LUNG FOUNDATION AUSTRALIA
"When you can't breathe...nothing else matters"

The Thoracic Society of Australia & New Zealand
LEADERS IN LUNG HEALTH

Post-market review of COPD medicines

Joint submission from Lung Foundation Australia (LFA) and Thoracic Society of Australia and New Zealand (TSANZ)

EXECUTIVE SUMMARY

- ***With the addition of new medicines for the treatment of COPD, there is no longer a 'one size fits all' management pathway for people with COPD. Rather, choice is available to suit severity and ability to tolerate individual medicines.***

- ***A simple approach to pharmacotherapy is required in COPD. In essence a step-up (or stepwise) approach with the aim of managing symptoms as they worsen. Attention also needs to be focused on comorbidities so these are acknowledged and treated.***

- ***The evidence supporting the new medicines is not widely known or understood by primary care clinicians. This has the potential to lead to considerable confusion about what medicine to use and when to use it. This lack of knowledge can lead to prescribing issues such as co-prescribing in the same class (eg. doubling up on a LAMA).***

- ***With the new medicines comes the corresponding range of inhaler devices. There is also a lack of understanding of how to use these new devices and importantly how to demonstrate correct use to patients.***

- ***Any cost-effectiveness analysis of COPD must assess the totality of the illness experience, (e.g. costs, quality of life, health care utilisation such as exacerbations and hospitalisations). We would reject any cost-effectiveness analysis that does not include measurement of both direct and indirect costs.***

- ***Education is needed and the LFA and TSANZ have a range of clinical training and resource options available. There are opportunities to work with primary care clinicians, organisations and government to deliver this education more broadly.***

- ***Accurate diagnosis with Spirometry is critical to ensure appropriate prescription of medicines.***

- ***Pulmonary Rehabilitation plays an important role in educating patients about the role of medicines and device usage.***

COPD affects as many as or one in seven or nearly 15% of Australians aged 40 or over [1]. The data suggest that 7.5% of Australians aged 40 or over have COPD that has progressed sufficiently to the stage where symptoms may already be present and affecting daily life. Half of these people will not know they have the condition [2].

Those with COPD experience significant disability as a result of their symptoms, particularly breathlessness. As disease progresses and patients become more breathless, they avoid activities that make them breathless. This leads to further deconditioning and even more severe breathlessness. This downward spiral continues until even simple activities of daily living, like making the bed and hanging the laundry or simply playing with children or grandchildren, can become impossible. COPD also has a significant impact on our hospitals, representing the second leading cause of avoidable hospital admissions nationally [3].

However, much can be done to improve quality of life, increase exercise capacity, and reduce morbidity and mortality in individuals with COPD.

Lung Foundation Australia (LFA) is a national organisation that works to reduce the impact of lung disease in Australia. We support patients, focus on research, develop education, train health professionals, and undertake community awareness activity and advocacy around Australia. All activities take an evidence-based approach.

The Thoracic Society of Australia and New Zealand (TSANZ) is the peak body representing all professional groups with an interest in improving knowledge and understanding of lung disease across Australia and New Zealand. It leads and supports all health care workers who aim to prevent, cure and relieve disability caused by lung disease.

Together we have a strong interest and proven experience in developing evidence-based guidelines and position statements for the clinical community. In particular we manage the Australian and New Zealand Guidelines for the diagnosis and management of COPD, *The COPD-X Plan: Australian and New Zealand Guidelines for the Management of Chronic Obstructive Pulmonary Disease*. In addition we have developed a suite of resources/decision support tools that translate the COPD guidelines and promote best practice across the care continuum.

We welcome the review of the PBS listed COPD medicines, with an emphasis on the quality use of medicines. With this solid focus, the review provides the opportunity to explore inconsistencies against the current evidence, and importantly recommend strategies to limit these. We are in favour of any work that concentrates on improving symptoms and clinical outcomes for people living with COPD.

We work with a broad range of clinical experts and, in developing this submission, have utilised the expertise of members of the LFA COPD-X Guideline and Executive Committees and TSANZ members, listed below. We have also included [redacted] story to provide your group with the critical insights of a person living with COPD.

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Yours faithfully,

Heather Allan, CEO,
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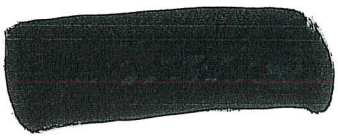

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Response to COPD Medicines review

The aim of pharmacological intervention in COPD is to treat symptoms such as breathlessness and to prevent deterioration (by decreasing exacerbations, reducing decline in lung function or quality of life). COPD medicines are divided into classes, each class having a designated function in disease management. A stepwise approach is recommended, irrespective of disease severity, until adequate control has been achieved.

In recent years, there has been a significant increase in the number of medicines and devices available for COPD management.

This increase in COPD medicines provides greater choice in management options for the prescriber and for the patient. The prescriber now has a range of options to best match the clinically indicated medicine to the patient's specific requirements and ability to tolerate individual medications' side effects. Each class of medication has a different side-effect profile, and although there are also some within-class differences, these tend to be small. In addition to medication preferences, different delivery mechanisms will suit different patients' abilities. A broader range of medicines can result in better outcomes for patients, as it can lead to greater adherence to prescribed pharmacotherapy, which is crucial in management of any disease process.

The recent increase in medicine options, however, has resulted in confusion amongst clinicians. This is particularly apparent in primary care where knowledge of the Australian COPD-X Guidelines is low. Primary Care clinician understanding of how to use the range of new devices is also low, making it difficult for them to teach their patients how to use them. Greater education for clinicians is an important step to ensuring adherence to evidence-based recommendations, thus facilitating better outcomes for patients.

Optimal management in primary care is necessary not only to improve symptom control, but to reduce exacerbations and preventable hospitalisations. A vast amount of work has already been undertaken by both LFA and TSANZ to drive evidence-based management of COPD, through the regularly updated *COPD-X Plan: Australian and New Zealand Guidelines for the Management of Chronic Obstructive Pulmonary Disease (COPD)*. Through this submission, reference is made to the COPD-X Plan, and the resources derived from it, *Stepwise Management of Stable COPD*, *COPD-X: Concise Guide for Primary Care*. For further information on these resources, refer to the section titled 'LFA and TSANZ investment in evidence-based COPD management'.

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TERMS OF REFERENCE RESPONSE

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

Long-acting bronchodilators (LAMAs and LABAs) are available on PBS for treatment of symptomatic COPD.
These medications are available as monotherapies or as fixed dose combinations (LAMA/LABA or LABA/ICS). Tiotropium has been available in Australia for many years, but a number of newer agents have recently become available. These include the LAMAs aclidinium, glycopyrronium and umeclidinium; and the LABAs indacaterol, olodaterol and vilanterol (the latter only available to use in combination with either a LAMA or an inhaled corticosteroid. A description of the relative efficacy of these medications is found below (see also review of safety and efficacy).

The PBS recommends that patients must have been stabilised on a combination of a LAMA and LABA before being prescribed a fixed dose combination.

This is overly restrictive. It is important to note that patients with COPD are virtually always symptomatic, even on optimal pharmacotherapy. Controversy remains regarding the relative benefits of dual versus mono-bronchodilator therapy for COPD. LAMAs as a class are effective in reducing symptoms, improving lung function and exercise capacity, and in reducing exacerbations. In a systematic review and in many individual RCTs, additional bronchodilation (as measured by FEV_1), when a LAMA is added to a LABA, and vice versa, has been demonstrated. However the effect of dual bronchodilators on FEV_1 is not additive and is not always reflected in patient reported outcomes such as quality of life. Nevertheless, on average dual bronchodilation produces an 80-150ml improvement in FEV_1, which is clinically meaningful in COPD patients. Within studies, it is clear that while on average there are benefits, this is not universal. Patients should therefore be trialled on, but not assumed to do better on, both compared to one class of bronchodilator.

To improve adherence and achieve a potentially better outcome, it would be logical to step up, trial and reassess response of dual (LAMA+LABA) bronchodilators in one device rather than two separate devices [4], [5]. Furthermore, the requirement to add a second inhaler device has the potential to lead to greater nonadherence and potential confusion for the patient and clinician in how to use the new device. The intermediate step of two separate inhalers, followed by a third is cumbersome and requires an additional visit to the prescriber and again the need to re-educate about yet another different device.

Costs and benefits of the fixed dose combinations (FDC) relative to their mono-components may, of course be relevant here, but we do not have these data.

ICS/LABA combinations
The PBS prescribing restrictions state combination therapies of ICS/LABA +/- LAMA for symptomatic treatment of COPD in patients with a forced expiratory volume in one second (FEV_1) less than 50% of predicted normal prior to therapy, AND a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy.

This is consistent with several studies of ICS-LABA vs LABA alone [6], [4], [7], [8] where, combination ICS-LABA conferred the greatest reduction in exacerbations in those with FEV_1 <50%. More recently there is published RCT evidence that patients with peripheral eosinophilia are those most likely to benefit from ICS, and that those who do not have this feature do not deteriorate when ICS are removed [9], [10], [11]. Further RCTs are required to confirm these findings, but as high dose ICS are associated with increased risk of pneumonia and lower RTI, it is likely that many patients will be optimally managed without ICS, but on dual bronchodilators alone. These and other studies highlight the need to differentiate different patient "phenotypes" in choosing optimal COPD pharmacotherapy. Easily applied biomarkers such as peripheral eosinophilia may be applied in future to assist with this.

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Note TGA indications are different and suggest an FEV_1 cut-off of 70% defines patients who would potentially benefit from ICS. This is reflected in MIMS where indication for combination treatment is COPD with FEV_1 < 70% predicted normal with repeated exacerbations despite regular beta2-agonists. In subgroup analyses of several papers examining the role of ICS, there is evidence that they may benefit patients who exacerbate, but have higher FEV_1 values [12], [13]. More RCTs are required to confirm this, and the interaction, if any between FEV_1 and eosinophilia in identifying patients most likely to benefit from ICS.

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.

LFA is unable to comment specifically on the evidence that has been provided previously to the PBAC on cost- effectiveness of COPD medicines, however clinical trial end-points in recently reported COPD trials usually include a number of physiological, clinical and patient-reported outcome measures such as lung function (principally FEV_1), dyspnoea, exercise capacity, physical activity, exacerbations, health status and mortality.

There has been considerable debate in the scientific community about the most relevant outcomes and measures that should be used with consideration given to the feasibility, strengths and limitations [14] of many of the more common measures.

Although the presence of airflow limitation, as measured by lung function tests, is mandated in order to confirm a diagnosis, COPD is a complex disorder and requires a multifaceted approach with regard to clinical assessment and response to therapy. Therefore multiple clinical trial endpoints are required to adequately reflect the success or failure of treatment. These include measures of functional capacity (eg TDI and 6MWT), symptom burden (eg CAT and SGRQ), and exacerbation rate as well as lung function parameters such as FEV_1.

Multidimensional scoring systems such as the BODE index which incorporate nutritional state (**B**MI), airflow limitation (**O**bstruction; FEV_1), breathlessness (MRC **D**yspnoea scale), and **E**xercise capacity (6MWD, distance walked in 6 minutes) also have their limitations. Although some have been validated as prognostic markers in a population of patients affected by mild-to-moderate COPD, there is lack of experience with their use in pharmacological intervention studies.

Since the aim of pharmacological intervention in COPD is to treat symptoms (eg. breathlessness) and prevent deterioration (either by decreasing exacerbations or by reducing decline in quality of life) [4] then these outcomes perhaps should be given higher priority than lung function measures when assessing treatments and management strategies for people with COPD. It is these measures that are also likely to be of more importance to people with COPD (so-called 'patient-reported outcomes'). Despite the widespread use of the FEV_1, it is poorly correlated with many of these outcomes [15], [16] and in addition is poorly responsive to treatment. It is a paradox that FEV_1 is so widely applied as a primary outcome in COPD studies, for a disease which, by definition, is characterized as having poorly reversible airflow limitation.

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.

The COPD-X guidelines cite recent studies of the efficacy and safety of these inhaled medicines in COPD. These are summarised below, with conclusions from studies and wording from the COPD-X guidelines included as appropriate:

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Efficacy:
Recent studies indicate that:
- LABA monotherapy has been shown to improve quality of life and lung function, and to have some benefit for exacerbation rates. For example, compared to placebo, indacaterol improves dyspnoea, FEV_1 and health-related quality of life, and reduces exacerbations [17]. Compared with twice daily beta-agonists (salmeterol, formoterol and eformoterol), indaceterol did not lead to a clinically significant difference in FEV_1, dyspnea or quality of life [17].

- LAMA monotherapy improves quality of life and lung function and, for some LAMAs, reduces exacerbations. This has been demonstrated for tiotropium, as summarised in a Cochrane systematic review [18]. A network meta-analysis showed that LAMAs have similar efficacy in terms of change in FEV_1, St. Georges Respiratory Questionnaire (SGRQ), dyspnoea index and rescue medications [19]. However, direct head to head comparisons are mostly not available, meaning that choice of LAMA inhaler depends on patient and clinician preferences.

- LAMA/LABA dual bronchodilator therapy, in various forms, has been shown in a wide rnage of RCTs to have beneficial effects on lung function, quality of life and (in some studies) exacerbations (see multiple studies cited in O1.2.3 Long-acting bronchodilator combinations (LAMA/LABA), in COPD-X). Adding tiotropium to LABAs provided small benefits, as shown in a Cochrane systematic review [20]. A network meta-analysis of LAMA/LABA combinations compared with monotherapies found that the fixed dose combinations provided small benefits in lung function and quality of life compared with their monocomponents, with no increase in adverse outcomes. LAMA/LABA therapy reduced moderate to severe exacerbations compared with LABA alone but not compared with LAMA alone. Effects on severe exacerbations were similar with both combination and monotherapies [21].

- ICS/LABA therapy has some benefits over each monocomponent, and significant benefits over placebo. A systematic review of 19 randomisedcontrolled trials (involving 10,400 COPD patients) of combined corticosteroids and long-acting beta2-agonists in one inhaler [22] found that, compared with placebo, both fluticasone/salmeterol and budesonide/formoterol reduced the rate of exacerbations (rate ratio 0.73; 95% CI 0.69 to 0.78). It was estimated that treatment with combined therapy would lead to a reduction of one exacerbation every two to four years. The three-year number needed to treat for an additional beneficial outcome (NNTB) with fluticasone/salmeterol to prevent one extra death was estimated at 42 (95% CI 24 to 775). Combined treatments improved health status to a small extent and improved lung function. Increased risk of pneumonia was observed with combined treatments compared with placebo (OR 1.62, 95% CI 1.36 to 1.94), with a three-year NNTH for one additional case of pneumonia estimated to be 17. However, exacerbations, hospitalisations or deaths did not increase. Overall, the authors concluded that there were no major differences between combined inhalers in terms of benefits, but the evidence was currently not strong enough to demonstrate that all are equivalent [22].

- ICS/LABA+LAMA therapy has been considered generally beneficial to some extent, although previous studies have not been entirely conclusive. The GLISTEN three arm study compared the addition of glycopyrronium or tiotropium or placebo to salmeterol/fluticasone propionate. The addition of either of the LAMAs demonstrated statistically significant improvements to FEV_1 (101ml at 12 weeks), a statistically but not clinically significant change in health status (2.15 units SGRQ) and reduced rescue medications (less than one puff per day) [23].

Safety:
- LABA monotherapy has generally been shown to be safe in COPD (in contrast to asthma, where LABA monotherapy should not be used), although there are relatively few large, long term studies.

- LAMA monotherapy has a good safety profile. Dry mouth and dyspepsia were the most common adverse events with tiotropium, each occurring in 4% of patients [24]. Cardiovascular safety was found to be similar between the Spiriva (tiotropium) Handihaler (18 mcg daily) and Respimat inhalers (2.5 mcg or 5 mcg daily) in a large RCT [25]. Long term safety data for other LAMAs are more limited.

- LAMA/LABA dual bronchodilator therapy has been shown to have similar safety profile to the monocomponents, in a range of RCTs (see multiple studies cited in O1.2.3 Long-acting bronchodilator combinations (LAMA/LABA), in COPD-X).

- ICS/LABA therapy and ICS/LABA+LAMA therapy: the main safety signals have been in relation to increased risk of pneumonia (please see below, for Prolonged ICS use).

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.

The COPD-X guidelines cite recent studies of the efficacy and safety of inhaled corticosteroids (ICS) in COPD. These are summarised below, with conclusions from studies and wording from the COPD-X guidelines included as appropriate:

ICS monotherapy is not indicated in COPD. In patients with coexisting asthma and COPD, ICS monotherapy can sometimes be used together with LAMA, LABA or LAMA/LABA fixed dose combination inhalers (as the ICS would be indicated for asthma).

ICS/LABA combination therapy is indicated for COPD patients with FEV_1 <50% predicted and frequent exacerbations, and has benefits for quality of life and exacerbations. Regarding safety, a Cochrane systematic review of 43 COPD studies (26 fluticasone studies, n =21,247; 17 budesonide studies, n = 10,150) has demonstrated an increased risk of pneumonia with use of inhaled corticosteroids, when given as monocomponents or in combination inhalers [26]. Non-fatal serious adverse pneumonia events (i.e. requiring hospital admission) were increased with fluticasone (OR 1.78, 95%CI 1.50 to 2.12) and budesonide (OR 1.62, 95% CI 1.00 to 2.62). There were no significant differences in serious adverse events or mortality when budesonide and fluticasone were compared indirectly. The risk of any pneumonia event was found to be higher with fluticasone than budesonide (OR 1.86, 95%CI 1.04 to 3.34), but this should be interpreted with caution due to differences in definitions of pneumonia in the trials. The authors recommended that safety concerns regarding increased pneumonia should be balanced against the benefits of reduced exacerbations and improved quality of life [26].

Withdrawal of ICS treatment in COPD patients has recently been studied in a large RCT. The 12 month Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trial studied patients with severe COPD who were stable on triple therapy (tiotropium, fluticasone propionate and salmeterol). Staged withdrawal of fluticasone propionate over 12 weeks was compared to continuation of fluticasone propionate, plus salmeterol and tiotropium [27]. 2,495 COPD patients with FEV_1 <50% predicted and a history of at least one exacerbation in the last 12 months were studied. The hazard ratio for the first COPD exacerbation that was moderate or severe was 1.06 with ICS withdrawal (95% CI 0.94 to 1.19) which was below the upper limit of the non-inferiority margin for the primary outcomes of exacerbation of 1.20. The mean reduction in FEV_1 was 43ml greater in the ICS withdrawal group at 52 weeks, which was statistically significant. At 52 weeks there was no statistically different significance in a mMRC dyspnoea score, and there was a small difference in change in SGRQ score, favouring ICS continuation. Although the authors concluded that in patients with severe COPD withdrawal of ICS in a tapered fashion was non-inferior to continuation of ICS, there were statistically significant reductions in FEV_1 and quality of life which may be clinically relevant to some patients (i.e. there may be a potential for adverse effects when withdrawing ICS in some patients).

Commentary regarding the study design of the WISDOM study includes the fact that only 39% of patients were already on long-term ICS/LABA+LAMA therapy when recruited for the trial; the remaining patients (61%) were commenced on triple therapy during the 6 week run-in, so may not necessarily be considered long-term users of triple therapy. This critical appraisal consideration should be taken into account when interpreting the results of this study.

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The COPD-X plan does not specifically recommend systematic withdrawal of ICS at present, given the uncertainty about the evidence (described above). Nevertheless, withdrawal of ICS is one of the options for clinicians and patients, and therefore the COPD-X guidelines include a comment stating that individual patient follow-up is recommended if the clinician and patient decide to withdraw ICS. Based on the current literature and expert opinion, withdrawal of ICS could be contemplated in COPD patients who develop pneumonia (since the ICS component may contribute to increased risk of pneumonia), or in patients who do not have frequent exacerbations (however, it is not clear from the literature or expert opinion as to whether the ICS component therefore has had benefit in reducing exacerbations in an individual patients and could be beneficial to continue, in order to maintain prevention of exacerbations). We would recommend that clinicians continue to adhere to the Stepwise Guide recommendation of 'considering ICS/LABA for COPD patients with FEV_1 <50% predicted and frequent exacerbations'.

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.

This is an important issue regarding the quality use of medicines, and appropriate adherence to guidelines and PBS indications. Whilst Lung Foundation Australia and TSANZ do not have ready access to data on current utilisation, we would be happy to comment on these if available.

We offer the following informal observations, based on the clinical experience of our COPD Committee members:

- Reliever inhalers: Firstly, a pMDI plus spacer or DPI is preferable in appropriate doses to nebulizers for maintenance medication and reliever admin at home. With respect to inhalers, it is important for clinicians and patients to ensure that ipratropium (Atrovent) SAMA inhaler is ceased if a LAMA or LAMA/LABA inhaler is commenced. In clinical practice, we still find some patients on both ipratropium and a LAMA inhaler at the same, which increases risk of adverse effects. The Stepwise guide provides an alert for clinicians: ***Once a LAMA is commenced, ipratropium (a SAMA) should be discontinued.***

- LABA: The one PBS-listed LABA (indacaterol) is generally appropriately used in COPD patients. Fortunately, there has not been widespread use of this LABA as therapy in asthma patients, which would be contraindicated. The Stepwise guide provides an alert for clinicians: ***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.***

- LAMA: The four LAMA inhalers are generally appropriately used in COPD patients, with tiotropium (Spiriva) Handihaler being the most widely used LAMA inhaler, available for many years now. There does not appear to be widespread use of LAMA inhalers in patients with asthma alone. Patients with chronic asthma characterised with chronic non-reversible airflow obstruction (fulfilling the definition of 'COPD') would technically qualify for use of a LAMA for this chronic airflow limitation, and there are some patients in this category who are prescribed LAMA inhalers. We recognise that an indication for LAMA therapy for asthma has been approved by the PBAC.
- Also seeing more of co-prescribing in Primary Care, ie two LABAs or two LAMAs particularly when the LABA is contained in a LABA-ICS as well. GPs may not even be aware that they are double prescribing and certainly reinforces the need for education about the appropriate use of new drugs.

- LAMA/LABA: This has been the most recent change in the PBS-listed medications for COPD. Our observations are that there is increasing use of LAMA/LABA inhalers, with a number of different routes leading to PBS authority streamline prescription e.g. (i) use of LABA, then addition of separate LAMA, then LAMA/LABA; (ii) use of LAMA, then addition of separate LABA, then LAMA/LABA; (iii) provision of a sample of a LAMA/LABA inhaler to the patient by the clinician, in

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order to 'stabilise' use, then formal prescription of the LAMA/LABA. There may be an opportunity to further optimise the prescription of LAMA/LABA inhalers. As noted above, the evidence does not yet define the sequence that should be taken towards LAMA/LABA prescription e.g. LAMA monotherapy first, or LABA monotherapy first, or then addition of these (or trial of the other class), or moving straight to a LAMA/LABA fixed dose combination inhaler after trialing one or more of the monocomponents. There does not appear to be widespread use of LAMA/LABA inhalers in patients with asthma alone. The Stepwise guide provides an alert for clinicians: ***If starting a fixed dose LAMA/LABA combination inhaler, discontinue existing inhalers containing a LAMA or LABA.***

- ICS: These are not indicated as monotherapy of COPD alone (i.e. without other long-acting inhalers such as LABA and/or LAMA inhalers). Generally we have not observed use of ICS monotherapy as initial therapy for COPD, since many patients (depending on their COPD severity) are commenced on a LAMA, LABA or (if severe) ICS/LABA. However, for patients with severe COPD and frequent exacerbations who are on a LAMA/LABA inhaler, some of these patients may be prescribed an inhaled steroid inhaler (e.g. ciclesonide, fluticasone or budesonide) to treat an asthma component. For this reason, we have included inhaled steroids in the images of inhalers in the Stepwise guide, to assist clinicians and patients in recognising these inhalers. It is possible that some COPD patients, without asthma, may be prescribed a LAMA/LABA and an inhaled steroid inhaler, even though they do not have asthma. The Stepwise guide provides an alert for clinicians: ***ICS monotherapy is not indicated for COPD without asthma.***

- ICS/LABA: The questions remains as to whether overprescribing of ICS/LABA is occurring in patients with COPD, who do not meet the spirometry criteria for severity, and the exacerbation frequency criteria. The PBS indication for ICS/LABA in COPD is clear, and this is stated in the Stepwise guide: ***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.*** A number of patients are on ICS / LABA because they have been given a diagnosis of asthma in the past (either confirmed or unconfirmed) but subsequent objective testing shows they have fixed airflow limitation and meet spirometric criteria for COPD (but not severe COPD) but clinicians are still uncertain as to whether they have asthma so remain on the ICS. The Stepwise guide also provides an alert for clinicians: ***If starting an ICS/LABA combination inhaler, discontinue existing inhalers containing a LABA.***

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.

Cost-effectiveness is an important consideration for any therapeutic intervention, in addition to clinical cost-benefit ratios. The COPD-X guidelines focus on the clinical aspects of diagnosis and management, and do not currently include information specifically on cost-effectiveness. This is because cost-effectiveness data for Australia are not widely available, and even internationally there are few publications relating to the cost effectiveness of COPD medications. In-house industry data on cost-effectiveness are not usually available in the public domain.

We strongly believe that a cost-effectiveness analysis can only be justified if it assesses the totality of the illness experience. It must accurately measure both direct and indirect costs and benefits (e.g. costs, quality of life, health care utilization such as exacerbations and hospitalisations etc). An approach that excludes indirect costs is fatally flawed as it denies much of the illness experience and costs that our patients suffer. We would reject any cost-effectiveness analysis in COPD that does not include both direct and indirect costs.

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Additional SIGNIFICANT ISSUES in COPD Management:

Diagnosis and Spirometry

Any discussion about the appropriate use of COPD medications should include mention of the continuing under-use of spirometry to confirm a diagnosis of COPD and therefore guide appropriate prescription of medication.

Recent population studies and clinical experience suggest that there is continuing inaccuracy in the diagnosis of airways disease, both asthma and COPD. This has been observed both in Australia and in similar settings internationally. At least part of this is due to low levels of performance of spirometry in primary care, and a tendency to diagnose airways disease clinically – or even empirically on the basis of a symptom improvement in response to treatment. Thus the natural resolution of post RTI (Respiratory Tract Infections) symptoms is put down to inhalers prescribed at the time (eg Inhaled Corticosteroid (ICS)/Long-acting Beta Agonists (LABA), and interpreted as a diagnosis and a reason for continuing prescription.

[redacted] Story: Diagnosis

In 2003 I began to experience subtle symptoms which belied the seriousness of the condition that I now live with. I was told I had COPD and had lost more than 25 per cent of my lung capacity. Fast forward to 2011, when I was eight years older, and despite all my bravado and self -deception, I was forced by events to confront reality. My breathing was now considerably worse and beginning to impact my everyday living. Things began to take longer to do. Everyday activities like fishing, gardening, playing with grandchildren were becoming a chore. Planning physical activity became a necessary part of every day to avoid increasing tiredness and the need to rest. I worked hard to hide the worst of my symptoms from my greatest supporter and most severe critic, my significant other. Work responsibilities also began to bear down on me as the disability spiral kicked up a gear. With another breathing test result now showing a 50 per cent loss of predicted capacity, I faced reality and my own mortality squarely in the eye for the very first time. I also set a firm retirement date.

The Australian BOLD data indicated that 30% of respondents who stated that their GP had told them they had COPD, did not have obstructive spirometry consistent with this diagnosis at the time of the study [1]. On the other hand, there are consistent and reasonable concerns that COPD is underdiagnosed in another group of patients who generally present late either with an acute exacerbation [28], or with moderately severe exertional dyspnea [29], by which time over 50% of their lung function has been lost. There are strong arguments therefore for earlier and more accurate detection of airways disease. The crucial issue in favour of early diagnosis concerns the availability of useful interventions that would alter the course of the disease were the patient diagnosed accurately and treated appropriately [4].

Guidelines are unequivocal in stating the requirement for spirometry to diagnose airways disease:

> The GOLD strategy/guidelines [30] state, "A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis in this clinical context, the presence of a postbronchodilator FEV_1 /FVC <0.7 confirms the presence of persistent airflow limitation and thus of COPD."
>
> The COPD-X Concise [31] guide for primary care states "The diagnosis of COPD requires spirometry to measure the presence of persistent airflow limitation (postbronchodilator FEV_1/FVC <0.7) since spirometry is the most reproducible and objective measurement of airflow limitation available." Further the concise guide states that COPD cannot be diagnosed reliably on clinical features and/or chest x-ray findings alone. "

Accurate diagnosis of COPD should be the first step, prior to regular medication prescription, and essential to ensure patients are prescribed the most effective and appropriate medications. Clinical assessment and spirometry together facilitate:

- Timely initiation of pharmacotherapy to address symptoms
- Appropriate additional treatment to prevent exacerbations and possible hospitalizations
- Minimising unnecessary use of ICS
- Appropriate initiation of non-pharmacologic management such as pulmonary rehabilitation, maintenance of physical activity, and influenza vaccination

Access to Pulmonary Rehabilitation

Pulmonary rehabilitation is a highly effective evidence-based intervention for people with COPD. Pulmonary rehabilitation programs have been shown to help people breathe easier, improve their quality of life and stay out of hospital.

Pulmonary rehabilitation consists of education and supervised exercise training. The exercise component aims to reverse the disability spiral experienced by COPD patients. The education component aims to facilitate good patient self-management, including understanding medications and how to use them appropriately. Studies show that 90% of those using inhaled medications are not using their devices appropriately and are, therefore, not maximizing the benefits of the medication. Despite the value of education, in randomisedcontrolled trials it is the exercise component that makes the difference in terms of improved exercise capacity, symptoms and health status.

After completing pulmonary rehabilitation many patients find that they have better health outcomes and can resume activities that they had previously given up. In Australia there is currently a patient population of approximately 750,000 who would benefit from pulmonary rehabilitation. Lung Foundation Australia estimates the current number of programs available only service approximately 5% of these patients.

[redacted] Story: Pulmonary Rehabilitation & exercise

I began pulmonary rehabilitation at the [redacted] Hospital along with eight or so patients from a cross section of the community in terms of age and background. For those not familiar with these programs, they typically comprise an initial assessment, a review of individual physical capability based on age or disability, followed by an eight week, twice weekly class including tailored gym exercise for an hour. This is usually followed by half an hour of plain language education sessions covering a variety of topics like lung pathology, understanding medication, diet, breathing techniques and management of anxiety. I could only admire and be totally impressed by the skill, commitment and care shown by this small group of health professionals.

Once the eight week pulmonary rehabilitation program was finished, the group was urged to 'maintain the gain' at weekly community group-based pulmonary maintenance exercise classes. The class I joined was held in the YMCA and called "Lungs in Action" – a Lung Foundation Australia program which can be found in communities right across Australia. I religiously attend this class twice weekly and I believe this is one of the most critical factors in maintaining good health for people with COPD. Evidence points to exercise being more beneficial or effective than most prescribed medications. Invariably, I feel better after a class, no matter how little I feel like going on the days when my symptoms or poor sleep tell me otherwise. It's taught me not to be too hard on myself. Living with COPD is a day to day proposition. I believe in doing what I can and being honest with myself. If I am breathless I always remember that in a while I will recover. To those who have asked me if they will feel better after exercise class, I usually say that if they do not attend, I can almost guarantee they will feel worse.

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Together with smoking cessation, pulmonary rehabilitation is one of the most evidence based interventions for people living with chronic lung disease. A Cochrane review [32] identified that it reduces hospital admissions and average length of stay, with the numbers needed to treat (NNT) with pulmonary rehabilitation to avoid one hospital admission, just four. Hence this intervention may have greater impact and be more cost effective than many pharmacotherapeutic options. NHMRC Level I & II [33], [34], [35], [36], [37], [32], [38] evidence to support the benefits:

- Reduces hospital admissions and length of stay
- Reduces re-admissions post exacerbation
- Reduces mortality
- Improves symptoms of anxiety and depression
- Increases quality of life and functional exercise capacity

Evidence also shows that continuing with a supervised pulmonary maintenance exercise program after completion of a pulmonary rehabilitation will extend the benefits of pulmonary rehabilitation [36].

Currently we are developing Pulmonary Rehabilitation guidelines. The guidelines will provide guidance and support consistency in translating this evidence based intervention in clinical practice.

[redacted] Story: This is now...

I am now more than twelve years post diagnosis and after completing pulmonary rehabilitation and commencing my volunteer work with Lung Foundation Australia, I can look back with some satisfaction at where I am and what I have achieved. My COPD is stable, despite having suffered a couple of exacerbations over the last couple of years while travelling overseas. Fortunately the exacerbations have not significantly reduced my lung capacity. The fact that I have travelled at all is testimony to the fact that there is life after diagnosis and my commitment to maintenance exercise and close attention to medication and preventative measures plays no small role in that. I repeated pulmonary rehabilitation after my first flare up and continue to learn more about lung disease. I have completed a clinical medication trial and will continue to look for further tests or trials in which I can participate. I have also informally counselled others who approached me to help them better understand their condition and recalled my experiences on a similar journey of discovery.

LFA and TSANZ investment in evidence-based COPD management:

COPD-X guidelines development

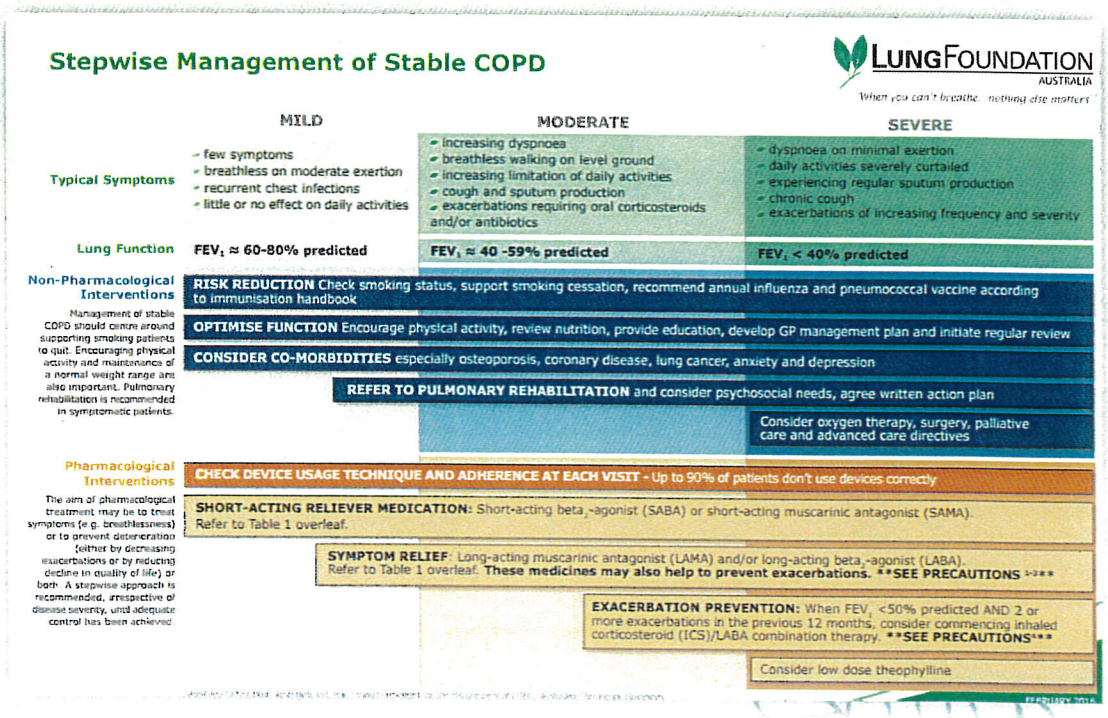
Over the years, Lung Foundation Australia has invested several million dollars in the development of the COPD-X clinical guidelines. This level of resource is required to manage a robust guideline process that ensures the regular production of a high-quality clinical resource. The Guidelines are prepared by Lung Foundation Australia's COPD Guidelines Committee, which consists of eight clinical members plus executive administrative support. Conflict of Interest statements from each Committee member are recorded regularly and published on the COPD-X website. The COPD Guideline Committee systematically searches, identifies and reviews the published evidence to ensure clinical currency. The Committee meets quarterly to appraise the latest published evidence and make recommendations on updating the guidelines.

The Guidelines were initially published in 2003 in the Medical Journal of Australia [39] and a Clinical Practice Update was published in 2005 [40]. Since then, regular updates have been available on a dedicated website administered by the Lung Foundation (www.copdx.org.au), with the latest version (2.44, December 2015) recently published online.

Guideline translation, resources and training

The COPD-X plan provides the foundation for our significant range of educational resources. These resources are utilised within our extensive education program which consists of both face to face and online elements. These cater for a range of health professionals including physicians, GPs, nurses, pharmacists and other allied health professionals. To date, this work has been completed without government funding. Additional resources would enable LFA and TSANZ to increase the reach of education, training and support for clinicians.

The key resource to aid the implementation of the evidence, is the 'Stepwise Management of Stable COPD'. This has been translated from the COPD-X guidelines and provides direction on the non-pharmacological and pharmacological therapies across the disease severities, advocating the evidence-based stepwise approach to management. This resource (pictured below) has been referred to several times throughout the body of this submission.



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Alongside this table, we have visually depicted each available medicine and device in its respective class and provided a 'Guide to addition of therapies' table. This provides a clear, evidence-based guide to the classes of COPD medicines and which can and, importantly cannot, be used together.

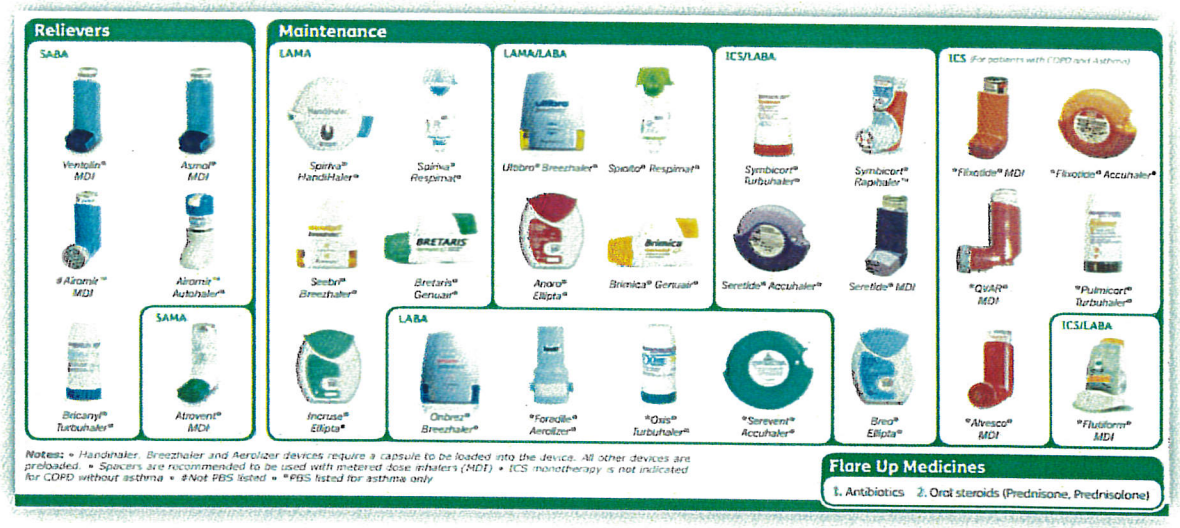


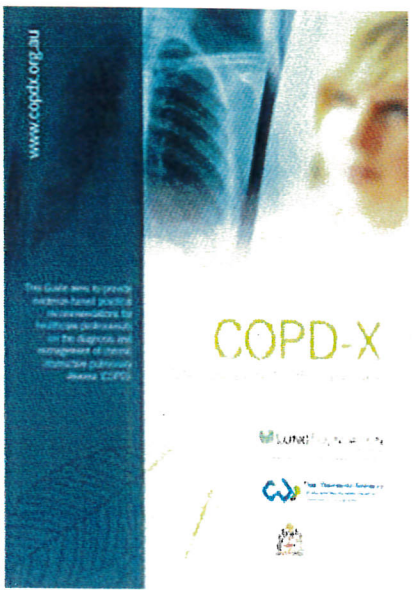
Table 1: Guide to addition of therapies

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™)	✓	✓	✓			

Additional evidence based tools have been developed, to further support the implementation of the guidelines:

a) **COPD-X Concise Guide for Primary Care**: This is designed to help busy GPs, nurses and the general practice team in the management of patients with COPD. It distils the evidence and recommendations in COPD-X to succinct recommendations and practice tips.



b) **COPD Action plan**: This action plan is for completion by the clinical in consultation with the patient. It helps the patient to recognise when their symptoms worsen and what action they need to take to manage them.

d) **Exacerbations Algorithm**: This provides health professionals with clear step-by-step instructions on how to manage COPD exacerbations and identifies when to refer to hospital.

e) **Primary Care Respiratory toolkit**: This online decision support tool includes a spirometry calculator and lung age estimator.

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