagonist (SAMA). Refer to Table 1 overleaf.

SYMPTOM RELIEF: Long-acting muscarinic antagonist (LAMA) and/or long-acting $beta_2$-agonist (LABA). Refer to Table 1 overleaf. **These medicines may also help to prevent exacerbations. **SEE PRECAUTIONS [1-3]****

EXACERBATION PREVENTION: When FEV_1 <50% predicted AND 2 or more exacerbations in the previous 12 months, consider commencing inhaled corticosteroid (ICS)/LABA combination therapy. ****SEE PRECAUTIONS[4]****

Consider low dose theophylline

Based on COPD-X Plan: Australian and New Zealand Guidelines for the Management of COPD; Australian Therapeutic Guidelines.

FEBRUARY 2016

PRECAUTIONS:

[1] An assessment should be undertaken to exclude asthma or check if asthma and COPD co-exist before initiating LABA monotherapy. LABA monotherapy should not be used when asthma and COPD co-exist.
[2] Once a LAMA is commenced, ipratropium (a SAMA) should be discontinued.
[3] If starting a fixed dose LAMA/LABA combination inhaler, discontinue existing inhalers containing a LAMA or LABA. Refer to Table 1 overleaf.
[4] If starting an ICS/LABA combination inhaler, discontinue existing inhalers containing a LABA. Refer to Table 1 overleaf.

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Table 1: Guide to addition of therapies

Green tick indicates therapies that can be used together

			SABA	SAMA	LAMA	LABA	LABA/ LAMA	ICS/ LABA
SABA	• salbutamol (Ventolin™, Airomir™, Asmol™)	• terbutaline (Bricanyl™)		✓	✓	✓	✓	✓
SAMA	• ipratropium (Atrovent™)		✓			✓		✓
LAMA	• tiotropium (Spiriva™) • glycopyrronium (Seebri™)	• aclidinium (Bretaris™) • umeclidinium (Incruse™)	✓			✓		✓
LABA	• salmeterol (Serevent™) • eformoterol (Oxis™, Foradile™)	• indacaterol (Onbrez™)	✓	✓	✓			
LABA/ LAMA	• indacaterol/glycopyrronium (Ultibro™) • umeclidinium/vilanterol (Anoro™)	• tiotropium/olodaterol (Spiolto™) • aclidinium/eformoterol (Brimica™)	✓					
ICS/ LABA	• fluticasone propionate/salmeterol (Seretide™) • budesonide/eformoterol (Symbicort™)	• fluticasone furoate/vilanterol (Breo™)	✓	✓	✓			

Relievers

SABA


Ventolin® MDI


Asmol® MDI


#Airomir™ MDI


Airomir™ Autohaler®

SAMA


Bricanyl® Turbuhaler®


Atrovent® MDI

Maintenance

LAMA

Spiriva® HandiHaler®


Spiriva® Respimat®

Seebri® Breezhaler®

Bretaris® Genuair®


Incruse® Ellipta®

LAMA/LABA

Ultibro® Breezhaler®


Spiolto® Respimat®


Anoro® Ellipta®

Brimica® Genuair®

ICS/LABA


Symbicort® Turbuhaler®


Symbicort® Rapihaler™


Seretide® Accuhaler®


Seretide® MDI

ICS *(For patients with COPD and Asthma)*


**Flixotide® MDI*


**Flixotide® Accuhaler®*


**QVAR® MDI*


**Pulmicort® Turbuhaler®*


**Alvesco® MDI*

LABA


Onbrez® Breezhaler®


**Foradile® Aerolizer®*


**Oxis® Turbuhaler®*


**Serevent® Accuhaler®*


Breo® Ellipta®

ICS/LABA


**Flutiform® MDI*

Notes: *• Handihaler, Breezhaler and Aerolizer devices require a capsule to be loaded into the device. All other devices are preloaded. • Spacers are recommended to be used with metered dose inhalers (MDI) • ICS monotherapy is not indicated for COPD without asthma • #Not PBS listed • *PBS listed for asthma only*

Flare Up Medicines

1. Antibiotics 2. Oral steroids (Prednisone, Prednisolone)

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Attachment 3

Summary of Clinical Outcomes compared in recent PBAC submissions of inhaled therapies for COPD

Product	Basis of PBS listing^	Duration of clinical trials comprising evidence[#]	Clinical outcomes compared[#]
LAMA			
Tiotropium (Spiriva Handihaler)	Cost-effectiveness to ipratropium	Not available	Not available
Tiotropium (Spiriva Respimat)	Cost-minimisation to tiotropium	4 weeks-2.3 years	Trough FEV_1, cardiovascular morbidity, exacerbations, adverse events
Aclidinium (Bretaris Genuair)	Cost-minimisation to tiotropium	6-24 weeks 52 weeks	Trough FEV_1 (6 & 12 weeks), adverse events SGRQ, exacerbations
Umeclidinium (Incruse Ellipta)	Cost-minimisation to tiotropium	12-24 weeks	Trough FEV_1 (12 & 24 weeks),TDI focal score, rescue medication, SGRQ, adverse events
Glycopyrronium (Seebri Breezhaler)	Cost-minimisation to tiotropium	12 weeks	Trough FEV_1 (12 weeks), adverse events
LABA			
Indacaterol (Onbrez Breezhaler)	Cost minimisation to fluticasone with salmeterol and tiotropium	12-26 weeks	Trough FEV_1 (12 weeks), adverse events
LAMA/ LABA			
Umeclidinium/ vilanterol (Anoro Ellipta)	Cost-minimisation to indacaterol and tiotropium with an adjustment to account for efficacy being less than the sum of components	24 weeks	Trough FEV_1 (12 and 24 weeks), adverse event data
Glycopyrronium/ indacaterol (Ultibro Breezhaler)	Cost-minimisation to umeclidinium/ vilanterol	4-64 weeks	Trough FEV_1 (4 weeks, 12 weeks), adverse event data
Tiotropium/ olodaterol (Spiolto Respimat)	Cost-minimisation to umeclidinium/ vilanterol and glycopyrronium/ indacaterol.	12-52 weeks	Trough FEV_1 (24 weeks), exacerbations, adverse event data
Aclidinium/ eformoterol (Brimica Genuair)	cost-minimisation basis to the existing LAMA/LABA fixed dose combinations, umeclidinium with vilanterol, and glycopyrronium with indacaterol.	24 weeks	Trough FEV_1 (24 weeks), adverse events

ICS/ LABA			
Budesonide/ eformoterol (Symbicort)*	Cost-minimisation to Seretide Rapihaler cost-minimised to Turbuhaler.	6 months-1 year	Pre- and post- dose FEV_1, SGRQ, rate of exacerbations, adverse events
Fluticasone/ salmeterol (Seretide)*	Cost-minimised to tiotropium MDI cost-minimised to Accuhaler	3 weeks -102 weeks	Exacerbations All cause mortality
Fluticasone/ vilanterol (Breo Ellipta)*	Cost-minimised to Seretide	12 weeks	Trough FEV_1, $FEV_{0\text{-}24hrs}$, SGRQ, EQ-5D, adverse events

*COPD only; #Based on Public Summary Documents;^based on Therapeutic Relativity Sheets. Abbreviations: FEV_1 forced expiratory volume in 1 second; SGRQ St George Respiratory Questionnaire; TDI Total Dyspnoea Index; EQ-5D EuroQoL questionnaire