Pharmaceutical Benefits Scheme

Post-market Review of

Chronic Obstructive Pulmonary Disease Medicines

Background and ToR 1

Final Report

August 2017

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Abbreviations

ABS	Australian Bureau of Statistics
ACCP	American College of Chest Physicians
ACL	Aclidinium
ACOS	asthma-COPD overlap syndrome
ACP	American College of Physicians
adj OR	adjusted odds ratio
AE	adverse event
AECOPD	acute exacerbation of COPD
AIHW	Australian Institute for Health and Welfare
AHRQ	Agency for Healthcare Research and Quality
AHS	Australian Health Survey
ARTG	Australian Register of Therapeutic Goods
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
AUC	area under the curve
AusPAR	Australian Public Assessment Reports for prescription medicines
BC	British Columbia
BCKQ	Bristol COPD Knowledge Questionnaire
BCSS	Breathlessness Cough and Sputum Scale
BD	twice daily
BDF	budesonide/eformoterol
BDI	Baseline Dyspnea Index
BEACH	Bettering the Evaluation and Care of Health
BEC	Beclomethasone
bid	twice daily
BMI	body mass index
BNF	British National Formulary
BODE	Body-mass index, airflow Obstruction, Dyspnea, and Exercise
BOLD	Burden of Obstructive Lung Disease
BUD	Budesonide

ABS	Australian Bureau of Statistics
CADTH	Canadian Agency for Drugs and Technologies in Health
CASIS	COPD and Asthma Sleep Impact Scale
CAT	COPD Assessment Test
CCQ	Clinical COPD Questionnaire
CDEC	Canadian Drug Expert Committee
CDER	Center for Drug Evaluation and Research
CDLM	Capacity of Daily Living during the Morning questionnaire
CDR	Common Drug Review
CEA	cost-effectiveness analysis
CI	confidence interval
CID	clinically important deterioration
CMA	cost-minimisation analysis
COPD	chronic obstructive pulmonary disease
CR10	Category Rating Dyspnea Score
CRQ	Chronic Respiratory Questionnaire
CRDQ	Chronic Respiratory Disease Questionnaire
CS	Corticosteroid
CSR	clinical study report
CT	computed tomography
CTC	Canadian Thoracic Society
CVD	cardiovascular disease
DHS	Department of Human Services
DLCO	diffusing capacity of the lung for carbon monoxide
DMQ-CAT	Dyspnea Management Questionnaire Computer Adaptive Test
DoD	Department of Defense (US)
DPI	dry powder inhaler
DPMQ	Dispensed Price for Maximum Quantity
DUSC	Drug Utilisation Sub Committee
EADL	Extended Activity of Daily Living
ECG	Electrocardiogram
ED	emergency department

ABS	Australian Bureau of Statistics
EFO	Eformoterol
EMA	European Medicines Agency
EQ-5D	EuroQoL Five Dimensions Questionnaire
ERS	European Respiratory Society
E-RS	EXACT – Respiratory Symptoms
ESC	Economics Sub Committee
ESS	Epworth Sleepiness Scale
ESWT	Endurance Shuttle Walking Test
EXACT	Exacerbations of Chronic Pulmonary Disease tool
EXACT-RS	EXAcerbations of Chronic pulmonary disease Tool-Respiratory Symptoms
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEV_1	forced expiratory volume at 1 second
FF/VI	fluticasone furoate/vilanterol
FLU	fluticasone
FPS	fluticasone propionate/salmeterol
FRC	functional residual capacity
FVC	forced vital capacity
GCSQ	Global Chest Symptoms Questionnaire
GINA	Global Initiative for Asthma
G-I-N	Guidelines International Network
GLY	glycopyrronium
GOLD	Global Initiative for chronic Obstructive Lung Disease
GP	general practitioner
GSK	GlaxoSmithKline
h	hours
HADS	Hospital Anxiety and Depression Scale
HCU	healthcare utilisation
HDC	high density credibility
HH	HandiHaler
HPA	hypothalamic–pituitary–adrenal

ABS	Australian Bureau of Statistics
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
HUI	Health Utilities Index
IC	inspiratory capacity
ICS	inhaled corticosteroids
ICU	intensive care unit
IND	indacaterol
IOS	impulse oscillometry
IQR	interquartile range
ISWT	Incremental Shuttle Walking Test
ITGV	intrathoracic gas volume
ITT	intention-to-treat
IU	international units
KCE	Belgian Health Care Knowledge Centre
LABA	long-acting beta-2 agonist
LABD	long-acting inhaled brochodilator
LAMA	long-acting muscarinic antagonist
LCADL	London Chest Activities of Daily Living
LFA	Lung Foundation Australia
LINQ	Lung Information Needs Questionnaire
LOCF	last observation carried forward
LOF	length of follow up
LOS	length of stay
LRTI	lower respiratory tract infection
LS	least squares
LSMD	least squares mean difference
MA	meta-analysis
MACE	major adverse cardiovascular event
µg	microgram
MCID	minimal clinically important difference

ABS	Australian Bureau of Statistics
MDI	metered dose inhaler
MDP	Multidimensional Dyspnea Profile
MHRA	Medicines and Healthcare products Regulatory Agency
min	minutes
mMRC	modified Medical Research Council
MOM	mometasone
MP	medical practitioner
mPEF	morning peak expiratory flow
MRC	Medical Research Council
MTC	mixed treatment comparison
NA	not applicable
NAC	N-acetylcysteine
NACA	National Asthma Council Australia
NCCHTA	National Coordinating Centre for Health Technology Assessment
NGC	National Guideline Clearinghouse
NHLBI	National Heart, Lung and Blood Institute
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NHS CRD	University of York NHS Centre for Reviews and Dissemination
NHS HTA	National Health Service Health Technology Assessment (UK)
NICE	National Institute of Health and Care Excellence
NiSCI	Night time Symptoms of COPD Instrument
NNT	number needed to treat
NP	nurse practitioner
NPS	National Prescribing Service
NR	not reported
NRS	Numeric Rating Scale
ns	not significant
OCS	oral corticosteroids
OLO	olodaterol
OR	odds ratio

ABS	Australian Bureau of Statistics
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	placebo
PBS	Pharmaceutical Benefits Scheme
PDE-4	phosphodiesterase-4
PERF	peak expiratory flow rate
PES	Pharmaceutical Evaluation Section
PFSDQ	Pulmonary Functional Status and Dyspnea Questionnaire
PFSS	Pumonary Function Status Scale
PI	Product Information
PICO	Population Intervention Comparator Outcome
PP	per protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PRAISE	Pulmonary Rehabilitation Adapted Index of Self-Efficacy
prn	as needed
PRO	patient-reported outcome
PSD	Public Summary Document
PSQI	Pittsburgh Sleep Quality Index
qd	once daily
QoL	quality of life
QUM	Quality Use of Medicines
QWB	Quality of Well Being
RCT	randomised controlled trial
RD	risk difference
Resp	Respimat
RG	Reference Group
RPBS	Repatriation Pharmaceutical Benefits Scheme
RR	risk ratio
RV/TLC	residual volume/total lung capacity
RVC	relaxed vital capacity
SABA	short-acting beta2-agonist
SAC	self-administered computerised

ABS	Australian Bureau of Statistics
SAE	serious adverse event
SAL	salmeterol
SAMA	short-acting muscarinic antagonist
SCD	standard coverage days
SD	standard deviation
SE	standard error
SF-36	36-item Short-Form Health Survey
SFC	salmeterol/fluticasone propionate combination
SF-CRQ	Short-Form Chronic Respiratory Disease Questionnaire
SGRQ	St George's Respiratory Questionnaire
SGRQ-C	St George's Respiratory Questionnaire for COPD
SIGN	Scottish Intercollegiate Guidelines Network
SMETT	sub-maximal constant-load cycle ergometry exercise tolerance test
SMI	soft mist inhaler
SOBDA	Shortness of Breath with Daily Activity
SR	systematic review
SR	sustained release
sRAW	specific airway resistance
SWT	Shuttle Walk Test
TB	tuberculosis
TDI	Transition Dyspnea Index
TGA	Therapeutic Goods Administration
TIO	tiotropium
TIOSPIR	TIOtropium Safety and Performance In Respimat
TLC	total lung capacity
ToR	Term of Reference
TSANZ	Thoracic Society of Australia and New Zealand
Tx	treatment
UCSD-SOBQ	University of California San Diego Shortness of Breath Questionnaire
UME	umeclidinium
URTI	upper respiratory tract infection

ABS	Australian Bureau of Statistics
USPSTF	United States Preventive Services Task Force
VA	Department of Veterans Affairs (US)
VAS	visual analogue scale
VC	vital capacity
VIL	vilanterol
vs	versus
VSRQ	Visual Simplified Respiratory Questionnaire
6-MWD	Six-Minute Walking Distance
6-MWT	Six-Minute Walking Test

Report Structure

This Report is presented in seven separate parts, as briefly outlined below. The Report has been structured in this way to address the Terms of Reference (ToR) of the Review.

Background	Provides the context and objectives of the Review, a brief description of COPD and its prevalence in Australia, the listing history for PBS listed COPD medications and their prescribing restrictions, and the ToR for the review.
Section 1	ToR 1: Compare the prescribing restrictions for PBS-listed COPD medicines for consistency with the current clinical guidelines.
Section 2	ToR 2: Review the clinical outcomes that are most important or clinically relevant to people with COPD and the extent to which these outcomes are included in the evidence previously provided to PBAC on the cost-effectiveness of these medicines.
Section 3	ToR 3: Review the evidence on the efficacy and safety of monotherapy and combinations of LABA/long-acting muscarinic antagonists (LAMA), ICS/LABA and LAMA + ICS/LABA (separate items or fixed dose combinations) for the treatment of COPD that PBAC has not previously considered.
Section 4	ToR 4: Review the published literature on the safety of prolonged ICS use in monotherapy and in combination with LABA and/or LAMA for COPD that PBAC has not previously considered.
Section 5	ToR 5: Analyse the current utilisation of PBS listed COPD medicines to identify the extent of co-prescribing and use that is inconsistent with clinical guidelines and/or PBS restrictions.
Section 6	ToR 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.

Background

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by chronic inflammation of the lung tissue, and obstruction of the airways that cannot be fully reversed by medication. A large array of inhaled medicines are available on the Pharmaceutical Benefits Scheme (PBS) for reducing the symptoms of COPD (and asthma), and the frequency and severity of exacerbations. The primary medicines are bronchodilators (beta2-agonists, anti-cholinergics/muscarinic agonists, phosphodiesterase inhibitors and methylxanthines) to reduce airway obstructions, and inhaled corticosteroids (ICS) to reduce inflammation.

The increase in COPD medicines provides greater choice in management options for the prescriber and the patient, which may result in greater adherence to prescribed pharmacotherapy. However, concerns have been raised that the recent increase in the number of new medicines and combinations of medicines delivered via new inhaler devices may lead to confusion amongst health professionals and consumers, resulting in inappropriate use of these medicines.

Context of the Review

At the March 2012 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) reviewed a submission from the sponsor of tiotropium, requesting exemption from a price reduction due to reference pricing against recently PBS-listed indacaterol for COPD. The PBAC concluded that the submission did not support its proposal against reference pricing and recommended that a comprehensive post-market review of the PBS medicines for COPD be undertaken to fully inform the assessment of comparative prices.

In November 2012, the then Minister for Health noted the PBAC's recommendation to commence a review of COPD medicines. The COPD review did not proceed, but remained on the work plan, and was also approved by the incoming Health Minister in April 2014.

In October 2013, the Drug Utilisation Sub Committee (DUSC) of the PBAC considered 12-month post-listing utilisation reviews of both indacaterol and the fixed-dose combination (FDC) of budesonide/efomoterol (400/12 µg) for COPD. In regard to indacaterol, DUSC noted that utilisation was lower than predicted at the time of the submission. DUSC also noted the occurrence of a significant amount of co-administration of respiratory medicines, and considered the co-administration of multiple long-acting beta-agonist (LABA) products in approximately 11% of new users (based on same day dispensing of multiple items) to be a significant quality use of medicines (QUM) issue.

DUSC considered it to be unlikely that multiple LABA products are intentionally prescribed to be used together and considered that there may be confusion among prescribers and pharmacists about the mechanism of action of indacaterol and other respiratory inhaler medicines. DUSC considered it possible that the various trade names of respiratory inhaler products may be a point of confusion and that the active ingredients may not be well understood.

In regard to budesonide with eformoterol, utilisation in the first year of the extension to PBS listing appeared to be substantially higher than predicted in the submission. DUSC suggested that this might be related to an increasing awareness and diagnosis of COPD and the arrival of new agents to the COPD market, with subsequent amendments to COPD guidelines. DUSC noted a trend towards more initiations in winter compared to summer months and considered that this may indicate some use of the product outside of COPD, for example respiratory tract infections and cough.

In August 2015, the PBAC reviewed its post-market review work plan and considered a background paper on COPD medicines. The PBAC advised the Minister for Health that a post-market review of COPD medicines should be prioritised for 2015-16. This Review was approved by the Minister on 28 September 2015.

Review Process

Purpose of the Review

The purpose of the Post-market Review of COPD Medicines is to review the utilisation, safety, efficacy and cost-effectiveness of PBS-listed COPD medicines, and to address QUM concerns associated with the apparent use of multiple products. The Review is being carried out under the Australian Government's PBS Post-Market Review Program, which aims to ensure the continued safe, cost-effective and quality use of medicines listed on the PBS. The Review will be conducted in accordance with the Post-Market Review Framework, which was developed following consultation with industry and published in March 2015.

Reference Group

A Reference Group (RG) was formed to provide an opportunity for stakeholder input to the Review and a platform for expert advice. Membership of the RG is at Appendix B.

Review Terms of Reference

The draft Review Terms of Reference (ToR) were open to public consultation for four weeks between 16 October and 13 November 2015. Comments on the draft ToR were received from twelve individuals and organisations including: six from industry; and six from health professionals, health professional peak bodies, research organisations and consumer groups.

Except where requested otherwise, public comments were published on the COPD Review Public Consultation website.

The PBAC considered the draft ToR and comments from stakeholders in December 2015. In February 2016, the Minister for Health approved the final Review ToR. Research questions relating to the ToR were developed to guide the technical review, and were discussed and further refined by the RG at their first meeting on 8 June 2016. The final ToR and research questions, approved by the RG Chair, are listed below.

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

> Q1. What are the relevant and current clinical guidelines in Australia and internationally for the treatment of COPD or mixed airways disease (asthma-COPD overlap)?
>
> Q2. Is there any impediment to a clinician's ability to prescribe the PBS listed medicines in accordance with the accepted clinical guidelines for management of COPD in Australia?
>
> Q3. Do the clinical guidelines used in Australia consider the evidence for clinical effectiveness and safety of COPD medicines?
>
> Q4. Do the clinical guidelines used in Australia consider the cost-effectiveness of COPD medicines?

ToR 2: Review the clinical outcomes that are most important or clinically relevant to people with COPD and the extent to which these outcomes are included in the evidence previously provided to PBAC on the cost-effectiveness of these medicines.

> Through a literature review:
>
> Q1. What are the usual primary and secondary outcome measures used in clinical trials for COPD? Where these are surrogate measures, has the validity of these in terms of long term health outcomes been established?
>
> Q2. What outcomes are important to patients? Does this change as COPD symptoms worsen and ability to function in daily life reduces?
>
> Q3. Is there evidence that measures of benefit and/or the extent of change in measures of benefit vary during the usual course of the disease?
>
> Q4. What do clinicians consider important measures of benefit to patients with COPD? What change in the measure is clinically important?
>
> Q5. What do patients consider important measures of benefit? What change in the measure is clinically important?
>
> Q6. Compare the measures of effect seen by the PBAC in clinical studies in submissions with current views on the most appropriate measures of benefit in the COPD population.

ToR 3: Review the evidence on the efficacy and safety of monotherapy and combinations of LABA/long-acting muscarinic antagonists (LAMA), ICS/LABA and LAMA + ICS/LABA (separate items or fixed dose combinations) for the treatment of COPD that PBAC has not previously considered.

Q1. Is there any new evidence from clinical trials and systematic meta-analyses regarding the effectiveness and safety of any of the PBS listed medicines for COPD? Identify studies and assess this new evidence.

Q2. Is there any new evidence from high quality observational studies regarding the effectiveness and safety of any of the medicines that are PBS listed for COPD? Identify studies and assess this new evidence.

Q3. Are the outcomes on effectiveness and safety in these studies different to those considered previously by the PBAC?

Q4. What are the risks and benefits of moving from monotherapy to FDC without a titration period using the individual agents?

Q5. Have clinical trials or observational studies in COPD included subjects with mixed airways disease? Is there any information about the prevalence of mixed airways disease, particularly patients with asthma and COPD?

ToR 4: Review the published literature on the safety of prolonged ICS use in monotherapy and in combination with LABA and/or LAMA for COPD that PBAC has not previously considered.

Q1. Are there safety and QUM concerns in patients with COPD who are on prolonged ICS use? What information is available from pharmacovigilance studies and major regulatory authorities?

ToR 5: Analyse the current utilisation of PBS listed COPD medicines to identify the extent of co-prescribing and use that is inconsistent with clinical guidelines and/or PBS restrictions.

Q1. Using established pharmaco-epidemiological methods:

Q2. Compare the PBS prescription supply patterns listed for COPD. Where appropriate, include medicines for asthma used by patients likely to have COPD as part of their airways disease.

Q3. What proportion of patients commence treatment with a LABA or LAMA?

Q4. What is the usual order of adding medicines to patient regimens?

Q5. Do patients change devices frequently or generally stay on the same device?

Q6. When are FDC therapies commenced?

Q7. What proportion of patients have inhaled therapies discontinued or are they additive?

Q8. Is there any information in the utilisation study to show differences or changes in adherence or persistence associated with increasing numbers of products being prescribed for COPD?

Q9. Does the utilisation of three respiratory inhaler treatments (LAMA, LABA and ICS) reflect use in either patients with mixed airways disease (asthma plus COPD) or severe COPD as defined in the PBAC restrictions: FEV_1 <50% and frequent exacerbations?

ToR 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.

Public submissions

Public submissions to the Review were open for seven weeks from 4 March to 22 April 2016. This process provided stakeholders with an opportunity to identify relevant issues, evidence or data that may inform the Review. Submissions were received from eight individuals and organisations. Except where requested otherwise, public submissions were published on the COPD Review Public Consultation website.

Stakeholder Forum

A Stakeholder Forum for the Post-market Review of COPD Medicines was held in Sydney, on 21 March 2017. Prior to the meeting, attendees were provided with a background discussion paper that included information on the Review ToR, and identified key issues and questions for the Forum. A brief summary of the clinical evidence and COPD medicines utilisation was presented at this Forum. Focus questions were posed at the Forum to prompt discussion and there was also an opportunity for open discussion not related to the focus questions. The Stakeholder Forum Summary is presented in full in Appendix F and is also available on the COPD Review website. Key findings from the Forum are summarised under each ToR.

Lung Foundation Australia consumer research

The Lung Foundation Australia was contracted to undertake a consumer engagement project to ascertain the views of COPD patients and carers on the Review ToR. The research sought to elicit consumer experience and knowledge regarding COPD medicines. The research was undertaken through:

- Two focus groups of eight participants (consumer support group members) conducted in Brisbane on 21 and 22 March 2017.
- Fifteen telephone interviews with consumer support group leaders and/or key consumer representatives across Australia, conducted between 15 and 23 March 2017.

A discussion guide was developed for the inverviews, which were conducted by Sprout Research. The results are presented in the form of key findings under ToR 1 and 2. Refer to Appendix G for the full Lung Foundation Australia (LFA) Consumer Research Report.

It should be noted that the patients surveyed were members of the LFA support group, and therefore may represent a cohort that is better educated about COPD and how to manage their condition than the general COPD population.

Overview of findings

The LFA research highlights it is critical to understand what consumers with COPD experience from both an emotional and practical perspective. People with COPD are chronically unwell and have often been so for a significant period of their lives.

The LFA research found that many COPD patients are in their old age, feel 'medically' isolated, and very much emotionally alone in their ordeal. As they are unwell and generally older, COPD patients may find it difficult to take in new information and to process it in the same way a well person would. Some patients have been on medications for a significant period of time and may begin to 'tune out' with regard to brand names, active ingredients and inhaler techniques. Some COPD patients may not ask questions about their medications unless they feel safe and cared for (e.g. from a nurse, other people with COPD). It is important to provide product support and information in a simple and easy to understand way. Overall, COPD patients expressed a need for greater information and support to understand medicines and how to use them correctly, particular ongoing support with inhaler device technique. The patients highlighted the need for timely, easy accessible, and reliable information across all modalities, including face to face interactions.

Public consultation on the draft Report

The draft COPD Review Report was made available for public comment between 29 May and 13 June 2017. Pharmaceutical sponsor companies were also provided with the opportunity to comment on the draft Report prior to consideration by DUSC and the Economic Sub Committee (ESC) of the PBAC, and again, prior to PBAC consideration.

COPD in Australia

Prevalence of COPD

Based on the most recent (2014-15) Australian Health Survey (AHS) from the Australian Bureau of Statistics (ABS), the prevalence of COPD is 4.9% in Australians aged 55-64 years, 7.0% in Australians aged 65-74 years, and 8.9% in Australians aged 75 years and over (as indicated by self-reported emphysema and/or bronchitis), which accounts for over 388,000 people (ABS, 2015). However, estimates of prevalence based on self-reporting of a doctor diagnosis of COPD are known to underestimate the true prevalence compared with objective measures, reflecting the widespread under-recognition and under-diagnosis of COPD (GOLD, 2016). Other estimates based on lung function suggest that the prevalence of COPD in Australia is likely to be higher. The Burden of Obstructive Lung Disease (BOLD) study tested

the lung function of nearly 10,000 people across 12 countries. In Australia, the prevalence of COPD (based on the GOLD definition of Stage 2 or higher) was estimated to be 7.5% for people aged 40 years and over and 29.2% for people aged 75 and over, which equates to over 770,000 Australians (based on 2011 population estimates; Toelle et al, 2013).

COPD is largely diagnosed and managed within the primary care sector and is one of the most frequently managed chronic problems in general practice (Britt et al, 2016). According to 2015-16 data from the BEACH (Bettering the Evaluation and Care of Health) program, COPD was managed by general practitioners (GPs) at a rate of 9 per 1000 encounters (asthma was managed by GPs at a rate of 20 per 1000 encounters). Using the BEACH method of extrapolation, this suggests that COPD was managed by GPs about 1,236,000 times per year nationally.

COPD is also one of the top ten health problems frequently referred to a hospital by a GP (Britt et al, 2015). In 2012-2013, there were 59,700 hospitalisations of Australians aged 55 years and over where COPD was the principal diagnosis. The rate of hospitalisation for COPD among those aged 55 and over was 1052 per 100,000 population (AIHW, 2015).

COPD is a leading cause of mortality in Australia. In 2012, 5923 Australians were recorded as having died from COPD (4% of all deaths in Australia), making it the fifth leading cause of death after ischaemic heart diseases, cerebrovascular diseases, dementia and lung cancer (ABS, 2014; AIHW, 2014).

Diagnosis of COPD

COPD is a serious, progressive and disabling condition that limits airflow in the lungs. Air flow obstruction leads to symptoms such as wheezing, shortness of breath, chest tightness, coughing and production of excess mucus. Worsening of these symptoms can be caused by irritants such as infection or exposure to noxious particles or gases (most commonly cigarette smoke), and can result in exacerbations, hospitalisations and death. The development of COPD occurs over many years and therefore mainly affects middle aged and older people.

Although airflow obstruction is a hallmark characteristic of both COPD and asthma, an accurate diagnosis of COPD or asthma (or another obstructive lung condition, such as bronchiectasis) is important because of its therapeutic and prognostic implications for the patient. Due to substantial improvements in understanding of the pathogenesis of both diseases, treatments for COPD and asthma are diverging and the correct diagnosis is vital in order to maximise the long-term outcome for the patient (Sims and Price, 2012).

In many cases, differentiation between COPD and asthma is relatively easy for a clinician (Abramson et al, 2016). In COPD, airflow obstruction is progressive and largely irreversible whereas in asthma, airway obstruction is typically intermittent and substantially – if not completely – reversible, either spontaneously or in response to a bronchodilator. However, there are some patients (particularly older patients, smokers and ex-smokers) in whom it is difficult to distinguish between asthma and COPD as the primary cause of their chronic

airflow limitation (ACAM, 2011; GINA, 2015). Longstanding or poorly controlled asthma can lead to chronic, irreversible airway narrowing. Furthermore, it is now recognised that some people may have components of both diseases, known as asthma-COPD overlap syndrome, or ACOS (GINA, 2015).

Making a correct diagnosis of COPD relies on clinical judgement based on a combination of symptoms, history, physical examination and confirmation of the presence of airflow obstruction using spirometry (GOLD, 2016). Due to low uptake of spirometry in Australia (Matheson et al, 2006; Abramson et al, 2012), it is possible that many patients are misdiagnosed (Walters et al, 2011; Zwar et al, 2011). Misdiagnosed patients may then go on to receive inappropriate therapy (potentially lifelong), exposing them needlessly to possible side effects (albeit usually minor) and costs, while the true underlying pathology remains untreated. The consequences of a missed diagnosis include preventable recurrent exacerbations, emergency department visits and hospital admissions (Boulet et al, 2013).

Pharmacological management of COPD

NPS MedicineWise provides an overview of the stepwise management of COPD[1], with the aim of managing symptoms as they worsen (see Section 2 for a review of relevant clinical practice guidelines, addressed in relation to ToR 1). Pharmacological management of stable COPD typically starts with a short-acting reliever, which may include either a short-acting beta-2 receptor agonist (SABA) or a short-acting anticholinergic/muscarinic receptor antagonist (SAMA), as needed for symptom relief. Maintenance therapy involves the addition of one or more long-acting bronchodilators (LABAs or LAMAs). Rather than increasing the dose of a single bronchodilator, patients are often prescribed a combination of two bronchodilators of different classes as this may improve efficacy and decrease the risk of side effects.

Combination therapy with a LABA and an ICS is indicated for patients who remain symptomatic after treatment with long-acting bronchodilators (and have a history of two or more exacerbations in the previous year). There is some evidence that triple therapy with a LABA plus a LAMA plus an ICS improves lung function and quality of life; however, the evidence base is limited. In patients with severe COPD for whom other treatments have failed to control symptoms adequately, the addition of theophylline may be considered.

There are some bronchodilator combinations that should be avoided; for example, doubling up on inhalers containing an anticholinergic (SAMA or LAMA) and doubling up on inhalers containing a LABA. A SABA may be used alongside all inhalers for symptom relief.

[1] NPS MedicineWise, Pharmacological therapies for chronic obstructive pulmonary disease in Australia, RADAR, 1 December 2014.

COPD medicines on the PBS

PBS listing history

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

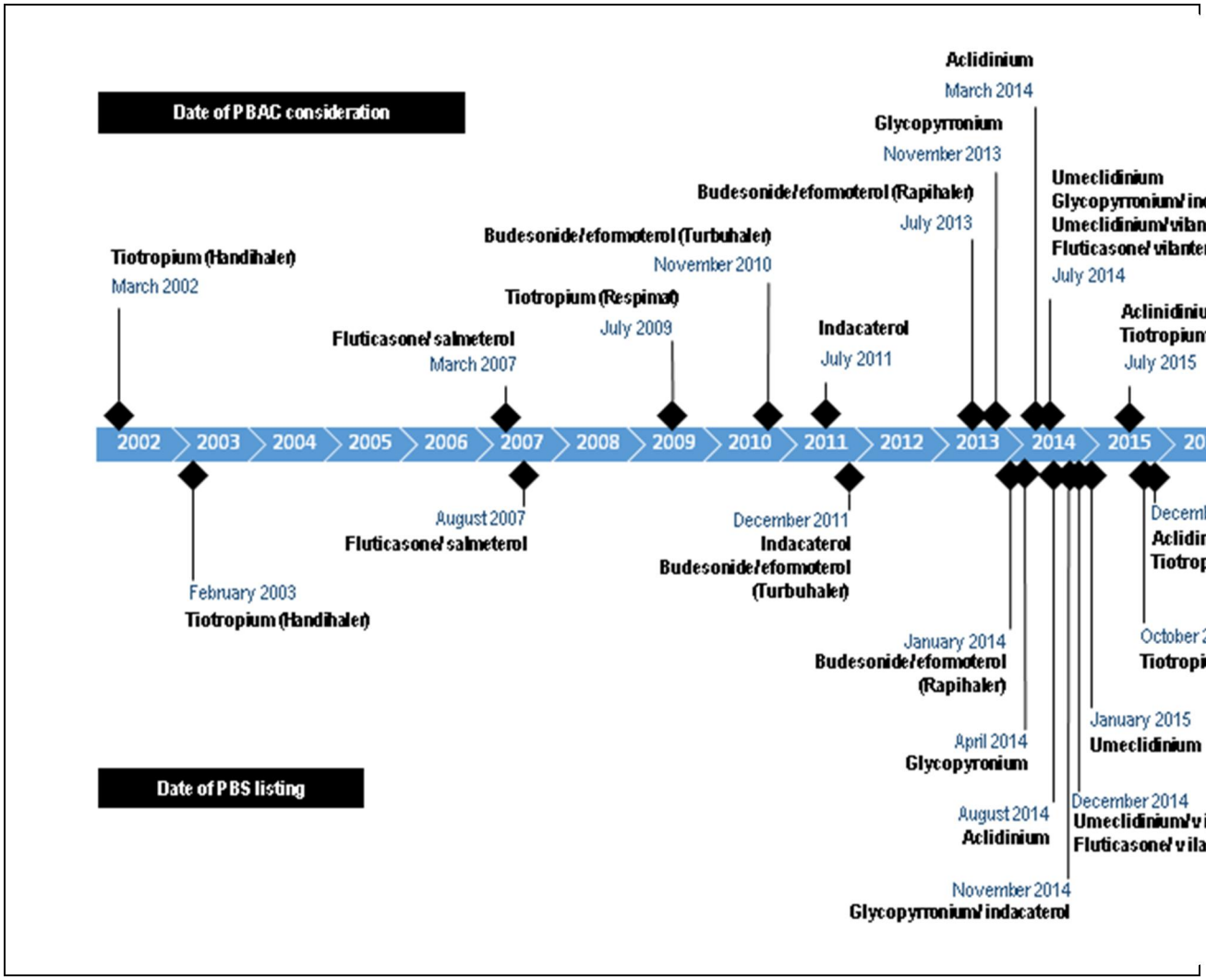

Table B.1 provides a list of the long-acting COPD medicines on the PBS for the management of COPD. The first medicine specifically listed on the PBS for COPD was tiotropium powder for oral inhalation (Spiriva®). The major submission that led to this listing was considered by the PBAC in March 2002, with the product formally listed in February 2003.

As tiotropium was the first long-acting bronchodilator, the submission chose the short-acting antimuscarinic agent, ipratropium bromide (Atrovent®), as the comparator. Tiotropium 18 µg once daily was recommended by the PBAC on the basis of superior efficacy compared with ipratropium 40 µg four times a day (total 160 µg/day), and similar or less toxicity.

The next COPD medicine listed on the PBS was the FDC fluticasone propionate/salmeterol (Seretide®, 500/50 µg and 250/25 µg) in 2007, which was recommended by the PBAC on the

basis of comparable effectiveness and safety to tiotropium[2]. The other ICS/LABA FDCs (budesonide/eformoterol 400/12 µg and fluticasone furoate/vilanterol 100/25 µg) were then listed on the basis of comparable effectiveness and safety to fluticasone propionate/salmeterol.

The only LABA listed on the PBS is indacaterol (Onbrez®, 150 µg and 300 µg), which was recommended by the PBAC in 2011 on the basis of comparable effectiveness and safety to fluticasone propionate/salmeterol, both in combination with tiotropium.

Since the introduction of tiotropium, three other LAMAs (glycopyrronium 50 µg, aclidinium 322 µg, and umeclidinium 62.5 µg) have been listed on the PBS. All three were recommended by the PBAC in 2013 and 2014 on the basis of comparable effectiveness and safety to tiotropium.

The LAMA/LABA FDC of umeclidinium/vilanterol (Anoro Ellipta®, 62.5/25 µg once daily) was recommended by the PBAC in July 2014 on the basis of comparable effectiveness to indacaterol (150 µg once daily) plus tiotropium (18 µg once daily) at 12 weeks, and a similar safety profile. The other LAMA/LABA FDCs were subsequently listed on the basis of comparable effectiveness and safety to umeclidinium/vilanterol.

Figure B.1 shows a timeline of PBAC consideration of COPD medicines (positive recommendations) and PBS listing dates (first use on the PBS). The time between a positive recommendation from the PBAC and listing on the PBS was generally less than one year for all medicines, with the exception of tiotropium (2.5 µg solution), which was recommended in July 2009 and became available on the PBS in October 2015.

Table B.2 summarises the basis of the economic analysis that was considered by the PBAC when they recommended the listing of each COPD medicine. As mentioned above, tiotropium (Spiriva HandiHaler) was recommended on the basis of a cost-effectiveness analysis against the SAMA, ipratropium, in 2003. All other individual LAMA products have been cost-minimised to each other. The newer LAMA/LABA FDCs have been listed on a cost-minimisation basis to tiotropium and indacaterol with an adjustment to account for efficacy being less than the sum of the individual components. Current PBS listing details for each COPD medicine, including the Dispensed Price for Maximum Quantity (DPMQ), are shown in Appendix C.

[2] The PBAC did not accept the claim in the submission that fluticasone propionate/salmeterol had significant advantages in terms of clinical effectiveness and toxicity over tiotropium.

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

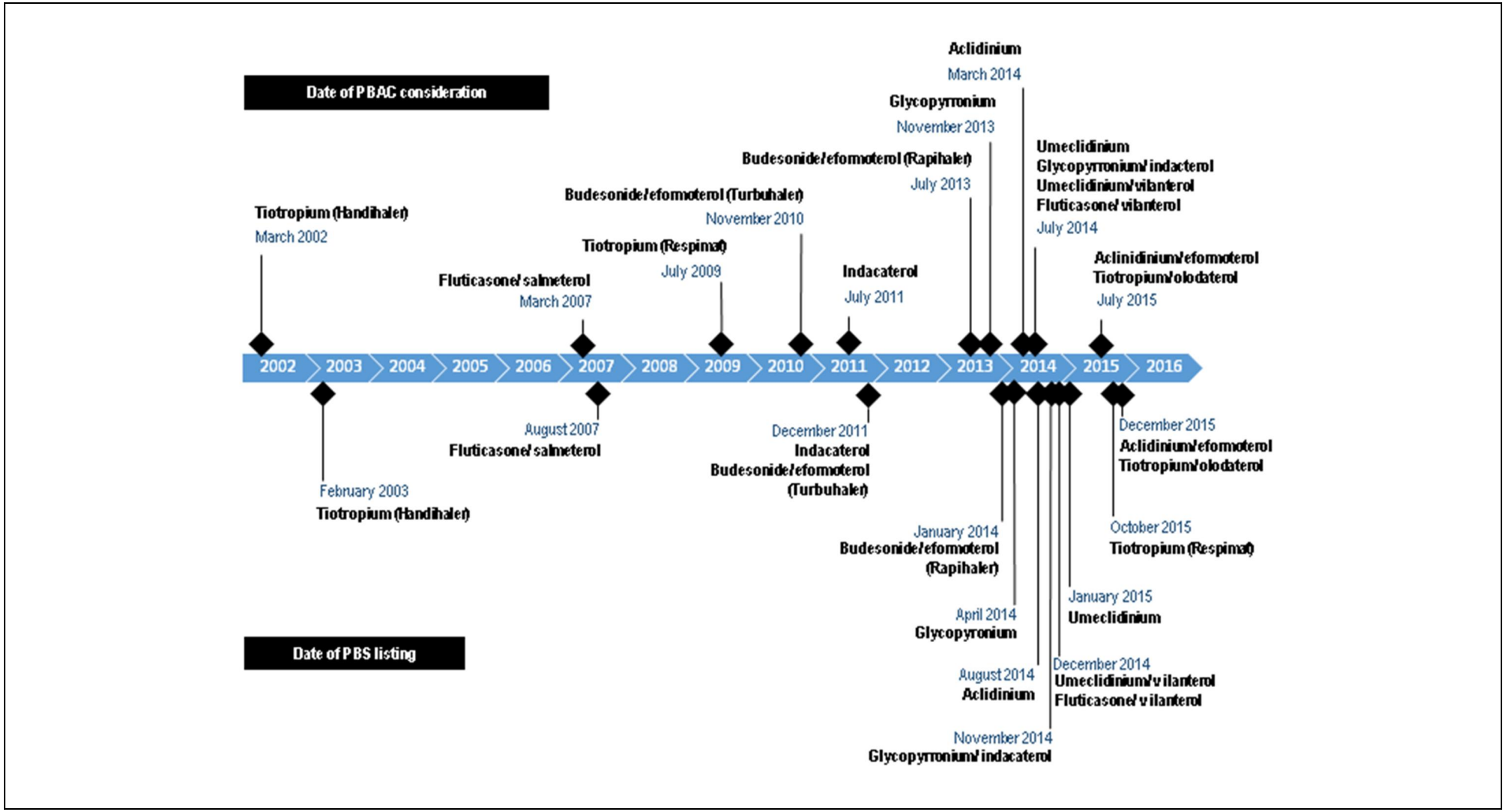

Table B.1 COPD medicines listed on the PBS

Active ingredient	Brand name & strength	Device type	Company	PBS item	Date of PBAC consideration	PBS listing date	PBS listing type
LAMA							
Aclidinium bromide	Bretaris Genuair 322 µg	Dry powder inhaler	A. Menarini	10124W	March 2014	August 2014	Restricted Benefit COPD
Glycopyrronium bromide	Seebri Breezhaler 50 µg	Dry powder inhaler	Novartis	10059K	November 2013	April 2014	Restricted Benefit COPD
Tiotropium bromide	Spiriva HandiHaler 18 µg	Dry powder inhaler	Boehringer Ingelheim	8626B	March 2002	February 2003	Restricted Benefit COPD
Tiotropium bromide	Spiriva Respimat 2.5 µg	Soft mist inhaler	Boehringer Ingelheim	10509D	July 2009	October 2015	Restricted Benefit COPD
Umeclidinium bromide	Incruse Ellipta 62.5 µg	Dry powder inhaler	GSK	10187E	July 2014	January 2015	Restricted Benefit COPD
LABA							
Indacaterol maleate	Onbrez 150 µg Onbrez 300 µg	Dry powder inhaler	Novartis	5134F 5137J	July 2011	December 2011	Restricted Benefit COPD
LAMA/ LABA							
Aclidinium/ eformoterol fumarate dehydrate	Brimica Genuair 340/12 µg	Dry powder inhaler	A. Menarini	10565C	July 2015	December 2015	Authority Required (Streamlined) COPD
Glycopyrronium bromide/ indacaterol maleate	Ultibro Breezhaler 50/110 µg	Dry powder inhaler	Novartis	10156M	July 2014	November 2014	Authority Required (Streamlined) COPD
Tiotropium bromide/ olodaterol	Spiolto Respimat 2.5/2.5 µg	Soft mist inhaler	Boehringer Ingelheim	10557P	July 2015	December 2015	Authority Required (Streamlined) COPD
Umeclidinium bromide/ vilanterol trifenatate	Anoro Ellipta 62.5/25 µg	Dry powder inhaler	GSK	10188F	July 2014	December 2014	Authority Required (Streamlined) COPD
ICS/ LABA							
Budesonide/ eformoterol	Symbicort Turbuhaler 400/12 µg	Dry powder inhaler	AstraZeneca	8750M	November 2010	December 2011 (for COPD)	Restricted Benefit COPD and asthma
Budesonide/ eformoterol	Symbicort Rapihaler 200/6 µg	Metered dose inhaler	AstraZeneca	10018G	July 2013	January 2014 (for COPD and asthma)	Restricted Benefit COPD and asthma
Fluticasone propionate/ salmeterol	Seretide Accuhaler 500/50 µg	Dry powder inhaler	GSK	8432T	March 2007	August 2007 (for COPD)	Restricted Benefit COPD and asthma
Fluticasone propionate/ salmeterol	Seretide MDI 250/25 µg	Metered dose inhaler	GSK	8519J	March 2007	August 2007 (for COPD)	Restricted Benefit COPD and asthma
Fluticasone furoate/ vilanterol	Breo Ellipta 100/25 µg	Dry powder inhaler	GSK	10199T	July 2014	December 2014 (for COPD and asthma)	Restricted Benefit COPD and asthma

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; PBS, Pharmaceutical Benefits Scheme.

Table B.2 COPD medicines listed on the PBS

Date of PBAC consideration	Active ingredient *Brand name and strength*	Basis of economic analysis[a]	Equi-effective doses[a]
March 2002	**Tiotropium bromide** Spiriva HandiHaler 18 µg	CEA compared with ipratropium	• N/A
March 2007	**Fluticasone propionate/ salmeterol** Seretide Accuhaler 500/50 µg Seretide MDI 250/25 µg	CMA compared with tiotropium	• fluticasone/ salmeterol 500/50 µg twice daily • tiotropium 18 µg once daily
July 2009	**Tiotropium bromide** Spiriva Respimat 2.5 µg	CMA compared with tiotropium HandiHaler	• tiotropium (solution) 5 µg once daily • tiotropium (powder) 18 µg once daily
November 2010	**Budesonide/ eformoterol** Symbicort Turbuhaler 400/12 µg	CMA compared with fluticasone propionate/ salmeterol	• budesonide/ eformoterol 400/12 µg twice daily • fluticasone propionate/ salmeterol 500/50 µg twice daily
July 2011	**Indacaterol maleate** Onbrez 150 µg; Onbrez 300 µg	CMA compared with fluticasone propionate/ salmeterol and tiotropium	• indacaterol 150 µg daily in combination with tiotropium 18 µg daily • fluticasone propionate/ salmeterol 250/25 µg, 2 puffs twice daily in combination with tiotropium 18 µg daily
July 2013	**Budesonide/ eformoterol** Symbicort Rapihaler 200/6 µg	CMA compared with budesonide/ eformoterol (Symbicort Turbuhaler)	• budesonide/ eformoterol 200/6 µg (Turbuhaler) two inhalations twice daily • budesonide/ eformoterol 400/12 (Rapihaler) one inhalation twice daily
November 2013	**Glycopyrronium bromide** Seebri Breezhaler 50 µg	CMA compared with tiotropium	• glycopyrronium 50 µg once daily • tiotropium 18 µg once daily
March 2014	**Aclidinium bromide** Bretaris Genuair 322 µg	CMA compared with tiotropium	• aclidinium 400 µg twice daily • tiotropium 18 µg once daily
July 2014	**Umeclidinium bromide** Incruse Ellipta 62.5 µg	CMA compared with tiotropium	• umeclidinium 62.5 µg once daily • tiotropium 18 µg once daily
July 2014	**Umeclidinium bromide/ vilanterol trifenatate** Anoro Ellipta 62.5/25 µg	CMA compared with tiotropium plus indacaterol[b]	• umeclidinium/ vilanterol 62.5/25 µg • tiotropium bromide 18 µg plus indacaterol 150 µg
July 2014	**Glycopyrronium bromide/ indacaterol maleate** Ultibro Breezhaler 50/110 µg	CMA compared with umeclidinium/ vilanterol	• glycopyrronium/ indacaterol 50/110 µg daily • umeclidinium/ vilanterol 62.5/25 µg daily
July 2014	**Fluticasone furoate/ vilanterol** Breo Ellipta 100/25 µg	CMA compared with fluticasone propionate/ salmeterol	• fluticasone furoate/ vilanterol 100/25 µg daily • fluticasone furoate/ salmeterol 500/50 µg twice daily
July 2015	**Aclidinium/ eformoterol fumarate dehydrate** Brimica Genuair 340/12 µg	CMA compared with umeclidinium/ vilanterol, and glycopyrronium/ indacaterol	• aclidinium/ eformoterol 340/12 µg twice daily • umeclidinium/ vilanterol 62.5/25 µg daily • glycopyrronium/ indacaterol 50/110 µg daily
July 2015	**Tiotropium bromide/ olodaterol** Spiolto Respimat 2.5/2.5 µg	CMA compared with umeclidinium/ vilanterol, and glycopyrronium/ indacaterol	• tiotropium bromide/olodaterol 5/5 µg, two inhalations daily • umeclidinium/vilanterol 62.5/25 µg daily • glycopyrronium/ indacaterol 50/110 µg daily

Abbreviations: CEA, cost-effectiveness analysis; CMA, cost-minimisation; COPD, chronic obstructive pulmonary disease; µg, microgram; PBS, Pharmaceutical Benefits Scheme.

a Taken from Public Summary Documents.

b With an adjustment to account for efficacy being less than the sum of components.

A more detailed summary of PBAC decision-making for each COPD medicine, including the studies and outcomes considered, is provided in Appendix D. The only FDC for COPD that has both components listed on the PBS for the same indication is glycopyrronium/indacaterol. Table B.3 shows the PBS listing status of the component products of the PBS-listed FDCs.

Table B.3 PBS listing status of component products of PBS-listed FDCs

FDC	PBS listing date	LAMA PBS listed for COPD	LABA PBS listed for COPD	ICS PBS listed for COPD
LAMA/ LABA				
Aclidinium/ eformoterol 340/12 µg	December 2015	Yes Listed August 2014	No Listed for asthma only	-
Glycopyrronium/ indacaterol 50/110 µg	November 2014	Yes Listed April 2014	Yes 150 and 300 µg doses listed December 2011	-
Tiotropium/ olodaterol 2.5/2.5 µg	December 2015	Yes Listed October 2015	No Submission rejected by PBAC in July 2014	-
Umeclidinium/ vilanterol 62.5/25 µg	December 2014	Yes Listed January 2015	No No PBAC submission	-
ICS/ LABA				
Budesonide/ eformoterol 400/12 µg	December 2011	-	No Listed for asthma only	Unrestricted
Budesonide/ eformoterol 200/6 µg	January 2014	-	No Listed for asthma only	Unrestricted
Fluticasone propionate/ salmeterol 500/50 and 250/25 µg	August 2007	-	No Listed for asthma only	Unrestricted
Fluticasone furoate/ vilanterol 100/25 µg	December 2014	-	No No PBAC submission	Unrestricted

Abbreviations: COPD, chronic obstructive pulmonary disease; FDC, fixed dose combination; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; PBS, Pharmaceutical Benefits Scheme.

PBS prescribing restrictions

The PBS prescribing restrictions for the COPD medicines are summarised in Table B.4. The four LAMAs (tiotropium, glycopyrronium, aclidinium and umeclidinium) are all PBS listed as Restricted Benefit for COPD. Spiriva Respimat 2.5 µg (tiotropium) has a more detailed Restricted Benefit listing for long-term maintenance treatment of bronchospasm and dyspnoea associated with COPD.

The only LABA listed on the PBS for COPD is indacaterol, which has a Restricted Benefit listing for COPD and a note that indacaterol should not be used for asthma. This is consistent with the product information (see Appendix E for a summary of indications and dosing regimens approved by the Therapeutic Goods Administration (TGA)).

All of the LAMA/LABA FDCs for COPD have the same Authority Required (STREAMLINED) PBS restriction, which also specifies that patients must have been stabilised on a combination of a LAMA and a LABA.

The three ICS/LABA FDCs are also PBS listed for asthma. 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 use for symptomatic treatment.

Table B.4 PBS prescribing restrictions for COPD medicines

Medicine	PBS restriction for COPD
LAMA	
• Aclidinium bromide • Glycopyrronium bromide • Tiotropium bromide (HandiHaler) • Umeclidinium bromide	**Restricted Benefit:** COPD
• Tiotropium bromide (Respimat)	**Restricted Benefit:** Bronchospasm and dyspnoea associated with COPD Treatment Phase: Long-term maintenance treatment.
LABA	
• Indacaterol maleate	**Restricted Benefit:** COPD *Note: This drug is not PBS-subsidised for the treatment of asthma.*
LAMA/ LABA	
• Aclidinium/ eformoterol fumarate dehydrate • Glycopyrronium bromide/ indacaterol maleate • Tiotropium bromide/ olodaterol • Umeclidinium bromide/ vilanterol trifenatate	**Authority Required (STREAMLINED):** COPD Clinical criteria: Patient must have been stabilised on a combination of LAMA and LABA. *Note: This product is not PBS-subsidised for the treatment of asthma.* *Note: This product is not indicated for the initiation of bronchodilator therapy in COPD.* *Note: The treatment must not be used in combination with an ICS/LABA, or LAMA or LABA monotherapy.* *Note: A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.* *Note: A LABA includes olodaterol, indacaterol, salmeterol, eformoterol or vilanterol.*
ICS/ LABA	
• Budesonide/ eformoterol (Turbuhaler) • Budesonide/ eformoterol (Rapihaler) • Fluticasone propionate/ salmeterol (Accuhaler) • Fluticasone propionate/ salmeterol (MDI) • Fluticasone furoate/ vilanterol	**Restricted Benefit:** COPD Clinical criteria: Patient must have an FEV_1 less than 50% of predicted normal prior to therapy; and patient must have a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy; and the treatment must be for symptomatic treatment. *Note: Not indicated for the initiation of bronchodilator therapy in COPD.* *Note: Patient must not be on a concomitant single agent long-acting beta-2 agonist.*

Sources: PBS General Schedule, accessed 23 November 2016.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; PBS, Pharmaceutical Benefits Scheme.

Other PBS medicines used to treat COPD

Table B.5 lists other medicines that are available on the PBS and are used in clinical practice for the treatment of COPD, including short-acting bronchodilators (SABAs and SAMAs) and corticosteroids. Section 2, which addresses ToR 1, provides recommendations from clinical practice guidelines regarding the use of these medicines in the treatment of COPD.

Ipratropium is a Restricted Benefit for COPD, and was listed on the PBS prior to 2003. All of the other medicines in Table B.5 have an unrestricted listing.

Table B.5 Other PBS medicines used to treat COPD

Medicine	Brand
SABA	
Salbutamol sulfate	Ventolin, Airomir, Asmol
Terbutaline sulfate	Bricanyl
SAMA	
Ipratropium bromide	Atrovent, Aeron, Ipratrin
ICS	
Beclomethasone diproprionate	Qvar
Budesonide	Pulmicort
Ciclesonide	Alvesco
Fluticasone proprionate	Flixotide
Oral corticosteroid	
Prednisone	Panafcort, Predsone
Methylxanthine	
Theophylline	Nuelin

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; ICS, inhaled corticosteroid; PBS, Pharmaceutical Benefits Scheme; SABA, short-acting beta-2 agonist; SAMA, short-acting muscarinic antagonist.

Consumer knowledge, attitude and behaviour

To better understand Australian patient perceptions and experiences of living with COPD, an evidence search of consumer views using the Medline database was conducted in November 2015. The results of the literature search findings have been summarised based on; patient diagnosis, quality of life impacts, COPD treatment, and quality use of medicines.

Diagnosis

- Consumers' reaction to a diagnosis of COPD ranged from emotional (including denial) to rational.
- Consumers reported the process involved in obtaining a diagnosis could be prolonged (Ansari et al, 2014; Lindgren et al, 2014).
- Consumers reported that unclear messages from clinicians such as a 'hint of COPD' or a 'slight form of asthma' lead to confusion (Ansari et al, 2014; Lindgren et al, 2014).

Quality of life impacts

- Breathlessness, phlegm production, cough, wheezing or chest tightness were commonly reported symptoms experienced by those with COPD. These symptoms often had an extensive impact on patients' quality of life (Kessler et al, 2011).
- Some consumers reported losing their independence, hobbies and social connections as a result of their COPD (Kessler et al, 2011).
- Anxiety and fear about disease progression and suffocation were common in people with moderate to severe COPD. A range of strategies were employed to assist in the management of this anxiety (Landers et al, 2015; Wortz et al, 2012).

COPD treatment

- Consumers commonly consulted their GP in the management of COPD. Some confusion was evident in terms of the role of the GP versus specialist in the management of this condition (Kirby et al, 2014; Ansari et al, 2014).
- Most people with COPD reported experiencing an exacerbation ('flare up') of their condition. Many, but not all, reported that they had been taught to recognise the signs of onset. Some people took a 'wait and see' approach to management while others were comfortable to self-medicate with antibiotics and steroids (referred to as 'back up medication') (Barnes et al, 2013; Hernandez et al, 2013; Williams et al, 2014).
- Over half of the respondents to a large survey indicated that they had experienced an exacerbation that resulted in hospitalisation. Fear associated with the symptoms of an exacerbation was involved in some consumers' presentation to hospital. Some reported that interaction with ambulance and/or hospital staff during an exacerbation of their physical symptoms reduced anxiety levels (Landers et al, 2015; Barnes et al, 2013).
- Little information was available on pulmonary rehabilitation in the Australian context, (Kirby et al, 2014). Feedback on the provision of such services in a Dutch study indicated that people with COPD found the information and strategies provided beneficial — although concerns were raised about the increased effort and motivation required to continue with exercise once at home (Meis et al, 2014).
- People with COPD described their medicines as 'improving breathing' and 'feeling the medicine open up/clear the lungs' if they were working effectively (Kawata et al, 2014). The ease of administering their medicines was important with difficulties in using devices reported by some consumers (Sharafkhaneh et al, 2013).

Quality use of Medicines

- Both intentional (due to a lack of perceived effect) and non-intentional non-adherence were reported by people with COPD. Non-adherence (accidental omissions) was significantly higher when patients perceived that they had to take too many medicines on a daily basis. Paradoxically, the actual number of medicines taken was not associated with adherence (Laforest et al, 2010; Khdour et al, 2012; Bereznicki et al, 2015).
- One study indicated that people with COPD felt that they had received information on COPD medicines with only a small proportion indicating they needed further education or were confused about their medicines (Scott et al, 2011).

NPS Medicinewise COPD Program

NPS MedicineWise launched a COPD educational program in February 2017. The program is titled 'COPD medicines and inhalers: stepping through the options'. This multifaceted program includes a suite of educational interventions such as one-to-one educational visits of GPs, NPS MedicineWise publications and online educational activities. The program goal is to improve the quality of life for Australians with COPD through improved medicines management in primary care.

This program will focus on the following issues:

- Diagnosis of COPD and the role of spirometry
- Stepwise medicine management with inhalers
- Inhaler technique and adherence.

Program delivery channels include:

- Face-to-face educational visits to health professionals mainly aimed at GPs
- Small group case-based meetings for health professionals
- MedicineInsight practice visits (for more information on MedicineInsight, visit the NPS MedicineWise webpage)
- NPS MedicineWise News (an online publication aimed at health professionals)
- National online case study (an online learning module exploring a clinical case scenario, available for GPs, pharmacists, nurses and others)
- PBS Feedback for GPs (provides GPs the opportunity to reflect on their prescribing pattern for COPD medicines)
- Pharmacy Practice Reviews (an online audit for pharmacists that aims to support program messages around stepwise medicines management, patient adherence and inhaler technique)
- Spirometry Consumer factsheet (a GP-mediated online factsheet for patients on spirometry, developed in collaboration with the Lung Foundation Australia, Asthma Australia and National Asthma Council Australia)
- Inhalers Checklist (an online resource for health professionals to use when assessing patients' inhaler technique).

Section 1: ToR 1
Concordance between prescribing restrictions and clinical guidelines

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

List of Tables

List of Figures

1.2 Key findings for ToR 1

Clinical guidelines in COPD

- The key clinical practice guidelines of relevance to Australian practice are the COPD-X Plan (2015/2016): Australian and New Zealand Guidelines for the Management of Chronic Obstructive Pulmonary Disease. There is also the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Strategy Report (2016): Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.
- Both documents are evidence-based and have target audiences in primary healthcare and respiratory specialties.
- The COPD-X guidelines have mild/moderate/severe COPD categories, primarily based on FEV_1 with associated symptoms and exacerbations. COPD-X guidelines advocate a stepped algorithm for prescribing pharmacologic therapy for COPD. Patients have medications added or modified in a stepwise manner according to the symptoms of

their disease. The most common treatment pathway for stable COPD following diagnosis is: step 1: SAMA or SABA; step 2: LAMA or LABA; step 3: LAMA/LABA; step 4: ICS/LABA (for patients with FEV_1 <50% predicted and ≥2 exacerbations in the previous year); step 5: various medications.

- The COPD-X guidelines and the GOLD Strategy Report do not explicitly mention adding an ICS to a LAMA/LABA combination. The Canadian guideline from the Medical Services Commission (2011) and the US guideline from the Department of Veterans Affairs (2014) both state that ICS could be added to tiotropium/LABA combination therapy (that is, triple therapy), without mentioning the prior use of ICS/LABA therapy. However, a recent Cochrane review (2016) did not identify any studies assessing the relative benefits and risks of adding ICS to LAMA/LABA dual therapy.
- Asthma-COPD overlap syndrome (ACOS) is generally treated by initiating an ICS, then adding a LABA or LAMA. As the treatment algorithms for COPD, asthma and ACOS are different, patients need to be correctly diagnosed using spirometry, to ensure the most appropriate therapy.
- COPD-X Concise Guidelines and the GOLD Strategy Report highlight the importance of providing education and confirming inhaler technique and adherence at each visit.

Inconsistencies between PBS-listed COPD medicines and clinical guidelines

- The LAMA/LABA FDCs have Authority Required (STREAMLINED) PBS restrictions, while dual therapy with ICS/LABA FDCs, which occur later in the treatment pathway, are a Restricted Benefit. The PBS Restricted Benefit listing for the ICS/LABA FDCs compared to the LAMA/LABA FDCs does not align with their place in therapy; that is, the desirability of delaying initiation of an ICS/LABA due to possible adverse effects.
- The LAMA/LABA FDCs have PBS restrictions that state that the patient must have been [already] stabilised on a LAMA and LABA. These restrictions are not based on treatment guidelines. The COPD-X Concise guidelines state that LAMA/LABA FDCs are recommended for patients who remain symptomatic despite monotherapy with either LAMA or LABA alone.
- If the LAMA/LABA FDC restriction were modifed, clinicians could initiate a patient on LAMA monotherapy with the expectation of prescribing that same LAMA as part of a LAMA/LABA FDC at a later stage, without the current need to introduce (and then possibly discontinue) indacaterol as an intermediate step.
- PBS restrictions do not require prescribers to review or confirm inhaler technique.
- Guidelines highlight that inappropriate combinations of agents should be avoided; for example, using a LABA in addition to an ICS/LABA or a LAMA/LABA. This potential for prescribing inappropriate combinations of agents is not systematically addressed for all COPD medicines in their PBS restrictions.

LFA consumer views

- Consumer awareness about medications and treatment guidelines is limited.
- Consumers assume that PBS listings for COPD medicines are consistent with guidelines, and expect GPs and specialists to prescribe in accordance with guidelines.
- Many consumers considered new medications as improved inhalers rather than new active ingredients.
- Consumers take a combination of medications, depending on the severity of their COPD and other co-morbidities, including a reliever, preventer, antibiotics and steroids.
- Consumers call for more support on inhaler techniques. They require easy and simple instruction that is consistent and provided by a health care professional, such as their GP, respiratory or practice nurse, or pharmacist.
- For further information, the LFA Consumer Research Report is available at Appendix G.

Stakeholder views (Forum and public consultations)

- Inconsistencies between the PBS restrictions and the COPD-X guidelines result in prescribers being directed away from evidence-based guidelines. In general, stakeholders supported the:
  - Removal of the requirement to stabilise patients on LAMA and LABA monotherapy (two separate devices) to be eligible for LAMA/LABA FDCs.
  - Addition of PBS notes on inappropriate combinations, and confirming inhaler technique and adherence at each visit to a clinician, and before recommending step up treatment.
- The clinical criteria in the ICS/LABA PBS restrictions are consistent with the COPD-X guidelines.
- A number of additional QUM issues were highlighted:
  - Need to include a PBS note for LABA/LAMA combinations: “Do not use in patients with a history of asthma without accompanying ICS”.
  - The use of spirometry to confirm COPD diagnosis is low. Increased eduational efforts and changes to the Medical Benefits Scheme (MBS) are required.
  - The increase in new COPD medicines, and various trade names, may be contributing to prescriber confusion and the prescribing of unsafe combinations.
  - Many health professionals are not confident or competent to confirm correct inhaler technique and may be confused about appropriate treatment for ACOS.
- A national standardised list of education materials for health professionals is required to improve overall adherence to COPD evidence-based guidelines and PBS restrictions, and to avoid health professional and patient confusion. Increased access to inhaler checklists could assist health professionals to confidently check inhaler technique.
- The updated GOLD Strategy Report (2017) is an important additional reference.

- For further information, the Stakeholder Forum Summary is available at Appendix F. A list of published references, and educational materials, provided by stakeholders is available at Appendix U and V, respectively.

1.3 Methodology

The methodology for ToR 1 involved the identification of relevant evidence-based guidelines from regulatory/funding/health technology assessment (HTA) bodies, guidelines databases and other relevant websites for the treatment of COPD. The current clinical guidance was summarised and compared with current PBS prescribing restrictions and the clinical place of COPD medicines as considered by the PBAC in Public Summary Documents (PSDs).

1.3.1 Identification of relevant guidelines

A search of guideline databases was undertaken to identify evidence-based clinical practice guidelines for COPD. A broad strategy was employed using the terms 'chronic obstructive pulmonary disease' or 'COPD' or 'respiratory' or 'emphysema' or 'chronic bronchitis'. To ensure that the clinical guidance was considered to be current, the search was restricted to Australian and international guidelines published from 2011 onwards.

Table 1.1 summarises the search and eligibility criteria that was used to address ToR 1.

Table 1.1 Eligibility criteria applied to the search for guidelines that address ToR 1

Limit	Eligibility criteria
Guidelines databases	• Australian Clinical Practice Guidelines Portal • AHRQ National Guidelines Clearinghouse • G-I-N • SIGN
Other means to identify relevant information	• Scan of public consultation submissions on the final ToR • Scan of PBAC PSDs for COPD medicines • Search of NICE website • Search of other relevant websites (e.g. LFA, TSANZ, NPS MedicineWise)
Publication types	• Australian and international evidence-based clinical practice guidelines on the pharmacological management of COPD • English language only
Search period	• 2011 onwards
Exclusion criteria	• Not an evidence-based clinical practice guideline: exclude guidelines and position statements that are entirely consensus-based. • Wrong patient population: guidance does not relate to COPD or mixed airways disease (e.g. ACOS). • Wrong intervention: does not provide guidance on pharmacological management.

Source: Final Research Protocol, approved by ERG on 2 August 2016.
Abbreviations: ACOS, asthma-COPD overlap syndrome; AHRQ, Agency for Healthcare Research and Quality; COPD, chronic obstructive pulmonary disease; FDA, Food and Drug Administration; G-I-N, Guidelines International Network; LFA, Lung Foundation Australia; NICE, National Institute for Health and Care Excellence; NPS, National Prescribing Service; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public Summary Document; SIGN, Scottish Intercollegiate Guidelines Network; TGA, Therapeutic Goods Administration; ToR, Term of Reference; TSANZ, Thoracic Society of Australia and New Zealand.

1.3.2 Summary of current clinical guidance

For each guideline, general information such as the title, guideline developer/affiliation or commissioning body, primary aim and focus, target audience and a brief summary of the method used to develop the guidance, has been tabulated. Relevant recommendations, evidence statements, practice tips/consensus statements and consideration of cost-effectiveness have also been tabulated, and other relevant guidance and general advice has been reported in the text. Where applicable, the system used to grade recommendations or the evidence base, has been summarised.

Journal citations and other references to the evidence base are not collated; rather, they can be found in the specified online website. In cases where there is not a clear link between the guidance provided in the guideline and the underlying evidence base, this has been noted.

1.3.3 Synthesis of findings

Current clinical guidance relating to appropriate use of COPD medicines was compared with current PBS prescribing restrictions and the clinical place of COPD medicines as considered by the PBAC in PSDs for COPD medicines. For each review question, the findings have been synthesised into an overall narrative. The analysis has considered the impact of recommendations in guidelines for non-PBS listed medicines, the need for a stabilisation period prior to initiating LAMA/LABA FDCs, recommendations relating to specific dosing and inhaler types, eligibility criteria (severity, prior disease and treatment history), and considerations relating to mixed airways disease.

1.4 Summary of current clinical guidance

1.4.1 COPD-X guidelines and GOLD Strategy Report

The two key clinical practice guidelines of relevance to Australian practice are:

- COPD-X Plan (2015/2016): Australian and New Zealand Guidelines for the Management of Chronic Obstructive Pulmonary Disease.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD) Strategy Report (2016): Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.

The COPD-X plan is a joint project by the Thoracic Society of Australia and New Zealand (TSANZ) and LFA. The focus of the guideline is described in its name:

- C – Case finding and confirm diagnosis
- O – Optimise function
- P – Prevent deterioration
- D – Develop a plan of care

- X – Manage eXacerbations.

The guideline describes diagnosis, initiation of therapy, management of established COPD and its exacerbations, and is directed at GPs, other primary health care clinicians, hospital based clinicians, and specialists working in respiratory health. The primary aim and focus of the guideline is to effect changes in clinical practice based on sound evidence and shift the emphasis from a predominant reliance on pharmacological treatment of COPD to a range of interventions including patient education, self-management of exacerbations, and pulmonary rehabilitation.

Importantly, the COPD-X guidelines are evidence-based, where published evidence is systematically searched for, identified, and reviewed regularly. The COPD Guidelines Evaluation Committee meets four times a year and determines whether the reviewed evidence needs incorporation into the guideline; hence, the main source document for COPD-X is an online version with interactive links that can be updated with new evidence as required. Each of the interactive links provides a connection to the clinical evidence in terms of outcome results, statistical significance, journal citations, and the assigned level of evidence according to the National Health and Medical Research Council (NHMRC) evidence grading system (which has been reclassified from the US National Heart, Lung and Blood Institute (NHLBI) grading scheme).

In addition to the online version, the COPD-X guideline is available as:

- a Concise Guide for Primary Care (2016)
- an algorithm for the stepwise management of stable COPD (2016)
- an algorithm for managing a COPD exacerbation in primary care (2015)
- a downloadable version of the full guideline (most recently dated June 2015).

The additional COPD-X formats are based on the online full version, and thus are also evidence-based. The online full COPD-X guideline, as well as the additional guideline formats, are summarised in Table 1.2.

The key international expert advice for COPD is the GOLD Strategy Report, updated in 2016, and titled the Global Strategy for the Diagnosis, Management, and Prevention of COPD. It is published and maintained by the Global Initiative for Chronic Obstructive Lung Disease in the United States, and has an international board of directors and science committee, as well as two panels of invited reviewers and national leaders. It is described as a strategy document for health care professionals to use as a tool to implement effective management programs based on available health care systems, with a target audience of GPs and any other primary care specialists. The GOLD Strategy Report is evidence-based, using a defined evidence grading system (evidence categories A to E) where the highest level of evidence comprises randomised controlled trials (RCTs) with a rich body of evidence, and the lowest level of evidence refers to panel consensus judgement. The original GOLD Strategy Report was published in 2001; updates have been released in January 2013, January 2014, and January

2015, and are based on scientific literature published since the completion of the 2011 document, while maintaining the same treatment paradigm.

As with the COPD-X guidelines, there are several different formats available to access the GOLD Strategy Report:

- the main document, containing the evidence-based material (Table 1.2)
- the GOLD Pocket Guide, based on the 2014 full GOLD Strategy Report (Table 1.2)
- the Asthma, COPD and 'Asthma-COPD Overlap Syndrome' (ACOS) guidelines, which is a consensus-based document from the Global Initiative for Asthma (GINA) and GOLD (see later section on ACOS, Table 1.5).

Table 1.2 COPD-X and GOLD prescribing guidelines for COPD

1. Name of publication or citation 2. Source 3. Country 4. Primary aim and focus 5. Target audience 6. Method used to develop the guidance 7. Developer/commissioning body	Prescribing summary for pharmacologic therapy (from 2011 inclusive)
LFA and TSANZ	
1. Yang IA, Dabscheck E, George J, Jenkins S, McDonald CF, McDonald V, Smith B, Zwar N. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2016. Version 2.46, June 2016. **2.** Online version of 2016 COPD-X guidelines: **3.** Australia and New Zealand. **4.** a. Effect changes in clinical practice based on sound evidence; and b. Shift the emphasis from a predominant reliance on pharmacological treatment of COPD to a range of interventions which include patient education, self-management of exacerbations and pulmonary rehabilitation. **5.** General practitioners, other primary health care clinicians, hospital based clinicians and specialists working in respiratory health. **6.** Evidence-based.[a] Published evidence is systematically searched for, identified, and reviewed on a regular basis. The COPD Guidelines Evaluation Committee meets four times a year and determines whether the reviewed evidence needs incorporation into the guideline. **7.** TSANZ and LFA.	Inhaled bronchodilators – Inhaled bronchodilators provide symptom relief and may increase exercise capacity [evidence level I]. • SABAs are now usually prescribed for use as rescue medication, i.e. for relief of breathlessness, rather than for regular use. • LAMAs: Tiotropium, glycopyrronium, or umeclidinium are used once daily. Aclidinium is used twice daily. Notes: A systematic review found that tiotropium improved mean QoL, increased the number of patients with a clinically significant improvement, and reduced the number of patients with a clinically significant deterioration in QoL [evidence level I]. Use of 18 µg per day of tiotropium in mild to moderate (FEV_1 50-80% of predicted) COPD over 7 months was associated with an 85 mL advantage in FEV_1, which is of uncertain clinical benefit, and inconsistent benefits in other outcomes, without assessment of QoL or health service utilisations [evidence Level II]. Tiotropium increased the time to first exacerbation by 42 days compared to salmeterol corresponding to a reduction in risk by 17% [evidence Level II]. A glycopyrronium trial randomised patients to placebo or tiotropium and found that glycopyrronium was not inferior with regards to spirometry, QoL and moderate to severe exacerbations compared to tiotropium [evidence Level II]. Aclidinium reduced the number of patients with exacerbations requiring hospitalisation by 13 per 1,000 over 4 to 52 weeks compared to placebo [evidence level I]. A network meta-analysis of clinical trials comparing the efficacy of LAMAs vs placebo showed that tiotropium dry powder inhaler was the only LAMA formulation which reduced severe exacerbations [evidence level I]. Another network meta-analysis showed that all current LAMAs have similar efficacy in terms of change in FEV_1, SGRQ, dyspnoea index and rescue medications [evidence level I]. • LABAs: Indacaterol or olodaterol are used once daily. Salmeterol or eformoterol are used twice daily. Notes: LABA treatment has been shown to reduce exacerbations, including those requiring hospitalisation, but the evidence is of moderate quality and confounded by concomitant ICS use. Indacaterol is an inhaled LABA that can be given as a once-daily maintenance therapy for COPD. Compared to placebo, indacaterol improves dyspnoea, FEV_1 and HRQoL, and reduces exacerbations [evidence level I]. Olodaterol is another once-daily LABA which improves FEV_1 and reduces rescue inhaler use compared with placebo. It appears to be generally safe and to have similar bronchodilator effects to BD formoterol [evidence Level II] and once daily indacaterol, although head-to-head studies with indacaterol have not been reported and the comparisons have been derived through network meta-analysis. • LAMA/LABA combinations: tiotropium/olodaterol; glycopyrronium/indacaterol; umeclidinium/vilanterol; aclidinium/eformoterol. Notes: A Cochrane systematic review of 10 studies found that the combination of tiotropium/LABA provided small improvements in HRQoL and bronchodilation, compared to tiotropium alone [evidence level I]. Dual bronchodilation with a combination of glycopyrronium/indacaterol, given once daily, was found to increase FEV_1 (pre-dose) compared to the mono-components, tiotropium or placebo [evidence Level II]. The combination of glycopyrronium/indacaterol showed favourable improvements in lung function over fluticasone propionate/salmeterol in a study of moderate to severe COPD patients without exacerbations in the previous year [evidence Level II]. Overall, these benefits of glycopyrronium/indacaterol were supported by systematic reviews [evidence level I]. Once-daily umeclidinium/vilanterol 62.5/25 µg was well tolerated and provided clinically significant improvements in lung function and symptoms compared with placebo in patients with COPD [evidence Level II]. Combination treatment with once-daily umeclidinium/vilanterol improved lung function compared with tiotropium monotherapy in patients with moderate to very severe COPD. There were no significant differences between treatment groups with respect to risk of COPD exacerbation, TDI focal score, SOBDA diary score or SGRQ scores [evidence Level II]. A systematic review of the efficacy and safety of umeclidinium/vilanterol for the treatment of COPD in patients with moderate to severe COPD found benefits in terms of mean trough FEV_1 of the dual bronchodilator compared with its mono-components or tiotropium or fluticasone propionate/salmeterol. Umeclidinium/vilanterol also reduced the likelihood of exacerbations compared with mono-components. There were no differences in dyspnoea, QoL, or exacerbation risk between umeclidinium/vilanterol and tiotropium [evidence level I]. Twice daily aclidinium/eformoterol had greater bronchodilation over placebo, and to a lesser extent, vs eformoterol or aclidinium alone in patients with COPD [evidence Level II].

1. Name of publication or citation 2. Source 3. Country 4. Primary aim and focus 5. Target audience 6. Method used to develop the guidance 7. Developer/commissioning body	Prescribing summary for pharmacologic therapy (from 2011 inclusive)
	Oral bronchodilators • Methylxanthines: Theophyllines have gone out of favour in many countries because of their narrow therapeutic index and potential for significant adverse effects. • PDE type-4 inhibitors: Cilomilast and roflumilast are not currently available in Australia. Corticosteroids – Long term use of systemic corticosteroids is not recommended [evidence level I]. • OCS – prednisolone. • ICS – ICS should be considered in patients with moderate to severe COPD and frequent exacerbations [evidence level I]. • Notes: Fluticasone[b] and budesonide[c] are discussed. The guidelines state that any potential benefits of ICS should be weighed against the potential risks of local oropharyngeal AEs and pneumonia. In people with COPD and diabetes mellitus, particular care should be taken not to exceed the recommended dose of corticosteroids as there is some evidence of a direct relationship between corticosteroid dose and glucose levels in such patients [evidence level III-2]. Withdrawal of ICS was not associated with any statistically significant increase in exacerbation rate in a systematic review of 4 RCTs in 901 patients [evidence level I]. COPD patients with FEV_1 50-80% predicted and no exacerbations in the past 12 months were able to be switched to indacaterol with no significant differences in FEV_1, dyspnoea score, SGRQ score or frequency of exacerbations over six months, providing reassurance that switching from fluticasone propionate/salmeterol to indacaterol appeared to be safe in this group of milder COPD patients [evidence Level II]. • ICS vs LABA: A systematic review of ICS vs LABA in COPD found similar benefits in exacerbation rates and mortality when comparing these treatments, but there was a higher rate of pneumonia with ICS. A systematic review of RCTs of ICS vs non-ICS therapy for COPD showed an increased risk of TB associated with ICS use, and no excess risk of influenza with ICS use [evidence level I]. Inhaled combination therapy • ICS/LABA: Fluticasone propionate/salmeterol and budesonide/formoterold reduce the rate of exacerbations. Fluticasone furoate/vilanterol is a new once-daily combination inhaled medicine. Notes: A systematic review of 19 randomised controlled trials involving 10,400 COPD patients of combined ICS and LABA in one inhaler [evidence level I] found that, compared with placebo, both fluticasone propionate/salmeterol and budesonide/formoterol reduced the rate of exacerbations. Data from 2010 [evidence level I] in 30,495 patients with COPD enrolled in trials of six months or greater duration found combination therapy, compared with placebo, was associated with a reduction in all-cause mortality. A systematic review in 2012 of 14 studies (11,784 participants) found low quality evidence for reduced exacerbation rates with ICS/LABA vs LABA alone [evidence level I]. A network meta-analysis of 21 clinical trials of ICS/LABA demonstrated that these combinations, except budesonide/formoterol and beclomethasone/formoterol, reduced moderate-to-severe exacerbations as compared with placebo and LABA; however, none of the combinations reduced severe exacerbations [evidence level I]. A systematic review of 15 RCTs involving 7,814 COPD patients of combined corticosteroids and LABAs in one inhaler vs inhaled steroids alone [evidence level I] found that, compared with ICS, exacerbation rates were significantly reduced with combination therapies. • ICS/LABA/LAMA: Studies of triple therapy with ICS and LABA and LAMA in combination have revealed conflicting results. A two-year double-blind, double-dummy RCT comparing tiotropium to triple therapy with tiotropium plus fluticasone propionate/salmeterol (500/50µg bd) found no difference in exacerbation rates between the groups, but the combination therapy group achieved a small, statistically significant benefit in QoL as well as the unexpected benefit of fewer deaths [evidence Level II]. A Cochrane systematic review found that the addition of combination treatment with LABA/ICS to tiotropium improves HRQoL and lung function compared to tiotropium alone [evidence level I]. A 12-week study of budesonide/formoterol with or without tiotropium [evidence Level II] found a significant increase in FEV_1 with triple therapy. However, a longer-term double-blind placebo-controlled RCT of one year comparing salmeterol or combined salmeterol/fluticasone propionate in addition to tiotropium did not find 'triple' therapy reduced the proportion of patients suffering at least one exacerbation, the primary study endpoint. Despite this, patients receiving 'triple' therapy did experience fewer hospitalisations for COPD and for all causes, as well as a clinically significant improvement in their quality of life [evidence Level II]. A large UK GP database study found frequent over-prescribing of triple therapy in COPD patients without asthma, severe airflow obstruction or history of frequent exacerbations

1. Name of publication or citation 2. Source 3. Country 4. Primary aim and focus 5. Target audience 6. Method used to develop the guidance 7. Developer/commissioning body	Prescribing summary for pharmacologic therapy (from 2011 inclusive)
	[evidence level III-2], highlighting the importance of commencing bronchodilators as initial pharmacological therapy for patients with symptomatic COPD, before considering adding ICS (as ICS/LABA inhalers) in patients who have both severe airflow obstruction (FEV_1 <50% predicted) AND frequent exacerbations (two or more in the past year). Combinations studied include budesonide/formoterol/tiotropium and fluticasone propionate/salmeterol/tiotropium.
1. Abramson M, Frith P, Yang I, McDonald C, Hancock K, Jenkins S, McDonald V, Zwar N, Maguire G, Halcomb E, Polak Scowcroft C. COPD-X Concise Guide for Primary Care. Brisbane. Lung Foundation Australia. 2016.[e] 2. COPD-X Concise Guide for Primary Care 3. Australia. 4. Concise version of the COPD-X full guidelines. 5. General practitioners. 6. Evidence-based. Underpinned by the comprehensive COPD-X full guidelines.[a] 7. GP Advisory Group, LFA.	For all symptomatic patients with COPD: • Follow a stepwise approach to pharmacological treatment until adequate control of breathlessness, functional capacity, and exacerbation frequency is achieved. • Use SABA (salbutamol, terbutaline) or SAMA (ipratropium) provide short-term relief of breathlessness [evidence level I]. For patients receiving short-acting bronchodilators who have persistent troublesome dyspnoea, add a LABA or LAMA (or both in combination if monotherapy is not adequate) for regular use. LABAs (salmeterol, eformoterol, indacaterol) or LAMAs (tiotropium, glycopyrronium, umeclidinium or aclidinium) may improve lung function, symptoms, QoL, and exacerbation frequency [evidence level I-II]. A LAMA and LABA in combination is better than either monotherapy [evidence Level II]. LAMA/LABA FDCs in a single inhaler (glycopyrronium/indacaterol, umeclidinium/vilanterol, tiotropium/olodaterol, aclidinium/eformoterol) are available for patients who remain symptomatic despite monotherapy with either alone. For patients with FEV_1 <50% predicted and ≥2 exacerbations in 12 months: • Initiate an ICS/LABA FDC and discontinue LABA monotherapy. ICS combined with LABAs alone (fluticasone propionate/salmeterol, budesonide/eformoterol, fluticasone/vilanterol) may reduce exacerbation frequency and improve QoL [evidence level I]. • For patients with moderate-to-severe COPD with frequent exacerbations who are not receiving a LAMA, consider addition of a LAMA to the ICS/LABA. Limited evidence suggests (and new evidence is being reviewed) that the use of a LABA + ICS + LAMA provides more benefit than the individual treatments alone. This combination of therapies may be useful for patients with moderate-to-severe COPD with repeated exacerbations. For severe COPD (FEV_1 <40% predicted), consider adding low-dose theophylline (100 mg twice daily). Theophylline has a moderate effect on lung function in patients with moderate to severe COPD. Low-dose theophylline may also help restore sensitivity to ICS and target eosinophilic airway inflammation [evidence level I-II]. Avoid long-term (>2 weeks) use of OCS.
1. Stepwise management of stable COPD. 2016.[f] 2. LFA Stepwise Management of Stable COPD 3. Australia. 4. Management of stable COPD and combination of therapies that can be used together. 5. Assume general practitioners. 6. Evidence-based. Underpinned by the comprehensive COPD-X full guidelines. Evidence levels are not specified in the algorithm. 7. LFA.	**PHARMACOLOGIC MANAGEMENT OF STABLE COPD** Mild, moderate or severe symptoms: • Check device usage technique and adherence at each visit - up to 90% of patients do not use devices correctly. • Short-acting reliever medication: SABA or SAMA. • Symptom relief: LAMA and/or LABA. Moderate or severe symptoms: • Exacerbation prevention: When FEV_1 <50% predicted and 2 or more exacerbations in the previous 12 months, consider commencing ICS/LABA therapy. Severe symptoms • Consider low-dose theophylline. Therapies • SABA: salbutamol, terbutaline. • SAMA: ipratropium. • LAMA: tiotropium, glycopyrronium, aclidinium, umeclidinium. • LABA: salmeterol, eformoterol, indacaterol.

1. Name of publication or citation 2. Source 3. Country 4. Primary aim and focus 5. Target audience 6. Method used to develop the guidance 7. Developer/commissioning body	Prescribing summary for pharmacologic therapy (from 2011 inclusive)
	• LABA/LAMA: indacaterol/glycopyrronium, umeclidinium/vilanterol, tiotropium/olodaterol, aclidinium/eformoterol. • ICS/LABA: fluticasone propionate/salmeterol, budesonide/eformoterol, fluticasone/vilanterol. Addition of therapies • SABA can be used with: SAMA, LAMA, LABA, LABA/LAMA, ICS/LABA. • SAMA can be used with: SABA, LABA, ICS/LABA. • LAMA can be used with: SABA, LABA, ICS/LABA. • LABA can be used with: SABA, SAMA, LAMA. • LABA/LAMA can be used with: SABA. • ICS/LABA can be used with: SABA, SAMA, LAMA.
1. Abramson M, Crockett AJ, Dabscheck E, Frith PA, George J, Glasgow N, Jenkins S, McDonald C, McDonald V, McKenzie DK, Wood-Baker R, Yang I, Zwar N, on behalf of Lung Foundation Australia and the Thoracic Society of Australia and New Zealand. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease. COPD-X Guidelines – Version 2.42 (June 2015). 2. COPD-X Plan 2015 3. Australia and New Zealand. a. Effect changes in clinical practice based on sound evidence; and b. Shift the emphasis from a predominant reliance on pharmacological treatment of COPD to a range of interventions which include patient education, self-management of exacerbations and pulmonary rehabilitation. 4. General practitioners, other primary health care clinicians, hospital based clinicians and specialists working in respiratory health. 5. Evidence-based. Published evidence is systematically searched for, identified, and	**PHARMACOLOGIC MANAGEMENT**[g] Inhaled bronchodilators. Inhaled bronchodilators provide symptom relief and may increase exercise capacity. *Short-acting bronchodilators* SABA – now usually prescribed for use as rescue medication, i.e. for relief of breathlessness, rather than for regular use. SAMA – ipratropium has been superseded by tiotropium (a LAMA). Short-acting bronchodilator combinations – combining two classes of bronchodilators (SABA and ipratropium bromide) may provide added benefits without compounding adverse effects. *Long-acting bronchodilators* LAMA – A systematic review found that tiotropium improved mean quality of life, increased the number of patients with a clinically significant improvement, and reduced the number of patients with a clinically significant deterioration in quality of life. Glycopyrronium and aclidinium are also reviewed. LABA – (e.g. indacaterol, salmeterol and eformoterol). A systematic review of RCTs found that compared to placebo, LABAs used for at least four weeks produce statistically significant benefits in lung function, quality of life, use of 'reliever' short-acting bronchodilators and acute exacerbations. LAMA/LABA – A Cochrane systematic review of five studies found that the combination of tiotropium and a LABA provided small improvements in HRQoL and bronchodilation, compared to tiotropium alone. *Assessment of response and continuation of bronchodilator therapy* Oral bronchodilators Methylxanthines – Theophylline has a modest effect on FEV_1 and FVC and slightly improves arterial blood gas tensions in moderate to severe COPD. However, theophyllines have gone out of favour in many countries because of their narrow therapeutic index and potential for significant adverse effects. Some patients with disabling breathlessness may, however, derive benefit from their use. PDE-4 inhibitors – PDE-4 inhibitors are promising candidates for the treatment of chronic obstructive pulmonary disease. Further research is required to determine their long-term impact and role when used with other treatments including corticosteroids. Corticosteroids

1. Name of publication or citation 2. Source 3. Country 4. Primary aim and focus 5. Target audience 6. Method used to develop the guidance 7. Developer/commissioning body	Prescribing summary for pharmacologic therapy (from 2011 inclusive)
reviewed on a regular basis. The COPD Guidelines Evaluation Committee meets four times a year and determines whether the reviewed evidence needs incorporation into the guideline.[a] **6.** TSANZ and LFA.	OCS – Some patients with stable COPD show a significant response to oral corticosteroids. Therefore, a short course (2 weeks) of prednisolone (20–50mg daily) may be tried with appropriate monitoring. ICS – Should be considered in patients with moderate to severe COPD and frequent exacerbations. ICS versus LABA – A systematic review supported LABAs as part of frontline therapy for COPD, with regular ICS therapy as an adjunct in patients experiencing frequent exacerbations. Inhaled combination therapy ICS/LABA – A systematic review of 19 RCTs involving 10,400 COPD patients of combined ICS and LABA in one inhaler found that, compared with placebo, both fluticasone propionate/salmeterol and budesonide/formoterol reduced the rate of exacerbations. ICS/LABA/LAMA – Studies of 'triple therapy' with ICS and LABA and LAMA in combination have revealed conflicting results.
GOLD http://goldcopd.org/	
1. Global strategy for the diagnosis, management and prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016.[h] **2.** GOLD Strategy 2016 **3.** United States. **4.** A strategy document for health care professionals to use as a tool to implement effective management programs based on available health care systems. **5.** General practitioners and any other primary care specialists. **6.** Evidence-based.[i] Updated reports of the original 2001 document were released in January 2013, January 2014, and January 2015, and are based on scientific literature published since the completion of the 2011 document but maintain the same treatment paradigm. **7.** Global Initiative for Chronic Obstructive Lung Disease (GOLD).	**PHARMACOLOGIC MANAGEMENT FOR STABLE COPD (formulations and doses are provided in Table 3.3 [p22] of the guidelines document and are summarised in Table 1.8 of this review)** **Bronchodilators** Bronchodilator medications are given on either an as-needed basis or a regular basis to prevent or reduce symptoms (Evidence A). *Beta-2 agonists* • SABA: Examples are fenoterol, levalbuterol, salbutamol (albuterol), terbutaline. Regular and as-needed use of SABA improve FEV_1 and symptoms (Evidence B). • LABA: Examples are formoterol, arformoterol, indacaterol, olodaterol, salmeterol, tulobuterol. Formoterol and salmeterol significantly improve FEV_1 and lung volumes, dyspnoea, HRQoL and exacerbation rate (Evidence A). Salmeterol reduces the rate of hospitalisation (Evidence B). Indacaterol is a once-daily LABA with a duration of action of 24 hours. The bronchodilator effect is significantly greater than that of formoterol and salmeterol, and similar to tiotropium (Evidence A). Indacaterol has significant effects on breathlessness, health status and exacerbation rate (Evidence B). *Anticholinergics* • Short-acting: Examples are ipratropium, oxitropium. • LAMA: Examples are aclidinium, glycopyrronium, tiotropium, umeclidinium. Tiotropium reduces exacerbations and related hospitalisations, improves symptoms and health status (Evidence A), and improves the effectiveness of pulmonary rehabilitation (Evidence B). *Methylxanthines* • Examples are aminophylline, theophylline (SR). Theophylline is less effective and less well tolerated than inhaled LAMAs or LABAs, and is not recommended if those drugs are available and affordable. However, there is evidence for a modest bronchodilator effect compared with placebo in stable COPD (Evidence A). There is also some evidence of symptomatic benefit compared to placebo. Addition of theophylline to salmeterol produced a greater improvement in FEV_1 and breathlessness than salmeterol alone (Evidence B). Low-dose theophylline reduces exacerbations but does not improve post-bronchodilator lung function (Evidence B). *Combination bronchodilator therapy* • Combination SABA/SAMA: Examples are fenoterol/ipratropium, salbutamol/ipratropium. Combinations of SABA and anticholinergics are superior compared to either medication alone in improving FEV_1 and symptoms (Evidence B). • Combination LAMA/LABA: Examples are formoterol/aclidinium, indacaterol/glycopyrronium, olodaterol/tiotropium, vilanterol/umeclidinium. Short-term combination

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	therapy using formoterol and tiotropium has been shown to have a bigger impact on FEV_1 than the single components (Evidence B). Combinations of a LAMA/LABA have shown a significant increase in lung function whereas the impact on patient-reported outcomes is still limited. There is still too little evidence to determine if a combination of LAMA/LABA is more effective than a long-acting anticholinergic alone for preventing exacerbations. *Recommendations for bronchodilators* • For both beta-2 agonists and anticholinergics, long-acting formulations (LABA and LAMA) are preferred over short-acting formulations. • The combined use of SABA or LABA and anticholinergics may be considered if symptoms are not improved with single agents. • Based on evidence of relatively low efficacy and more side effects, treatment with theophylline is not recommended unless other LABA and LAMA are unavailable or unaffordable. <u>Corticosteroids</u> *ICS* • Examples are beclomethasone, budesonide, fluticasone. Regular treatment with ICS improves symptoms, lung function, and QoL, and reduces the frequency of exacerbations in COPD patients with an FEV_1 <60% predicted (Evidence A). Regular treatment with ICS does not modify the long-term decline of FEV_1 nor mortality in patients with COPD (Evidence A). *Combination ICS/LABA* • Examples are formoterol/beclomethasone, formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone propionate, vilanterol/fluticasone furoate. An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate (Evidence B) to very severe COPD (Evidence A). A large prospective clinical trial failed to demonstrate a statistically significant effect of combination therapy on mortality, but a subsequent meta-analysis found that combination therapy may reduce mortality with a NNT of 36,254 (Evidence B). Combination therapy is associated with an increased risk of pneumonia, but no other significant side effect (Evidence A). The addition of an ICS/LABA combination to tiotropium improves lung function and QoL and may further reduce exacerbations (Evidence B) but more studies of triple therapy are needed. *Oral/systemic corticosteroids* • Examples are prednisone, methyl-prednisolone. **<u>PDE-4 inhibitor</u>** • Roflumilast reduces moderate and severe exacerbations treated with corticosteroids by 15-20% in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations (Evidence A). The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators (Evidence A). *Recommendations for corticosteroids and PDE-4 inhibitors* • There is no evidence to recommend a short-term therapeutic trial with OCS in patients with COPD to identify those who will respond to ICS or other medications. • Long-term treatment with ICS is recommended for patients with severe and very severe COPD and frequent exacerbations that are not adequately controlled by long-acting bronchodilators. • Long-term monotherapy with OCS is not recommended in COPD. • Long-term monotherapy with ICS is not recommended in COPD because it is less effective than the combination of ICS with LABA. • Long-term treatment containing ICS should not be prescribed outside their indications, due to the risk of pneumonia and the possibility of an increased risk of fractures following long-term exposure. • The PDE-4 inhibitor, roflumilast, may also be used to reduce exacerbations for patients with chronic bronchitis, severe and very severe COPD, and frequent

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	exacerbations that are not adequately controlled by LABA and LAMA. **Other pharmacologic treatments** Vaccines, alpha-1 antitrypsin augmentation therapy, antibiotics, mucolytic and antioxidant agents, immunoregulators, antitussives, vasodilators, narcotics.
1. Global initiative for chronic obstructive lung disease. Pocket guide to COPD diagnosis, management and prevention. A guide for health care professionals. Updated 2015. 2. GOLD Pocket Guide 2015 3. United States. 4. Management and prevention. 5. Health care professionals. 6. Evidence-based. Developed from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), updated 2014. 7. Global Initiative for Chronic Obstructive Lung Disease (GOLD).	**PHARMACOLOGIC MANAGEMENT** (see Table 1.6 for Patient Group definitions) • Patient Group A – Low risk patients with fewer symptoms: ➢ First choice: SAMA prn or SABA prn; ➢ Alternative choice: LAMA or LABA or SABA/SAMA; ➢ Other possible treatments[i]: theophylline. • Patient Group B – Low risk patients with more symptoms: ➢ First choice: LAMA or LABA; ➢ Alternative choice: LAMA/LABA; ➢ Other possible treatments[c]: SABA and/or SAMA; theophylline. • Patient Group C – High risk patients with fewer symptoms: ➢ First choice: ICS/LABA or LAMA; ➢ Alternative choice: LAMA/LABA or LAMA/PDE-4 inhibitor or LABA/PDE-4 inhibitor; ➢ Other possible treatments[c]: SABA and/or SAMA; theophylline. • Patient Group D – High risk patients with more symptoms: ➢ First choice: ICS/LABA and/or LAMA; ➢ Alternative choice: ICS/LAMA/LABA or ICS/LABA/PDE-4 inhibitor or LAMA/LABA or LAMA/PDE-4 inhibitor; Other possible treatments[c]: carbocysteine; SABA and/ or SAMA; theophylline.

Abbreviations: AE, adverse effect; BD, twice daily; COPD, chronic obstructive pulmonary disease; FDC, fixed dose combination; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GP, general practitioner; GOLD, Global initiative for chronic obstructive lung disease; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; LFA, Lung Foundation Australia; NHMRC, National Health and Medical Research Council; NNT, number needed to treat; OCS, oral corticosteroids; PDE-4, phosphodiesterase-4; prn, as needed; QoL, quality of life; RCT, randomised controlled trial; SABA, short-acting beta-2 agonist; SAMA, short-acting muscarinic antagonist; SGRQ, St George's Respiratory Questionnaire; SOBDA, Shortness of Breath with Daily Activity; SR, sustained release; TB, tuberculosis; TDI, transition dyspnoea index; TSANZ, Thoracic Society of Australia and New Zealand; vs, versus.

a Corresponds to NHMRC levels of evidence. Evidence level 1: Evidence obtained from a systematic review of all relevant randomised controlled trials; Evidence Level II: Evidence obtained from at least one properly designed randomised controlled trial; Evidence level III-2: Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.

b Fluticasone propionate monotherapy has an unrestricted PBS listing. The TGA indication does not include treatment for COPD.

c Budesonide monotherapy is either PBS listed for conditions other than COPD, or PBS listed with an unrestricted listing but not TGA indicated for COPD.

d Budesonide/eformoterol is PBS listed. Formoterol and eformoterol are used interchangeably in this Review.

e A superseded 2014 version of this document was identified: Superceded COPD-X Concise Guide for Primary Care.

f These algorithms are also presented as a figure in the COPD-X Concise Guide for Primary Care, but one of the links for a full page view does not work in that guide.

g Evidence levels are provided in this document, similar to the full online COPD-X guidelines; however, they have not been repeated in this tabulation of the downloadable version. A top line summary only has been included. See the summary for the online version for a full description of the evidence.

h A superseded 2011 version of these guidelines was identified: Superceded GOLD Strategy.

i Evidence category A: RCTs, rich body of data; B: RCTs, limited body of data; C: non-randomised trials or observational studies; D: panel consensus judgement.

j Medications may be used alone or in combination with those listed as first or alternative choices.

1.4.2 Other guidelines

As well as the leading COPD-X guidelines and GOLD Strategy Report, there are several other sources of relevant guidelines from guidelines databases, summarised in Table 1.3 and listed below:

- Agency for Healthcare Research and Quality (AHRQ) National Guidelines Clearinghouse (NGC):
  - Criner et al (2015). Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline (ACCP, CTS) (NGC:010698).
  - Medical Services Commission (2011). Chronic obstructive pulmonary disease (COPD). British Columbia Medical Services Commission; (NGC:009466).
  - Management of Chronic Obstructive Pulmonary Disease Working Group (2014). Veterans Affairs/Department of Defense clinical practice guideline for the management of chronic obstructive pulmonary disease (NGC:010629).
  - Qaseem et al (2011). Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (ACP, ACCP, ATS, ERS) (NGC:008641).
- National Institute of Health and Care Excellence (NICE):
  - NICE Pathway (2016) for managing stable COPD and exacerbations of COPD.

The guidelines from the NGC and NICE are also evidence-based, with various systems used to grade the levels of evidence (see footnotes to Table 1.3). The NICE Pathway, published in 2016, was developed from the COPD NICE guideline CG101 (2010), which is currently being updated. NICE guideline CG101 is not listed in Table 1.3 as the guidelines are restricted to those published from 2011 onwards.

NPS MedicineWise has published a topic specific report: Chronic Obstructive Pulmonary Disease (COPD), in March 2016 (commercial-in-confidence). The report identifies three Australian guidelines and one international report:

- Therapeutic Guidelines: Respiratory. Version 5, 2015 (based on COPD-X guidelines).
- COPD-X guidelines.
- COPD: pulmonary rehabilitation, HANDI: the Handbook of non-drug interventions, Royal Australian College of General Practitioners (RACGP), 2013 (not relevant to this Review).
- GOLD Strategy Report.

The report states that the COPD guidance in Therapeutic Guidelines is based on the COPD-X guidelines; therefore, the guidance from Therapeutic Guidelines is not described in Table 1.3.

Table 1.3 Prescribing guidelines for COPD, other than COPD-X and GOLD

1. Name of publication or citation 2. Source 3. Country 4. Primary aim and focus 5. Target audience 6. Method used to develop the guidance 7. Developer/commissioning body	Prescribing summary for pharmacologic therapy (from 2011 inclusive)
AHRQ NGC	
1. Medical Services Commission. Chronic obstructive pulmonary disease (COPD). Victoria (BC): British Columbia Medical Services Commission; 2011 Jan 1. 17 p. NGC:009466 2. Medical Services Commission COPD Guideline 3. Canada. 4. Diagnosis and management of COPD. 5. Family physicians in British Columbia. 6. Evidence-based. Review of the recommendations of the Canadian Thoracic Society and other international strategies for the management of COPD. 7. Medical Services Commission, British Columbia.	**PHARMACOLOGIC MANAGEMENT** Bronchodilators are the mainstay of COPD pharmacotherapy. Pharmacological treatment of COPD has not been shown to reverse, slow, or prevent progressive decline in lung function, but can improve symptoms, reduce exacerbations and hospitalisations, and improve quality of life. Bronchodilators reduce air-trapping, dyspnoea, and improve QoL even if improvement is not seen on spirometry. • Patients with mild COPD should be prescribed an inhaled SABA or ipratropium to be used as needed. • If symptoms persist, then consider regular use of ipratropium or a long-acting bronchodilator (tiotropium or a LABA). • If the patient continues to be symptomatic despite the addition of tiotropium or LABA, the other may be added. • Concurrent use of tiotropium and ipratropium is not recommended. • Regular use of ICS could be added to combination tiotropium and LABA therapy for patients with moderate to severe COPD with a history of exacerbations (one or more per year, on average, for two consecutive years) to reduce exacerbations, or if asthma coexists. • Long term OCS therapy is not recommended. • If indications for both a LABA and an ICS exist, then consider a combination product containing both medications. • Theophylline may be useful in select patients with persistent symptoms despite optimal inhaled therapy. • Evaluate the patient's inhaler technique regularly. Consider prescribing a spacer for metered dose inhalers. Dry powder inhalers are not used with a spacer.
1. Management of Chronic Obstructive Pulmonary Disease Working Group. VA/DoD clinical practice guideline for the management of chronic obstructive pulmonary disease. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014 Dec. 94 p. Originally published 1999. NGC:010629 2. VA/DOD Clinical practice guideline for the management of COPD Original source: VA/DOD Clinical practice guideline for the management of COPD 3. United States. 4. Assessment of disease, optimisation of therapy, minimisation of complications and emphasis of care. 5. Primary care providers to patients in the VA/DoD health	• Prescribe SABAs to patients with confirmed COPD for rescue therapy as needed (strong evidence in favour). • Use spacers for patients who have difficulty actuating and coordinating drug delivery with MDIs (weak evidence in favour). • Offer long-acting bronchodilators to patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnoea, cough) (strong evidence in favour). • Offer tiotropium (LAMA) as first-line maintenance therapy in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g. dyspnoea, cough) (weak evidence in favour). • Use inhaled tiotropium as first-line therapy for patients with confirmed, stable COPD who have respiratory symptoms (e.g. dyspnoea, cough) and severe airflow obstruction (i.e., post-bronchodilator FEV_1 <50%) or a history of COPD exacerbations (strong evidence in favour). • For clinically stable patients with a confirmed diagnosis of COPD and who have not had exacerbations on SAMAs, continue with this treatment, rather than switch to long-acting bronchodilators (weak evidence in favour). • For patients treated with a SAMA who are started on a LAMA to improve patient outcomes, discontinue the SAMA (weak evidence in favour). • Do not offer an ICS in symptomatic patients with confirmed, stable COPD as a first-line monotherapy (strong evidence against). • Do not use of LABAs without an ICS in patients with COPD who may have concomitant asthma (strong evidence against). • In patients with confirmed, stable COPD who are on inhaled LAMAs (tiotropium) or inhaled LABAs alone and have persistent dyspnoea on monotherapy, use combination therapy with both classes of drugs (strong evidence in favour). • In patients with confirmed, stable COPD who are on combination therapy with LAMAs (tiotropium) and LABAs and have persistent dyspnoea or COPD

1. Name of publication or citation 2. Source 3. Country 4. Primary aim and focus 5. Target audience 6. Method used to develop the guidance 7. Developer/commissioning body	Prescribing summary for pharmacologic therapy (from 2011 inclusive)
care delivery systems. 6. Evidence-based. The Guideline Work Group converted the USPSTF strengths of the recommendations from the 2007 guideline to the GRADE system.[a] It is based on a systematic review of both clinical and epidemiological evidence. 7. Department of Defense, Department of Veterans Affairs, Veterans Health Administration.	exacerbations, add ICS as a third medication (weak evidence in favour). • Do not offer roflumilast in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist (weak evidence against). • Do not offer chronic macrolides in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist (weak evidence against). • Do not offer theophylline in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist (weak evidence against). • Insufficient evidence to recommend for or against the use of NAC preparations in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnoea, cough). • Do not withhold cardio-selective beta-blockers in patients with confirmed COPD who have a cardiovascular indication for beta-blockers (weak evidence in favour). • Use non-pharmacologic therapy as first-line therapy and use caution in prescribing hypnotic drugs for chronic insomnia in primary care for patients with COPD, especially for those with hypercapnoea or severe COPD (weak evidence in favour). • For patients with COPD and anxiety, consult with a psychiatrist and/or a pulmonologist to choose a course of anxiety treatment that reduces, as much as possible, the risk of using sedatives/anxiolytics (weak evidence in favour).
1. Qaseem A, Wilt TJ, Weinberger SE, et al. (2011) Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med 2;155(3):179-191. NGC:008641 Update of 2007 guideline. 2. Diagnosis and management of stable COPD 3. United States and Europe. 4. Diagnosis and management of stable COPD. 5. Physicians. 6. Evidence-based. Updated literature search of the 2007 version using Medline for clinical studies and systematic reviews. Evidence was graded according to the American College of Physicians' Guideline Grading System.[b] 7. American College of Chest Physicians, American College of Physicians, American Thoracic Society, European Respiratory Society.	• For stable COPD patients with respiratory symptoms and FEV_1 between 60% and 80% predicted, treatment with inhaled bronchodilators may be used (weak recommendation, low quality evidence). • For stable COPD patients with respiratory symptoms and FEV_1 <60% predicted, treat with inhaled bronchodilators (strong recommendation, moderate-quality evidence). • Prescribe monotherapy using either inhaled LAMA or inhaled LABA for symptomatic patients with COPD and FEV_1 <60% predicted (strong recommendation, moderate-quality evidence). • Administer combination inhaled therapies (inhaled LAMA, inhaled LABA, or ICS) for symptomatic patients with stable COPD and FEV_1 <60% predicted (weak recommendation, moderate-quality evidence). • Prescribe pulmonary rehabilitation for symptomatic patients with an FEV_1 <50% predicted (strong recommendation, moderate-quality evidence). Consider pulmonary rehabilitation for symptomatic or exercise-limited patients with an FEV_1 >50% predicted (weak recommendation, moderate-quality evidence).

1. Name of publication or citation 2. Source 3. Country 4. Primary aim and focus 5. Target audience 6. Method used to develop the guidance 7. Developer/commissioning body	Prescribing summary for pharmacologic therapy (from 2011 inclusive)
NICE https://www.nice.org.uk	
1. NICE Pathway (2016). Managing stable COPD. Managing exacerbations of COPD. 2. NICE Pathways: COPD 3. United Kingdom. 4. Visual representation of NICE's recommendations on a topic, and access to the products that NICE has produced to support implementation of its guidance. 5. Health and social care professionals, public health experts, those who commission or provide health and social care services, employers and members of the public. 6. Evidence-based. Developed from guidance and supporting information from all NICE work programmes. Based on COPD NICE guideline CG101 (2010) – this guideline is being updated (see Appendix H). 7. NICE.	**PHARMACOLOGIC MANAGEMENT** Pulmonary rehabilitation: • **Inhaled therapy** – Drug: corticosteroids and/or short-acting bronchodilators, followed by long-acting bronchodilators. Delivery system: inhalers and/or spacers, followed by nebulisers. Notes: Corticosteroids – be aware of the potential risk of developing side effects (including non-fatal pneumonia) in people with COPD treated with ICS and be prepared to discuss with patients; short-acting bronchodilators – should be the initial empirical treatment for the relief of breathlessness and exercise limitation; long-acting bronchodilators – the effectiveness of bronchodilator therapy should not be assessed by lung function alone but should include a variety of other measures such as improvement in symptoms, activities of daily living, exercise capacity, and rapidity of symptom relief. Offer once-daily LAMA in preference to four-times-daily SAMA to people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, and in whom a decision has been made to commence regular maintenance bronchodilator therapy with a muscarinic antagonist. The BNF states that a SAMA should be discontinued when a LAMA is started. In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, offer the following as maintenance therapy: (1) if FEV_1 ≥50% predicted: either LABA or LAMA (2) if FEV_1 <50% predicted: either LABA with an ICS in a combination inhaler, or LAMA. In people with stable COPD and an FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA: (1) consider LABA + ICS in a combination inhaler (2) consider LAMA in addition to LABA where ICS is declined or not tolerated. Offer LAMA in addition to LABA + ICS to people with COPD who remain breathless or have exacerbations despite taking LABA + ICS, irrespective of their FEV_1. Consider LABA + ICS in a combination inhaler in addition to LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with LAMA irrespective of their FEV_1. The choice of drug(s) should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and cost. • **Oral therapy** – corticosteroids and/or mucolytics and/or roflumilast and/or theophylline. Drugs not recommended are antibiotics, antioxidants or antitussives. Notes: Maintenance use of OCS therapy in COPD is not normally recommended. Some patients with advanced COPD may require maintenance OCS when these cannot be withdrawn following an exacerbation. In these cases, the dose of OCS should be kept as low as possible. Mucolytic drug therapy should be considered in patients with a chronic cough productive of sputum. Mucolytic therapy should be continued if there is symptomatic improvement (for example, reduction in frequency of cough and sputum production). Do not routinely use mucolytic drugs to prevent exacerbations in people with stable COPD. Roflumilast is recommended only in the context of research as part of a clinical trial for adults with severe COPD (for the purposes of this guidance defined as FEV_1 post-bronchodilator <50% predicted) associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment. Theophylline should only be used after a trial of short-acting bronchodilators and long-acting bronchodilators, or in patients who are unable to use inhaled therapy, as there is a need to monitor plasma levels and interactions. – Followed by combined inhaled and oral therapies: effective combinations include beta-2 agonist and theophylline, or anticholinergic and theophylline.

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; BNF, British National Formulary; COPD, chronic obstructive pulmonary disease; DoD, Department of Defense (US); FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; MDI, metered dose inhaler; NAC, N-acetylcysteine; NGC, National Guideline Clearinghouse; NICE, The National Institute of Health and Care Excellence; OCS, oral corticosteroids; SABA, short-acting beta-2 agonist; SAMA, short-acting muscarinic antagonist; USPSTF, United States Preventive Services Task Force; VA, Department of Veterans Affairs (US).
a The GRADE system is described in Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: The significance and presentation of recommendations. J Clin Epidemiol. Jul 2013;66(7):719-725.
b Based on the American College of Physicians' Guideline Grading System, where a strong recommendation indicates that benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits; a weak recommendation indicates that benefits are finely balanced with risks and burden.

1.4.3 Treatment algorithm

Most of the COPD guidelines described in Table 1.2 and Table 1.3 indicate that there is a stepped algorithm for prescribing pharmacologic therapy for COPD. Implicit in the stepped approach is that patients have medications added or modified in a stepwise manner according to the symptoms of their disease. The algorithm for medicines to treat stable COPD is shown in Figure 1.1.

Figure 1.1 Basic treatment algorithm for prescription medicines for stable COPD in Australian and international COPD guidelines

Diagnosis → SAMA or SABA → LAMA or LABA→ LAMA/LABA[a] → ICS/LABA[a] → various[b]

Abbreviations: FDC, fixed-dose combination; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist;.
a A '/' can denote FDC or two separate products.
b Treatments for high risk COPD patients vary between guidelines.

The guidelines show small variations according to exactly which agents or combinations are available in respective countries; however, the general message in most guidelines is consistent: after diagnosis, begin treatment with SABA or SABA/SAMA, progress to LAMA or LABA, progress to a LAMA/LABA combination (either fixed dose or separate administration), then progress to an ICS/LABA combination (either fixed dose or separate administration).

COPD-X guidelines recommend that patients can step up from LABA or LAMA or LABA/LAMA to ICS/LABA, and that ICS/LABA is recommended for patients with FEV_1 ≤50% predicted and two or more exacerbations in the previous 12 months. In the reviewed GOLD Strategy Report, the ICS/LABA combination is listed as the first choice of therapy for high risk COPD patients; therefore, in cases where patients do not present until they have severe COPD, some patients may be prescribed an ICS/LABA before trialling a LAMA/LABA. Many guidelines recommend avoiding monotherapy with ICS or OCS. Once the high risk end of the algorithm is reached, various therapies or combinations are suggested, including triple therapy with ICS/LAMA/LABA, PDE-4 inhibitors, or methylxanthines. Note that SAMAs and SABAs are often referred to in guidelines as initial therapy; however, aside from ipratropium, these agents are beyond the scope of this report as they are accessed over the counter (OTC) in Australia.

One notable deviation from the algorithm shown in Figure 1.1 is apparent in two guidelines from the NGC (Table 1.3). The Canadian guideline from the Medical Services Commission (2011) and the US guideline from the Department of Veterans Affairs (2014) both state that ICS could be added to tiotropium/LABA combination therapy (that is, triple therapy), without mentioning the prior use of ICS/LABA dual therapy. A recent Cochrane review, addressing the question '*Should ICS be used with combination LABA/LAMA inhalers in stable COPD?,*' found that there are no studies assessing the relevant benefits and risks of these two treatment strategies, that is, ICS/LABA/LAMA vs LABA/LAMA.[3] The authors concluded that they cannot

[3] See the Cochrane review website.

confirm any benefit of adding ICS to a combination LABA/LAMA inhaler for the treatment of stable COPD.

The treatment algorithm implies that the LAMA is removed once ICS/LABA is initiated, although this is not explicitly stated. The COPD-X Concise guidelines state that patients with exacerbations should initiate an ICS/LABA FDC and discontinue LABA monotherapy; they do not say to discontinue a LAMA. The guidelines do state that clinical evidence for triple therapy is weak. Further implications of initiating an ICS/LABA are that a patient will have to change devices and be re-educated on inhaler technique.

It should be noted that the COPD-X Concise guidelines and GOLD Strategy Report highlight the importance of checking inhaler technique and adherence at each visit. Also the Canadian Medical Services Commission guidelines recommend that clinicians should 'evaluate the patient's inhaler technique regularly.' PBS restrictions do not currently specify that patients must have demonstrated adherence or correct inhaler technique before changing treatments.

1.4.4 Acute exacerbations

Management of COPD acute exacerbations is also described in the identified guidelines. Some guidelines have an integrated description for pharmacotherapy for stable COPD and acute exacerbations; these are summarised in Table 1.2 and Table 1.3 above. The guidelines that make recommendations for pharmacotherapy specifically for COPD acute exacerbations are summarised in Table 1.4, and are from the following sources:

- GOLD (both the full Strategy Report and the pocket guide)
- COPD-X (concise guidelines and a treatment algorithm specifically for exacerbations)
- AHRQ NGC (American Society of Chest Physician and Canadian Thoracic Society)
- NICE Pathway.

In general, an ICS/LABA is used as prophylaxis to reduce the frequency of exacerbations. Once an exacerbation has occurred, the possible treatments are:

- increase doses/frequency of SABAs and/or SAMAs
- combine SABAs and anticholinergic bronchodilators
- consider OCS or intravenous (IV) corticosteroids
- consider antibiotics.

Table 1.4 Prescribing guidelines for COPD acute exacerbations

1. Name of publication or citation 2. Source 3. Country 4. Primary aim and focus 5. Target audience 6. Method used to develop the guidance 7. Developer/commissioning body	Prescribing summary for pharmacologic therapy (from 2011 inclusive)
LFA and TSANZ	
1. Abramson M, Frith P, Yang I, McDonald C, Hancock K, Jenkins S, McDonald V, Zwar N, Maguire G, Halcomb E, Polak Scowcroft C. COPD-X Concise Guide for Primary Care. Brisbane. Lung Foundation Australia. 2016.[a] 2. COPD-X Concise Guide for Primary Care 3. Australia. 4. Concise version of the COPD-X full guidelines. 5. General practitioners. 6. Evidence-based. Underpinned by the comprehensive COPD-X full guidelines.[b] 7. GP Advisory Group, LFA.	**ACUTE EXACERBATIONS** For patients receiving short-acting bronchodilators who have persistent troublesome dyspnoea, add a LABA or LAMA (or both in combination if monotherapy is not adequate) for regular use. LABAs (salmeterol, eformoterol, indacaterol) or LAMAs (tiotropium, glycopyrronium, umeclidinium or aclidinium) may improve lung function, symptoms, QoL, and exacerbation frequency [evidence level I-II]. A LAMA and LABA in combination is better than either monotherapy [evidence Level II]. LAMA/LABA FDCs in a single inhaler (glycopyrronium/indacaterol, umeclidinium/vilanterol, tiotropium/olodaterol, aclidinium/eformoterol) are available for patients who remain symptomatic despite monotherapy with either alone. For patients with FEV_1 <50% predicted and ≥2 exacerbations in 12 months: • Initiate an ICS/LABA FDC and discontinue LABA monotherapy. ICS combined with LABAs (fluticasone propionate/salmeterol, budesonide/eformoterol, fluticasone furoate/vilanterol) may reduce exacerbation frequency and improve QoL [evidence level I]. • For patients with moderate-to-severe COPD with frequent exacerbations who are not receiving a LAMA, consider addition of a LAMA to the ICS/LABA. Limited evidence suggests (and new evidence is being reviewed) that the use of a LABA + ICS + LAMA provides more benefit than the individual treatments alone. This combination of therapies may be useful for patients with moderate-to-severe COPD with repeated exacerbations. For severe COPD (FEV_1 <40% predicted), consider adding low-dose theophylline (100 mg twice daily). Theophylline has a moderate effect on lung function in patients with moderate to severe COPD. Low-dose theophylline may also help restore sensitivity to ICS and target eosinophilic airway inflammation [evidence level I-II]. Avoid long-term (>2 weeks) use of OCS.
1. Algorithm – Managing a COPD exacerbation in primary care. 2015. 2. LFA: Managing a COPD exacerbation in primary care 3. Australia. 4. COPD exacerbations managed in primary care. 5. General practitioners. 6. Evidence-based. Underpinned by the comprehensive COPD-X full guidelines. Evidence levels are not specified in the algorithm. 7. GP Advisory Group, LFA.	**ACUTE EXACERBATIONS** Patient is feeling unwell and finding it harder to breathe than usual or experiencing any of the following: more coughing, more phlegm, thicker phlegm than usual – recommend they start using more SABA e.g. salbutamol 4-8 puffs (400-800 µg), via MDI and spacer every 3-4 hours, titrated to response. ↓ Patient is feeling worse: 3-4 hourly SABA not relieving symptoms adequately – recommend to commence oral prednisolone 30-50mg daily for 5 days, then stop. If clinical features of infection are present: a change in colour and/or volume of phlegm, with or without fever – recommend to also commence oral antibiotics (amoxicillin or doxycycline) for 5 days. ↓ Patient is still unwell 2-5 days after treatment commenced – recommend review by GP or specialist. Review and reinforce the use of the COPD Action Plan. ↓

1. Name of publication or citation 2. Source 3. Country 4. Primary aim and focus 5. Target audience 6. Method used to develop the guidance 7. Developer/commissioning body	Prescribing summary for pharmacologic therapy (from 2011 inclusive)
	When the patient is feeling better – recommend step down short-acting bronchodilator use, return to usual daily prescribed medicines, write or review and reinforce the use of the COPD Action Plan. If patient has frequent exacerbations (2 or more in last 12 months) they are at higher risk of further exacerbation and mortality – recommend early review to: optimise pharmacotherapy following 'Stepwise Management of Stable COPD' (see below entry in this table), check immunisation status, check smoking status, refer to pulmonary rehabilitation, arrange a follow-up review when stable.
GOLD http://goldcopd.org/	
1. Global strategy for the diagnosis, management and prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016.[c] 2. GOLD Strategy 2016 3. United States. 4. A strategy document for health care professionals to use as a tool to implement effective management programs based on available health care systems. 5. General practitioners and any other primary care specialists. 6. Evidence-based.[d] Updated reports of the original 2001 document were released in January 2013, January 2014, and January 2015, and are based on scientific literature published since the completion of the 2011 document but maintain the same treatment paradigm. 7. Global Initiative for Chronic Obstructive Lung Disease (GOLD).	**ACUTE EXACERBATIONS** • Bronchodilators: ➢ Increase doses and/or frequency of short-acting bronchodilators; ➢ Combine SABA and anticholinergics; ➢ Use spacers or air-driven nebulisers. • Add oral or intravenous corticosteroids. • Consider antibiotics (oral or occasionally intravenous) when signs of bacterial infection.
1. Global initiative for chronic obstructive lung disease. Pocket guide to COPD diagnosis, management and prevention. A guide for health care professionals. Updated 2015. 2. GOLD Pocket Guide to COPD 2015 3. United States. 4. Management and prevention. 5. Health care professionals. 6. Evidence-based. Developed from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), updated 2014. 7. Global Initiative for Chronic Obstructive Lung Disease (GOLD).	**ACUTE EXACERBATIONS** • Bronchodilators: inhaled SABA with or without SAMA; • Systemic corticosteroids: prednisone 40 mg/day for 5 days; • Antibiotics: should be given to patients - ➢ with increased dyspnoea, increased sputum volume and increased sputum purulence; ➢ with increased sputum purulence and one other symptom listed above; ➢ who require mechanical ventilation.
AHRQ National Guidelines Clearinghouse www.guideline.gov	
1. Criner GJ, Bourbeau J, Diekemper RL, et al (2015). Prevention of acute	**In patients who are at risk of an acute exacerbation of COPD:**

1. Name of publication or citation 2. Source 3. Country 4. Primary aim and focus 5. Target audience 6. Method used to develop the guidance 7. Developer/commissioning body	Prescribing summary for pharmacologic therapy (from 2011 inclusive)
exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. Chest 147(4):894-942. NGC:010698 2. Prevention of acute exacerbations of COPD 3. Canada. 4. Exacerbations of COPD with respect to maintenance therapy and previous/current smokers. 5. Clinicians. 6. Evidence-based. Grades of recommendation are consensus-based, according to the American College of Chest Physicians grading system.[e] Evidence considered is from RCTs or observational studies. 7. American College of Chest Physicians and the Canadian Thoracic Society.	• PICO 2: Does maintenance inhaled therapy prevent or decrease the rate of acute exacerbations of COPD? Inhaled therapies recommended are (strong evidence, level 1): ➢ LABA ➢ LAMA ➢ ICS/LABA ➢ LABA/(anticholinergic or ICS) or anticholinergic monotherapy. Inhaled therapies suggested are (weak evidence, level 2): ➢ SAMA/SABA ➢ SAMA/LABA ➢ SAMA ➢ LABA ➢ LAMA/ICS/LABA. **In patients who are at risk of an acute exacerbation of COPD:** • PICO 3: In patients aged >40 years who are previous or current smokers with COPD, does oral therapy prevent or decrease the rate of acute exacerbations of COPD? Pharmacological oral therapies suggested are (weak evidence, level 2): ➢ Long term macrolides ➢ OCS in first 30 days after exacerbation ➢ PDE-4 inhibitors ➢ Theophylline ➢ N-acetylcysteine ➢ Carbosysteine. Pharmacological oral therapies not recommended are (strong evidence, level 1): ➢ OCS in an attempt to decrease acute exacerbation of COPD >30 days after initial event ➢ Statins.
1. Medical Services Commission. Chronic obstructive pulmonary disease (COPD). Victoria (BC): British Columbia Medical Services Commission; 2011 Jan 1. 17 p. NGC:009466 2. Medical Services Commission: COPD 3. Canada. 4. Diagnosis and management of COPD. 5. Family physicians in British Columbia. 6. Evidence-based. Review of the recommendations of the Canadian Thoracic Society and other international strategies for the management of COPD.	**ACUTE EXACERBATIONS** Acute exacerbations are characterised by sustained (≥48 hours) worsening of shortness of breath and coughing, with or without sputum. Develop an exacerbation plan with the patient. Severe acute exacerbation COPD complicated by acute respiratory failure is a medical emergency. Therapies should include: • Therapy with SABAs and anticholinergic bronchodilators. • OCS (e.g., prednisone 25-50 mg/day) for less than two weeks in most moderate-severe COPD patients. A dose of 30-40 mg of prednisone equivalent per day has been used in practice. Antibiotic use is based on risk factors.

1. Name of publication or citation 2. Source 3. Country 4. Primary aim and focus 5. Target audience 6. Method used to develop the guidance 7. Developer/commissioning body	Prescribing summary for pharmacologic therapy (from 2011 inclusive)
7. Medical Services Commission, British Columbia.	
NICE https://www.nice.org.uk	
1. NICE Pathway (2016). Managing stable COPD. Managing exacerbations of COPD. 2. NICE Pathways: COPD 3. United Kingdom. 4. Visual representation of NICE's recommendations on a topic, and access to the products that NICE has produced to support implementation of its guidance. 5. Health and social care professionals, public health experts, those who commission or provide health and social care services, employers and members of the public. 6. Evidence-based. Developed from guidance and supporting information from all NICE work programmes. Based on COPD NICE guideline CG101 (2010) – this guideline is being updated. 7. NICE.	**ACUTE EXACERBATIONS** Delivery systems for inhaled therapy: • Nebulisers • Hand-held inhalers Treatment options are: • Antibiotics – used in patients with a history of more purulent sputum. Initial treatment should be an aminopenicillin, a macrolide or a tetracycline. • OCS – prednisolone. – Followed by hospital therapy: IV theophylline, invasive ventilation, non-invasive ventilation and doxapram.

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; COPD, chronic obstructive pulmonary disease; FDC, fixed-dose combination; FEV_1, forced expiratory volume in 1 second; GP, general practitioner; GOLD, Global initiative for chronic obstructive lung disease; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; LFA, Lung Foundation Australia; MDI, metered dose inhaler; NGC, National Guideline Clearinghouse; NICE, The National Institute of Health and Care Excellence; OCS, oral corticosteroids; PICO, Population Intervention Comparator Outcome; QoL, quality of life; RCT, randomised controlled trial; SABA, short-acting beta-2 agonist; SAMA, short-acting muscarinic antagonist; TSANZ, Thoracic Society of Australia and New Zealand.

a A superseded 2014 version of this document was identified: Superceded COPD-X Guideline.

b Corresponds to NHMRC levels of evidence. Evidence level 1: Evidence obtained from a systematic review of all relevant randomised controlled trials; Evidence Level II: Evidence obtained from at least one properly designed randomised controlled trial; Evidence level III-2: Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.

c A superseded 2011 version of these guidelines was identified: Superceded GOLD Strategy.

d Evidence category A: RCTs, rich body of data; B: RCTs, limited body of data; C: non-randomised trials or observational studies; D: panel consensus judgement.

e Levels of evidence are defined in source document by Criner et al (2015), Table 4, in Prevention of Acute Execarbations of COPD, *Chest*.

1.4.5 Asthma-COPD Overlap Syndrome

ACOS refers to patients who exhibit features of both COPD and asthma, and is relevant to the treatment of COPD patients because they may have underlying eosinophyilic inflammation that responds better to ICS compared with other therapies or combinations of therapies (Barrecheguren et al, 2015). Patients with both COPD and asthma are also referred to as having mixed airways disease, although this is potentially a wider condition as it may also include patients with bronchiectasis (Athanazio, 2012). The following guidelines are sources of recommendations for patients with ACOS:

- The 2015 update of the GOLD Stategy Report includes an Appendix on ACOS, which comprises consensus-based material prepared jointly by the US-based GOLD and GINA Science Committees.
- The National Asthma Council Australia (NACA) recently updated their Australian Asthma Handbook, in October 2016; version 1.2 includes a section on medication recommendations for patients who exhibit characteristics of both asthma and COPD.

The Australian Asthma Handbook provides an informative and simple overview of the pertinent issues:

> *Asthma and COPD are quite distinctive and readily distinguishable from each other when they occur in their most characteristic forms. However, many adult patients show features of both these conditions.*
>
> *The possibility of COPD as an alternative diagnosis and the possibility of asthma-COPD overlap should be considered during diagnostic investigation of respiratory symptoms in adults, particularly in smokers, ex-smokers and older adults.*
>
> *Current asthma guidelines and COPD guidelines make contrasting recommendations for pharmacotherapy, based on differing safety findings in each population. Asthma guidelines generally recommend inhaled corticosteroids for most adults and recommend against long-acting beta2 agonist without concomitant or combination inhaled corticosteroid therapy, whereas COPD guidelines recommend a long-acting beta2 agonist as initial treatment and inhaled corticosteroids only for patients with more severe disease. Special considerations are therefore needed when a patient has features of both diagnoses.*

Summaries for the two above-mentioned guidelines are shown in Table 1.5. In general, the recommendations from the guidelines are consistent. The pharmacologic treatment algorithm for ACOS is, in a stepwise fashion, to initiate an ICS, then add a LABA or LAMA. Both guidelines make a note of the importance of treating ACOS with an ICS. A point of difference is that the NACA guideline makes the same treatment recommendations for all ACOS patients, whereas the GOLD/GINA guideline distinguishes between the following three groups and their corresponding treatment:

- ACOS patients who favour an asthma diagnosis – treat with ICS, with add-on treatment if needed, e.g. add-on LABA and/or LAMA.
- ACOS patients who favour a COPD diagnosis – treat with bronchodilators (LABA and/or LAMA) or combination therapy, but not ICS monotherapy.
- ACOS patients who are evenly balanced between COPD and asthma – treat with an ICS, usually also add a LABA and/or LAMA, or continue these together with ICS if already prescribed.

In terms of differentiating treatment for COPD from that for asthma, the COPD-X guidelines (full version) state that 'the use of drugs in COPD does not involve back titration, which is a core principle in asthma management. The exception is when OCS have been given for an acute exacerbation [of COPD]. There is at present no evidence for back titration [in COPD] and further clinical trials are required.' This point does not apply specifically to ACOS patients, rather it is a general point of difference between COPD and asthma treatment doctrines.

The NACA guideline references the 2012 full COPD-X guideline (version 2.34) on its website for some treatment recommendations; however, no reference to ACOS could be found in the current COPD-X guideline, and the 2012 version has been removed from the internet.

It should be noted that LAMA monotherapy and LAMA/LABAs are not PBS listed for asthma, nor are they approved for asthma or mixed airways disease by the TGA. ICS/LABAs (budesonide/eformoterol, fluticasone propionate/salmeterol, and fluticasone furoate/vilanterol) are PBS listed for both COPD and asthma. This is consistent with the guidelines recommending the use of ICS in ACOS patients.

Table 1.5 Prescribing guidelines for asthma-COPD overlap syndrome

1. Name of publication or citation 2. Source 3. Country 4. Primary aim and focus 5. Target audience 6. Method used to develop the guidance 7. Developer/commissioning body	Prescribing summary for pharmacologic therapy (from 2011 inclusive)
GOLD	
1. Asthma, COPD and asthma-COPD overlap syndrome (ACOS). Based on the global strategy for asthma management and prevention and the global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. 2015. 2. GOLD: Asthma, COPD and asthma-COPD overlap syndrome 3. United States. 4. Identification of relevant patients, distinguish asthma from COPD and ACOS, prescribe initial treatment and/or need for referral. 5. Primary care or non-pulmonary clinicians. 6. Consensus-based. 7. Global Initiative for Asthma (GINA); Global Initiative for Chronic Obstructive Lung Disease (GOLD).	If the syndromic assessment favours asthma as a single diagnosis: Pharmacotherapy is based on ICS, with add-on treatment if needed, e.g. add-on LABA and/or LAMA. If the syndromic assessment favours COPD as a single diagnosis: Pharmacotherapy starts with symptomatic treatment with bronchodilators (LABA and/or LAMA) or combination therapy, but not ICS alone (as monotherapy). If the differential diagnosis is equally balanced between asthma and COPD (i.e. ACOS): If the syndromic assessment suggests ACOS, the recommended default position is to start treatment for asthma until further investigations have been performed. This approach recognises the pivotal role of ICS in preventing morbidity and death in patients with uncontrolled asthma symptoms, for whom even seemingly mild symptoms might indicate significant risk of a life-threatening attack. • Pharmacotherapy for ACOS includes an ICS (low or moderate dose, depending on symptoms); • Usually also add a LABA and/or LAMA, or continue these together with ICS if already prescribed. However, if there are features of asthma, do not treat with LABA without ICS (often called LABA monotherapy).
NACA	
1. Australian Asthma Handbook v1.2. 2016. 2. Australian Asthma Handbook 2016 3. Australia. 4. Management considerations for patients with asthma-COPD overlap 5. Primary care. 6. Evidence and consensus-based. Links to source documents, clinical experience, position statements or expert opinion are provided for each recommendation. 7. National Asthma Council Australia (NACA).	• Prescribe long-term ICS (at a low dose, if possible, or at the lowest effective dose) to reduce the risk of asthma flare-ups. Monitor closely for lower respiratory tract infections, and advise patients to get medical advice immediately if they develop symptoms of a lower respiratory tract infection. • Consider treatment with both an ICS and a long-acting bronchodilator, as (either of): (1) combination ICS/LABA in a single inhaler (or separate inhalers if the preferred combination is not available in a single inhaler); (2) concomitant treatment with an ICS and a LAMA agent such as tiotropium. • Note: The use of separate inhalers for concomitant treatment with an ICS and a long-acting bronchodilator (LABA or LAMA) in patients with asthma should be avoided if possible, even if the person also has COPD. If no combination product is available for the desired combination, carefully explain to the patient that it is very important that they continue taking the ICS. • In addition to prescribing ICS in combination with long-acting bronchodilators, manage co-existing asthma and COPD according to the individual's clinical features, comorbidities and response to treatment. Do not prescribe a long-acting bronchodilator (LABA or LAMA) without an ICS in these patients.

Abbreviations: ACOS, asthma-COPD overlap syndrome; COPD, chronic obstructive pulmonary disease; GINA, Global Initiative for Asthma; GOLD, Global initiative for chronic obstructive lung disease; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; NACA, National Asthma Council Australia.

1.4.6 Excluded guidelines

Guidelines that have been identified and excluded from this analysis are shown in Appendix H. Many of these are from the Guidelines International Network (G-I-N); they are either not in English, published before 2011, under review, or in development. Other excluded guidelines are from GOLD, and have been superseded, or in the case of the 'at-a-glance outpatient management reference,' is wholly included in the GOLD Pocket Guide summarised in Table 1.2. The British NICE website refers to the COPD Clinical Guideline CG101 (2010), upon which the NICE Pathway for COPD is based (see Table 1.3). As discussed, the CG101 guideline is being updated. There are two early COPD-X publications from 2003 and 2006 that have been superseded. The COPD entry from the Australian resource 'Therapeutic Guidelines', is based on the COPD-X guidelines, and has also been excluded as an original source. Notably, the NHMRC does not have any entries for COPD, emphysema or bronchitis. Likewise, the SIGN website in Scotland has a respiratory section, but does not list anything for COPD or similarly described conditions.

1.5 Synthesis of findings

A comparison between the GOLD Strategy Report and COPD-X guidelines allows a few points to be raised, as follows:

- Regarding disease severity, the COPD-X categories all have greater airflow limitation in terms of FEV_1 compared with the corresponding GOLD category. Unlike the GOLD Strategy Report, there is no 'very severe' category in the COPD-X guidelines.
- GOLD Strategy Report treatment recommendations are based on Patient Groups, whereas COPD-X recommendations are based on a stepwise algorithm with no explicit consideration of the severity of disease at diagnosis.
- Specific doses are itemised for each agent or combination in GOLD Strategy Report, whereas doses in COPD-X guidelines are mentioned *ad hoc*.

1.5.1 Severity categories for lung function

Normal lung function is characterised by the ratio FEV_1/forced vital capacity (FVC) ≥0.7 and FEV_1 >80% predicted. For all diagnoses of COPD, FEV_1/FVC is <0.7. COPD staging/severity of airflow limitation according to the GOLD Stategy Report and COPD-X guidelines are shown in Table 1.6.

The GOLD grade corresponds to FEV_1 predicted score, and is incorporated into the overall Patient Group category (A, B, etc.). The GOLD Strategy Report states that the concept of staging has been abandoned, as a staging system based on FEV_1 alone was inadequate and the evidence for an alternative staging system does not exist. The Patient Group approach that is now used in the GOLD guidelines, combined with an assessment of potential comorbidities, is

intended to reflect the complexity of COPD better than the unidimensional analysis of airflow limitation previously used for staging the disease.

The COPD-X guidelines have mild/moderate/severe COPD categories, primarily based on FEV_1 with associated symptoms. Unlike the GOLD Strategy Report, there is no 'very severe' category, although the COPD-X categories all have greater airflow limitation in terms of FEV_1 compared with the corresponding GOLD category.

The PBS restrictions for the ICS/LABAs (patient must have a FEV_1 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) correspond with GOLD Patient Group C in terms of air flow limitation and acute exacerbations (typically GOLD 3 or GOLD 4 [severe or very severe airflow limitation]; and/or ≥2 exacerbations per year or ≥1 with hospitalisation for exacerbation).

There is no equivalent COPD-X category for the ICS/LABA PBS restrictions, where moderate COPD is defined as FEV_1 40-59% predicted, and severe COPD is defined as FEV_1 <40% predicted.

The pocket GOLD guidelines recommend treatment based on the staging of Patient Groups shown in Table 1.6. For example, for Patient Group A, the recommended first choice therapy is SAMA as needed, or SABA as needed, with an alternative choice of LAMA or LABA or SABA/SAMA, and other possible treatments listed as theophylline. Recommended therapies for Patient Groups B, C and D can be found in Table 1.2. The advantage of this system is that patients can be diagnosed and allocated to a group with a corresponding treatment recommendation, rather than using a stepped approach.

Table 1.6 COPD staging/severity of airflow limitation for GOLD Strategy Report and COPD-X guidelines

Severity	GOLD (previous)	GOLD (revised)[a]	COPD-X[b]
Mild	• FEV_1 ≥80% predicted[c,d] • Corresponds to GOLD Grade 1[e,f] • Corresponds to Patient Group A or B.	**Patient Group A**[g] – low risk, fewer symptoms. Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation); and/or 0-1 exacerbation per year and no hospitalisation for exacerbation; and CAT score <10 or mMRC Grade 0-1.	FEV_1 60-80% predicted • Few symptoms • Breathlessness on moderate exertion • Recurrent chest infections • Little or no effect on daily activities.
Moderate	• FEV_1 50-79% predicted[c,d] • Corresponds to GOLD Grade 2[e,f] • Corresponds to Patient Group A or B.	**Patient Group B**[g] – low risk, more symptoms. Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation); and/or 0-1 exacerbation per year and no hospitalisation for exacerbation; and CAT score ≥10 or mMRC Grade ≥2.	FEV_1 40-59% predicted • Increasing dyspnoea • Breathlessness walking on level ground • Increasing limitation of daily activities • Cough and sputum production • Exacerbations requiring corticosteroids and/or antibiotics.
Severe	• FEV_1 30-49% predicted[c,d] • Corresponds to GOLD Grade 3[e,f] • Corresponds to Patient Group C or D.	**Patient Group C**[g] – high risk, fewer symptoms. Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation); and/or ≥2 exacerbations per year or ≥1 with hospitalisation for exacerbation; and CAT score <10 or mMRC Grade 0-1.	FEV_1 <40% predicted • Dyspnoea on minimal exertion • Daily activities severely curtailed • Experiencing regular sputum production • Chronic cough • Exacerbations of increasing frequency and severity.
Very severe	• FEV_1 <30% predicted, or <50% predicted with chronic respiratory failure[c,d] • Corresponds to GOLD Grade 4[e,f] • Corresponds to Patient Group C or D.	**Patient Group D**[g] – high risk, more symptoms. Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation); and/or ≥2 exacerbations per year or ≥1 with hospitalisation for exacerbation; and CAT score ≥10 or mMRC Grade ≥2.	N/A

Abbreviations: CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV, forced expiratory volume; FVC, forced vital capacity; GOLD, Global initiative for chronic obstructive lung disease; mMRC, modified Medical Research Council; N/A, not applicable; PSD, Public Summary Document.

a From GOLD Strategy 2016, Table 2.5 p14.

b From Concise Guide and LFA Stepwise management of stable COPD.

c From WebMD: What are the stages of COPD?.

d The GOLD guidelines state that the concept of staging has been abandoned, as a staging system based on FEV_1 alone was inadequate and the evidence for an alternative staging system does not exist.

e GOLD grade of airflow limitation: GOLD 1 (mild); GOLD 2 (moderate); GOLD 3 (severe); GOLD 4 (very severe).

f Applies to patients with FEV_1/FVC <0.7.

g The Patient Group approach, combined with an assessment of potential comorbidities, reflects the complexity of COPD better than the unidimensional analysis of airflow limitation previously used for staging the disease.

1.5.2 PBS prescribing restrictions and clinical guidelines

The concordance between PBS prescribing restrictions and clinical guidelines for COPD medications is shown in Table 1.7. The included guidelines are discussed for each PBS-listed agent and combination of agents. Guidelines that refer to the relevant agent by drug class are also discussed. The guideline-PBS concordance is summarised according to the following medication classes and combinations.

SAMA

Ipratropium is generally recommended to provide initial treatment or short-term relief of breathlessness. It is recommended as a treatment in all guidelines as a specific agent or drug class except the ACP, ACCP, ATS, and ERS guidelines. Ipratropium has an unrestricted benefit for a pressurised inhaler, and a restricted benefit (asthma or COPD) for a nebuliser where patients cannot use an inhaler.

LAMA

Aclidinium, glycopyrronium, tiotropium and umeclidinium are all mentioned by name in the GOLD Stategy Report and COPD-X guidelines for use as monotherapy and LAMA/LABA combination therapy. Two guidelines from the NGC (British Columbia Medical Services Commission, 2011; Department of Veterans Affairs, 2014) discuss tiotropium, only, as an example of a LAMA. Tiotropium was the first of the LAMAs to be listed on the PBS in 2003 and aclidinium, glycopyrronium, and umeclidinium have all been evaluated for subsidy on the basis of non-inferiority to tiotropium. This is consistent with the reviewed guidelines, which do not advocate any particular LAMA above another, although the two above-mentioned NGC guidelines may appear to put undue emphasis on tiotropium by omitting the other agents. All four agents have a Restricted Benefit listing for COPD on the PBS; tiotropium is the only agent that has a listing that includes prevention of exacerbation. The PSDs for aclidinium, glycopyrronium, and umeclidinium all state that the submitted evidence to the PBAC supported these agents for monotherapy over combination therapy[4].

LABA

The only LABA that is PBS listed for COPD monotherapy is indacaterol. It is recommended in the GOLD Strategy Report and COPD-X guidelines for use as monotherapy, and as combination therapy with glycopyrronium (a LAMA). The other guidelines do not refer to indacaterol specifically, but do recommended LABA monotherapy and LAMA/LABA combination therapy. It has a Restricted Benefit listing for COPD.

[4] Aclidinium, glycopyrronium, and umeclidinium are all available as monotherapy or as FDCs with other agents. The LAMA/LABA FDCs (aclidinium/eformoterol, glycopyrronium/indacaterol and umeclidinium/vilanterol) were evaluated by the PBAC and recommended for listing in 2014-15. However, there is potential for aclidinium or umeclidinium to be used in combination with the LABA indacaterol, as a LAMA/LABA treatment that may not be supported by evidence. Note that neither the COPD-X nor the GOLD guidelines refer to using aclidinium or umeclidinium with indacaterol.

LAMA/LABA

The PBS listed LAMA/LABA FDCs are aclidinium/eformoterol, glycopyrronium/ indacaterol, tiotropium/olodaterol and umeclidinium/vilanterol. All four have an Authority Required (STREAMLINED) listing for COPD that states that the patient must have been [already] stabilised on a LAMA and LABA. This requirement is not based on recommendations or evidence from any guidelines, but based on the PSD for glycopyrronium/indacaterol (July 2014), is an attempt to address inappropriate prescribing of a LAMA/LABA, particularly in the first-line setting.

OCS

The only OCS agent referred to is prednisolone, which is recommended for short-term therapy only and has an unrestricted listing on the PBS.

ICS/LABA

The GOLD Stategy Report and COPD-X guidelines indicate that ICS/LABA combinations should be introduced after the LAMA/LABA combinations, in the interests of confining ICS to patients with more severe disease. As discussed, the PBS restrictions for the ICS/LABAs correspond with GOLD Patient Group C in terms of air flow limitation (<50% predicted) and repeated acute exacerbations. Although there is no equivalent COPD-X category for the ICS/LABA PBS restrictions, the COPD-X guidelines do refer to this restriction in terms of reducing acute exacerbations (see Table 1.4).[5] There is a note in the PBS restriction for ICS/LABAs that patients must not be on a single agent LABA; this note could be taken further, that patients should not be on a single agent LABA or a LAMA/LABA FDC.

In conclusion, the PBS restriction for ICS/LABAs, which limits use to FEV_1 <50% predicted, aligns with both the COPD-X guidelines and GOLD Strategy Report.

Analysis

An issue with the LAMA/LABA PBS restrictions and COPD treatment guidelines is reflected in the PSD for the minor submission for umeclidinium/vilanterol, which was rejected in November 2014. The submission requested that the recommended restriction for umeclidinium/vilanterol be amended to also include patients who have symptoms that persist despite regular bronchodilator treatment with a LAMA and/or LABA in addition to those already stabilised on a combination of a LAMA and LABA. The PSD states that the PBAC considered that the proposed restriction did not address the concerns that patients may initiate a FDC before clinically appropriate. The guidelines state that it is clinically appropriate to progress from a LAMA or a LABA to a LAMA/LABA FDC if symptoms are persisting. This issue reflects an inconsistency between the current PBS listings of LAMA/LABAs and the reviewed guidelines.

[5] The March 2014 PSD for fluticasone furoate/vilanterol states: 'According to the Australian guidelines for COPD (COPD-X), ICS plus LABA is recommended in the treatment algorithm for patients with COPD where FEV_1 is <50% predicted and the patient has had two or more exacerbations in the previous 12 months.' This statement is made in the COPD-X guidelines in the context of reducing exacerbations.

A modified restriction for LAMA/LABA FDCs in line with the umeclidinium/vilanterol submission would provide potential advantages for patients, as currently the process is confusing and cumbersome. As the public submission for this review from the LFA/TSANZ points out, 'the requirement to add a second inhaler device has the potential to lead to greater non-adherence and potential confusion for the patient and clinician in how to use the new device. The intermediate step of two inhalers, followed by a third [LAMA/LABA FDC] is cumbersome and requires an additional visit to the prescriber and again the need to re-educate about another different device.' The issue of non-adherence in COPD is not acknowledged in either the reviewed guidelines or the PSDs/restrictions of the PBS-listed medicines.

A complicating factor is that some individual components of all but one of the PBS-listed LAMA/LABA FDCs are not currently available on the PBS for COPD (eformoterol, olodaterol and vilanterol), which may encourage prescribers to initiate dual therapy that is inappropriate under the current PBS restrictions. The Guidelines for Preparing Submissions to the PBAC state that it is preferable that the components of the FDC are also listed on the PBS. The PSD for umeclidinium/vilanterol (March 2014) states:

> *The PBAC agreed with the ESC that having a combination product available without having the individual components available was problematic. Patients with COPD cannot be treated in the stepwise manner recommended without changing the LABA and LAMA medications. The PBAC considered there were also risks that patients may transition to combination therapy earlier than clinically necessary due to the individual components being unavailable, or that patients will be prescribed triple therapy with UMEC/VI plus a LABA or LAMA single agent.*

Therefore, the PBS restrictions for the LAMA/LABA FDCs (that patients must be previously stabilised on a LAMA and a LABA) reflect a complex situation where:

- the individual components of the FDC are not available on the PBS
- the restrictions are not consistent with treatment guidelines
- it is preferable to have LAMA/LABAs and ICS/LABAs listed on the PBS in a way that delays the introduction of ICS/LABA
- clinicians may be encouraged to prescribe an ICS/LABA if symptoms are not controlled with LAMA or LABA monotherapy
- there may be medicines wastage and increased costs for patients and government.

The utilisation analysis undertaken for ToR 5, demonstrates that, despite the PBS restriction, a small but growing proportion of COPD patients are initiating COPD therapy on LAMA/LABA combinations (see Section 5.6).

Some recent clinical trials have assessed the appropriateness of initiating treatment with dual LAMA/LABA therapy. For example, the TONADO studies, shown in Section 3 conducted subgroup analyses according to severity of COPD (e.g. GOLD 2), showing that moderately severe patients also benefited from initiating treatment with LAMA/LABA dual therapy. This

benefit in treatment-naïve patients was comparable to the difference observed in treatment-experienced patients.

The LAMA/LABA FDCs currently have higher prices than the monotherapies; therefore, clinical evidence to support initiation onto dual therapy would be required to maintain the higher price of the FDCs if the restriction were changed to allow initiation without prior use of a LAMA or LABA. This issue reflects the fact that cost-effectiveness is not discussed in any of the guidelines, while the PBS restrictions that are based on both clinical evidence and economic evaluation.

The TGA indications in Table 1.7 reflect the PBS restrictions for the LAMAs and the only listed LABA (indacaterol); however, they do not reflect the PBS requirement for FDCs to be used second-line (and after stabilisation on an individual LAMA and LABA). The TGA indication for FDC LAMA/LABA is identical to the TGA indication for LAMA and LABA monotherapies, allowing first-line use.

The TGA indications do reflect the PBS requirement for patients taking ICS/LABA to have a FEV_1 less than 50% of predicted normal prior to therapy (with the exception of <70% for fluticasone furoate/vilanaterol), and have a history of repeated exacerbations. This is also reflected in the COPD-X guidelines and GOLD Strategy Report. Both the TGA indications and the PBS restrictions for ICS/LABAs are clear in that they are not indicated for the initiation of bronchodilator therapy in COPD, which is consistent with the reviewed guidelines. These conditions are imposed to restrict patients from inappropriately initiating ICS therapy. This is actively stated in the GOLD Strategy Report (that long-term treatment with ICS is recommended [only] for patients with severe and very severe COPD) and indicated in their stepwise nature. The previous GOLD Strategy Report state that severe or very severe airflow limitation reflects FEV_1 <50% predicted (Table 1.6), although the revised GOLD guidelines are less explicit in that they state that patients with severe/very severe COPD have severe/very severe airflow limitation (but do not give an actual FEV_1 value).

The PSD for umeclidinium/vilanterol states that input was received from TSANZ regarding the clinical place of LAMA/LABA FDCs in the treatment of COPD. Reasoning behind the recommendation for PBS listing of umeclidinium/vilanterol is as follows:

> *The PBAC noted that the treatment algorithm for COPD is changing. The PBAC considered it was appropriate to delay the introduction of ICS/LABA combination therapy in less severe disease, given the potential safety risks associated with ICS use. The PBAC considered that use of the combination of a LAMA and a LABA (as single agents given concurrently or as a fixed dose combination) was preferred to the earlier introduction of an ICS/LABA combination. Such use would be consistent with the Australian COPD-X guidelines, where introduction of an ICS is recommended for patients with more severe disease (FEV_1 <50% predicted and the patient has had two or more exacerbations in the previous 12 months).*

Importantly, for ICS/LABAs, the COPD-X and GOLD Strategy Report reflect both the TGA indications and PBS restrictions that patients must have a FEV_1 less than 50% of predicted normal prior to therapy, and must have a history of repeated exacerbations. These conditions are imposed to restrict patients from inappropriately initiating ICS therapy. This is actively stated in the GOLD Strategy Report (that long-term treatment with ICS is recommended [only] for patients with severe and very severe COPD) and indicated in their stepwise nature. The previous GOLD Strategy Report state that severe or very severe airflow reflects FEV_1 <50% predicted (Table 1.6), although the revised GOLD Strategy Report are less explicit in that they state that patients with severe/very severe COPD have severe/very severe airflow limitation (but do not give an actual FEV_1 value). There is nothing in the PBS restrictions or the TGA indications to stop patients who are prescribed a LAMA or LABA progressing in their therapy straight to an ICS/LABA, as long as the severity restrictions for an ICS/LABA (FEV_1 <50% predicted and repeated exacerbations) are met.

The COPD-X guidelines distinguish between the FEV_1 values used to describe disease severity, and the FEV_1 threshold for taking medication to prevent an exacerbation. According to COPD-X, mild disease is characterised by FEV_1 60-80% predicted, moderate disease is 40-59% predicted, and severe disease is <40% predicted (shown in Table 1.6). The COPD-X guidelines specify that exacerbation prevention with medication (ICS/LABA) should occur when FEV_1 is <50% predicted with two or more exacerbations in the previous 12 months, which is consistent with the PBS restrictions for these medications. This means that a patient who is prescribed an ICS/LABA could have either moderate or severe COPD, according to the COPD-X guidelines.

The ICS/LABA FDCs are further along the 'stepped' treatment algorithm and used for more severe COPD with exacerbations. However, the ICS/LABAs all have a Restricted Benefit listing based on COPD severity, rather than the more onerous Authority Required (STREAMLINED) listing that applies to the LAMA/LABAs. The method of restriction for the LAMA/LABAs and the ICS/LABAs does not align with their position in the treatment algorithm.

In December 2014, as part of the Post-market Review of Authority Required Medicines, the PBAC recommended that there should be two key criteria for determining whether a pharmaceutical benefit should require an Authority Required listing on initial listing:

1. Potential for use in a population in which the medicines is not cost effective or where the PBAC has not determined the comparative effectiveness and cost.
2. Potential for high cost per patient or high total cost to the health system and Government's budget.

The PBAC also recommended that the following additional factors may need to be considered:

- QUM factors
- safety
- administrative burden.

As already discussed in relation to ICS/LABAs, there is a note in the PBS restriction for ICS/LABAs that patients must not be on a single agent LABA, which could be expanded to

state that patients should not be on a single agent LABA or a LAMA/LABA FDC. For consistency, an analogous note could be added to the restriction for indacaterol that patients should not be on LAMA/LABA or ICS/LABA.

Table 1.7 Concordance between PBS prescribing restrictions and clinical guidelines for COPD medications

Name of active ingredient (brand name[a])	1. PBS prescribing restriction for COPD (listing date) 2. TGA indication for COPD (AusPAR date)	Intended use based on PSD and concerns of PBAC or sponsor	PBS or TGA restrictions for asthma, bronchospasm or mixed airways disease (October 2016)	Concordance between COPD PBS prescribing restrictions and clinical guidelines
SAMA				
Ipratropium (a. Atrovent 20 µg actuations b. Atrovent 250, 500 µg/mL inhalation solution)	1a. Unrestricted (pressurised inhaler) 1b. Restricted Benefit (nebuliser) COPD. Patient must be unable to use this drug delivered from an oral pressurised inhalation device via a spacer (pre-2003). 2a. Bronchodilator for maintenance treatment of bronchospasm associated with asthma and COPD (no AusPAR, first included on the ARTG April 2003). 2b. Not indicated for COPD (no AusPAR, first included on the ARTG September 2000).	N/A	PI (Indications): Moderate asthmatic attacks; chronic forms of asthma; asthma in patients with diminished cardiac reserve; chronic obstructive bronchitis with bronchospasm; bronchospasm during or after surgery, use during assisted ventilation with a respirator.	✓[e] GOLD: recommended as SAMA monotherapy and SABA/SAMA combination therapy with salbutamol or fenoterol. ✓[e] COPD-X[b]: Ipratropium is recommended to provide short-term relief of breathlessness. AHRQ NGC: ✓[e] BC Medical Services Commission (Canada): recommended as monotherapy. Not recommended for use with tiotropium. ✓[e] Department of Veterans Affairs (US): SAMAs recommended as first-line monotherapy. SAMAs not recommended for use with LAMAs. ×[e] ACP, ACCP, ATS, ERS: Ipratropium or SAMAs not discussed. ×✓[e] NICE PATHWAY: short-acting bronchodilators recommended as initial treatment. SAMAs should be discontinued when a LAMA is started.
LAMA				
Aclidinium (Bretaris Genuair 400 µg actuations)	1. Restricted Benefit COPD (August 2014). 2. Long-term maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD (September 2014).	• Cost-minimisation against tiotropium. • PBAC concerned that there was a risk in the PBS listing of a third LAMA that a combination of LAMA agents may be inadvertently used together. • PBAC noted that no trial data were presented for use of aclidinium bromide in combination with a LABA or a LABA+ICS. Sponsor claimed in the pre-PBAC response that there is no pharmacological reason to suggest that aclidinium bromide treatment could not be combined for co-administration with other agents for COPD.	PI (Precautions): Aclidinium should not be used in asthma; clinical trials of aclidinium bromide in asthma have not been conducted.	✓ GOLD: recommended as LAMA monotherapy and LAMA/LABA combination therapy with formoterol. ✓ COPD-X: used twice daily as LAMA monotherapy and LAMA/LABA combination therapy with eformoterol. AHRQ NGC: × BC Medical Services Commission (Canada): Aclidinium not discussed. LAMAs not discussed, aside from tiotropium. × Department of Veterans Affairs (US): Aclidinium not discussed. LAMAs not discussed, aside from tiotropium. ×✓ ACP, ACCP, ATS, ERS: Aclidinium not discussed. LAMAs recommended as monotherapy or combination therapy. ×✓ NICE PATHWAY: Aclidinium not discussed. LAMAs recommended as monotherapy or combination therapy as

Name of active ingredient (brand name[a])	1. PBS prescribing restriction for COPD (listing date) 2. TGA indication for COPD (AusPAR date)	Intended use based on PSD and concerns of PBAC or sponsor	PBS or TGA restrictions for asthma, bronchospasm or mixed airways disease (October 2016)	Concordance between COPD PBS prescribing restrictions and clinical guidelines
				LAMA/LABA. LAMAs also recommended as triple therapy with ICS/LABA.
Glycopyrronium (Seebri Breezhaler 50 µg inhalation capsules)	1. Restricted Benefit COPD (April 2014). 2. Once-daily maintenance bronchodilator treatment to relieve symptoms of patients with COPD (July 2013).	• Cost-minimisation against tiotropium. • The submission proposed that glycopyrronium will be used instead of tiotropium in: monotherapy; add-on to LABA; and add-on to LABA and ICS. However, the PBAC noted that the studies that best supported the non-inferiority claim were the trials presented for monotherapy.	PI (Precautions): Not indicated for the treatment of acute episodes of bronchospasm, i.e. as a rescue therapy.	✓ GOLD: recommended as LAMA monotherapy and LAMA/LABA combination therapy with indacaterol. ✓ COPD-X: recommended as LAMA monotherapy and LAMA/LABA combination therapy with indacaterol. AHRQ NGC: × BC Medical Services Commission (Canada): Glycopyrronium not discussed. LAMAs not discussed, aside from tiotropium. × Department of Veterans Affairs (US): Glycopyrronium not discussed. LAMAs not discussed, aside from tiotropium. ×✓ ACP, ACCP, ATS, ERS: Glycopyrronium not discussed. LAMAs recommended as monotherapy or combination therapy. ×✓ NICE PATHWAY: Glycopyrronium not discussed. LAMAs recommended as monotherapy or combination therapy as LAMA/LABA. LAMAs also recommended as triple therapy with ICS/LABA.
Tiotropium (Spiriva 18 µg inhalation capsules)	1. Restricted Benefit COPD (February 2003). 2. Long term maintenance treatment of bronchospasm and dyspnoea associated with COPD. For the prevention of COPD exacerbations (no AusPAR, first included on the ARTG May 2002).	N/A	PI (Precautions): Should not be used for the treatment of acute episodes of bronchospasm, i.e. rescue therapy.	✓ GOLD: recommended as LAMA monotherapy and LAMA/LABA combination therapy with olodaterol. ✓ COPD-X: recommended as LAMA monotherapy and LAMA/LABA combination therapy with olodaterol. AHRQ NGC: ✓ BC Medical Services Commission (Canada): recommended as monotherapy and LAMA/LABA combination therapy. Also recommended as triple therapy with ICS/LABA. ✓ Department of Veterans Affairs (US): recommended as first-line monotherapy and LAMA/LABA combination therapy. Also recommended as triple therapy with ICS/LABA. ×✓ ACP, ACCP, ATS, ERS: Tiotropium not discussed. LAMAs recommended as monotherapy or combination therapy. ×✓ NICE PATHWAY: Tiotropium not discussed. LAMAs

Name of active ingredient (brand name[a])	1. PBS prescribing restriction for COPD (listing date) 2. TGA indication for COPD (AusPAR date)	Intended use based on PSD and concerns of PBAC or sponsor	PBS or TGA restrictions for asthma, bronchospasm or mixed airways disease (October 2016)	Concordance between COPD PBS prescribing restrictions and clinical guidelines
				recommended as monotherapy or combination therapy as LAMA/LABA. LAMAs also recommended as triple therapy with ICS/LABA.
Tiotropium (Spiriva Respimat 2.5 µg actuations)	1. Restricted Benefit Bronchospasm and dyspnoea associated with COPD. Treatment Phase: Long-term maintenance treatment (October 2015). 2. Long term maintenance treatment of bronchospasm and dyspnoea associated with COPD. For the prevention of COPD exacerbations (no AusPAR, first included on the ARTG May 2002).	N/A	PI (Indications): Add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of ICS (≥800 µg budesonide/day or equivalent) and LABAs and who experienced one or more severe exacerbations in the previous year. PI (Precautions): Should not be used for the treatment of acute episodes of bronchospasm or for the relief of acute symptoms. Should not be used as a first-line treatment for asthma.	As above.
Umeclidinium (Incruse Ellipta 62.5 µg actuations)	1. Restricted Benefit COPD (January 2015). 2. Long-term once-daily maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD (July 2015).	• Cost-minimisation against tiotropium. • The submission proposed that umeclidinium as monotherapy will provide an alternative LAMA for the symptomatic relief of COPD. If symptoms persist in the absence of exacerbations, treatment involves a stepwise approach whereby umeclidinium will be used in combination with a LABA. If a patient then starts to experience exacerbations, treatment may be escalated to a fixed-dose ICS/LABA plus LAMA combination. • The PBAC noted that data presented in the submission was only for umeclidinium as monotherapy, and that there was heterogeneity in the trials included in the meta-analysis.	PI (Precautions): Asthma. Not recommended in patients with asthma.	✓ GOLD: recommended as LAMA monotherapy and LAMA/LABA combination therapy with vilanterol. ✓ COPD-X: recommended as LAMA monotherapy and LAMA/LABA combination therapy with vilanterol. AHRQ NGC: × BC Medical Services Commission (Canada): Umeclidinium not discussed. LAMAs not discussed, aside from tiotropium. × Department of Veterans Affairs (US): Umeclidinium not discussed. LAMAs not discussed, aside from tiotropium. ×✓ ACP, ACCP, ATS, ERS: Umeclidinium not discussed. LAMAs recommended as monotherapy or combination therapy. ×✓ NICE PATHWAY: Umeclidinium not discussed. LAMAs recommended as monotherapy or combination therapy as LAMA/LABA. LAMAs also recommended as triple therapy with ICS/LABA.

Name of active ingredient (brand name[a])	1. PBS prescribing restriction for COPD (listing date) 2. TGA indication for COPD (AusPAR date)	Intended use based on PSD and concerns of PBAC or sponsor	PBS or TGA restrictions for asthma, bronchospasm or mixed airways disease (October 2016)	Concordance between COPD PBS prescribing restrictions and clinical guidelines
LABA				
Indacaterol (Onbrez 150 µg, 300 µg inhalation capsules)	1. Restricted Benefit COPD (December 2011). 2. Long-term, once-daily, maintenance bronchodilator treatment of airflow limitation in patients with COPD (October 2010).	• Cost-minimisation against tiotropium. • The PBAC expressed uncertainty about the clinical place of indacaterol, because of concerns about the long-term safety of a LABA, without ICS therapy, and because the submission did not provide any data on the comparative efficacy and safety of indacaterol and LABA/ICS combinations, which the PBAC considered indacaterol would also replace in clinical practice. • These concerns were addressed in a resubmission.	PI (Precautions): Should not be used in asthma. A differential diagnosis should be made to exclude asthma or mixed airways disease before initiating.	✓ GOLD: recommended as LABA monotherapy and LAMA/LABA combination therapy with glycopyrronium. ✓ COPD-X: used once daily as LABA monotherapy and LAMA/LABA combination therapy with glycopyrronium. AHRQ NGC: ×✓ BC Medical Services Commission (Canada): Indacaterol not discussed. LABAs recommended as monotherapy and LAMA/LABA combination therapy with tiotropium. ×✓ Department of Veterans Affairs (US): Indacaterol not discussed. LABA recommended as monotherapy and LAMA/LABA combination therapy with tiotropium. LABA also recommended as triple therapy by adding ICS to LAMA/LABA. ×✓ ACP, ACCP, ATS, ERS: Indacaterol not discussed. LABA recommended as monotherapy or combination therapy with LAMA or ICS. ×✓ NICE PATHWAY: Indacaterol not discussed. LABA recommended as monotherapy and LAMA/LABA combination therapy. LABA also recommended as triple therapy by adding ICS to LAMA/LABA.
LAMA/LABA FDC				
Aclidinium/ eformoterol[c] (Brimica Genuair 340/12 µg actuations)	1. Authority Required (Streamlined) COPD. Patient must have been stabilised on a combination of a LAMA and LABA[d] (December 2015). 2. Long-term twice daily maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD (no AusPAR, first included on the ARTG May 2015).	• Cost-minimisation against existing LAMA/LABA FDCs glycopyrronium/indacaterol FDC and umeclidinium/vilanterol FDC.	PI (Precautions): Asthma BRIMICA GENUAIR 340/12 should not be used for the treatment of asthma; clinical studies of BRIMICA GENUAIR 340/12 in the treatment of asthma have not been conducted.	✓ GOLD: recommended as combination therapy with formoterol.[c] GOLD does not specify second line therapy after previous stabilisation on a LAMA and LABA. ✓ COPD-X: available for patients who remain symptomatic despite monotherapy with either agent alone. COPD-X does not specify that patients must have been previously stabilised on a LAMA and LABA. AHRQ NGC: × BC Medical Services Commission (Canada): Aclidinium/eformoterol not discussed. LAMAs not discussed, aside from tiotropium. × Department of Veterans Affairs (US): Aclidinium/eformoterol not discussed. LAMAs not discussed, aside from tiotropium.

Name of active ingredient (brand name[a])	1. PBS prescribing restriction for COPD (listing date) 2. TGA indication for COPD (AusPAR date)	Intended use based on PSD and concerns of PBAC or sponsor	PBS or TGA restrictions for asthma, bronchospasm or mixed airways disease (October 2016)	Concordance between COPD PBS prescribing restrictions and clinical guidelines
				×✓ ACP, ACCP, ATS, ERS: Aclidinium/eformoterol not discussed. LAMA recommended as combination therapy with a LABA. ×✓ NICE PATHWAY: Aclidinium/eformoterol not discussed. LAMA recommended as combination therapy with a LABA.
Glycopyrronium/ indacaterol (Ultibro Breezhaler 50/110 µg inhalation capsules)	1. Authority Required (Streamlined) COPD. Patient must have been stabilised on a combination of a LAMA and LABA[d] (November 2014). 2. Once-daily maintenance bronchodilator treatment to relieve symptoms in patients with COPD (October 2014).	• Cost-minimisation against the components given concomitantly. The submission presented evidence for the FDC compared to: 1. LAMA (glycopyrronium) 2. LABA (indacaterol) 3. LAMA + LABA (glycopyrronium + indacaterol); 4. LAMA + LABA (tiotropium + indacaterol); 5. ICS/LABA + LAMA (tiotropium). • The PBAC noted that the position of ICS/LABA in the treatment algorithm for COPD is changing, and ICS/LABA is currently recommended in patients with very severe disease. The PBAC therefore considered that the comparisons with LAMA + LABA presented in the submission were the most relevant. • While other treatments for [more severe] COPD are currently Restricted Benefits [i.e. ICS/LABAs], the PBAC considered it would be appropriate for indacaterol/glycopyrronium to be listed as a Streamlined Authority in an attempt to address inappropriate prescribing of the product, particularly in the first-line setting. The PBAC noted clinical input that confirmed initial treatment will be as monotherapy, with patients likely to be transitioned to FDC treatment only when clinically necessary.	PI (Precautions): Asthma and mixed airways disease ULTIBRO BREEZHALER 110/50 should not be used for the treatment of asthma due to the absence of data in this indication. A differential diagnosis should be made to exclude asthma or mixed airways disease before initiating ULTIBRO BREEZHALER 110/50.	✓ GOLD: recommended as combination therapy. GOLD does not specify second line therapy after previous stabilisation on a LAMA and LABA. ✓ COPD-X: available for patients who remain symptomatic despite monotherapy with either agent alone. COPD-X does not specify that patients must have been previously stabilised on a LAMA and LABA.. AHRQ NGC: × BC Medical Services Commission (Canada): Glycopyrronium/indacaterol not discussed. LAMAs not discussed, aside from tiotropium. × Department of Veterans Affairs (US): Glycopyrronium/indacaterol not discussed. LAMAs not discussed, aside from tiotropium. ×✓ ACP, ACCP, ATS, ERS: Glycopyrronium/indacaterol not discussed. LAMA recommended as combination therapy with a LABA. ×✓ NICE PATHWAY: Glycopyrronium/indacaterol not discussed. LAMA recommended as combination therapy with a LABA.
Tiotropium/ olodaterol (Spiolto Respimat 2.5/2.5 µg actuations)	1. Authority Required (Streamlined) COPD. Patient must have been stabilised on a combination of a LAMA and LABA[d] (December 2015). 2. Once-daily maintenance bronchodilator	• Cost-minimisation against the main comparators: 1. glycopyrronium/indacaterol FDC 2. umeclidinium/vilanterol FDC. • Cost-minimisation against the additional	PI (Precautions): Asthma Should not be used in the treatment of asthma as the efficacy and safety have not been studied in this indication.	✓ GOLD: recommended as combination therapy. GOLD does not specify second line therapy after previous stabilisation on a LAMA and LABA. ✓ COPD-X: available for patients who remain symptomatic despite monotherapy with either agent alone.

Name of active ingredient (brand name[a])	1. PBS prescribing restriction for COPD (listing date) 2. TGA indication for COPD (AusPAR date)	Intended use based on PSD and concerns of PBAC or sponsor	PBS or TGA restrictions for asthma, bronchospasm or mixed airways disease (October 2016)	Concordance between COPD PBS prescribing restrictions and clinical guidelines
	treatment to relieve symptoms in adult patients with COPD (no AusPAR, first included on the ARTG June 2015).	supportive comparators: 3. tiotropium monotherapy or olodaterol monotherapy 4. tiotropium plus olodaterol concurrently.	Acute bronchospasm Not indicated for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy.	COPD-X does not specify that patients must have been previously stabilised on a LAMA and LABA. AHRQ NGC: ✓ BC Medical Services Commission (Canada): tiotropium recommended as combination therapy with a LABA. ✓ Department of Veterans Affairs (US): tiotropium recommended as combination therapy with a LABA. ×✓ ACP, ACCP, ATS, ERS: Tiotropium/olodaterol not discussed. LAMA recommended as combination therapy with a LABA. ×✓ NICE PATHWAY: Tiotropium/olodaterol not discussed. LAMA recommended as combination therapy with a LABA.
Umeclidinium/ vilanterol (Anoro Ellipta 62.5/25 µg actuations)	1. Authority Required (Streamlined) COPD. Patient must have been stabilised on a combination of a LAMA and LABA[d] (December 2014). 2. Long-term once-daily maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD (April 2015).	• Cost-minimisation against tiotropium plus indacaterol. • The PSD for the March 2014 PBAC meeting states that, according to the COPD-X guidelines, LABAs and LAMAs are recommended in the treatment algorithm for patients with moderate, severe and very severe COPD, and some patients with mild COPD who may be experiencing high levels of breathlessness. If patients are beginning to experience further exacerbations then a bronchodilator with an ICS is currently recommended. • Given the current practice to prescribe ICS/LABA when stepping up therapy in persistently symptomatic patients from regular LAMA, LAMA/LABAs are likely to provide an effective, convenient and potentially safer alternative. Their availability would promote the current evidence-based recommendation of stepwise care and reduce the overuse of ICS [associated with increased risk of pneumonia]. • The PBAC noted that the treatment algorithm for COPD is changing. The PBAC considered it was appropriate to delay the introduction of ICS/LABA combination therapy in less severe	PI (Precautions): Asthma Should not be used in patients with asthma since it has not been studied in this patient population.	✓ GOLD: recommended as combination therapy. GOLD does not specify second line therapy after previous stabilisation on a LAMA and LABA. ✓ COPD-X: available for patients who remain symptomatic despite monotherapy with either agent alone. COPD-X does not specify that patients must have been previously stabilised on a LAMA and LABA. AHRQ NGC: × BC Medical Services Commission (Canada): Umeclidinium/vilanterol not discussed. LAMAs not discussed, aside from tiotropium. × Department of Veterans Affairs (US): Umeclidinium/vilanterol not discussed. LAMAs not discussed, aside from tiotropium. ×✓ ACP, ACCP, ATS, ERS: Umeclidinium/vilanterol not discussed. LAMA recommended as combination therapy with a LABA. ×✓ NICE PATHWAY: Umeclidinium/vilanterol not discussed. LAMA recommended as combination therapy with a LABA.

Name of active ingredient (brand name[a])	1. PBS prescribing restriction for COPD (listing date) 2. TGA indication for COPD (AusPAR date)	Intended use based on PSD and concerns of PBAC or sponsor	PBS or TGA restrictions for asthma, bronchospasm or mixed airways disease (October 2016)	Concordance between COPD PBS prescribing restrictions and clinical guidelines
		disease, given the potential safety risks associated with ICS use. The PBAC considered that use of the combination of a LAMA + LABA or LAMA/LABA [FDC] was preferred to the earlier introduction of an ICS/LABA combination.		
OCS				
Prednisolone (Solone 5 mg, 25 mg tablets)	1. Unrestricted. 2. Wherever corticosteroid therapy is indicated (no AusPAR, first included on the ARTG March 1997).	N/A	N/A	✓ GOLD: mentioned as an example of OCS. Long-term monotherapy with OCS is not recommended in COPD. ✓ COPD-X: can be used as monotherapy. Long term use of OCS is not recommended. AHRQ NGC: ✓ ACCP, CTS[f]: recommended for use in first 30 days after exacerbation. Not recommended to decrease acute exacerbation of COPD >30 days after initial event. ×✓ BC Medical Services Commission (Canada): Prednisolone not discussed. Long term OCS therapy not recommended. OCS (prednisone) recommended for use for less than 2 weeks after acute exacerbation. × Department of Veterans Affairs (US): Prednisolone not discussed. OCS therapy not discussed. × ACP, ACCP, ATS, ERS: Prednisolone not discussed. OCS therapy not discussed. ✓ NICE PATHWAY: prednisolone is mentioned for acute exacerbations of COPD.
ICS/LABA FDC				
jk	1. Restricted Benefit COPD • Patient must have a FEV_1 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	• Cost-minimisation against fluticasone propionate/salmeterol.	Restricted Benefit Asthma • Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids. • Patient must be aged 12 years or over. Note: Not recommended nor PBS-subsidised for use as 'maintenance and	✓ GOLD: recommended as combination therapy. Notes from GOLD Strategy Report: • Long-term treatment with ICS is recommended for patients with severe and very severe COPD and frequent exacerbations that are not adequately controlled by long-acting bronchodilators. • Long-term treatment containing ICS should not be prescribed outside their indications, due to the risk of pneumonia and the possibility of an increased risk of fractures following long-term exposure.

Name of active ingredient (brand name[a])	1. PBS prescribing restriction for COPD (listing date) 2. TGA indication for COPD (AusPAR date)	Intended use based on PSD and concerns of PBAC or sponsor	PBS or TGA restrictions for asthma, bronchospasm or mixed airways disease (October 2016)	Concordance between COPD PBS prescribing restrictions and clinical guidelines
	concomitant single agent LABA. This product is not indicated for the initiation of bronchodilator therapy in COPD (December 2011 (for COPD)) 2. Symptomatic treatment of moderate to severe COPD (FEV_1 ≤50% predicted normal) in adults with frequent symptoms despite long-acting bronchodilator use, and/or a history of recurrent exacerbations. Not indicated for the initiation of bronchodilator therapy in COPD (October 2010).		reliever' therapy.	✓ COPD-X: recommended as combination therapy. Guidelines state that budesonide/formoterol reduce the rate of exacerbations. AHRQ NGC: ×✓ ACCP, CTSG[f]: Budesonide/eformoterol not discussed. ICS/LABA recommended to prevent/decrease acute exacerbations of COPD. × BC Medical Services Commission (Canada): Budesonide/eformoterol not discussed. ICS/LABA not discussed, instead recommends triple therapy with LAMA/LABA/ICS. × Department of Veterans Affairs (US): Budesonide/eformoterol not discussed. ICS/LABA not discussed, instead recommends triple therapy with LAMA/LABA/ICS. × ACP, ACCP, ATS, ERS: Budesonide/eformoterol not discussed. ICS/LABA not discussed, instead recommends triple therapy with LAMA/LABA/ICS. ×✓ NICE PATHWAY: Budesonide/eformoterol not discussed. ICS recommended as combination therapy with a LABA.
Budesonide/ eformoterol (Symbicort Rapihaler 200/6 µg actuations)	1. As above (January 2014 (for COPD and asthma)). 2. Symptomatic treatment of moderate to severe COPD (FEV_1 ≤50% predicted normal) in adults with frequent symptoms despite long-acting bronchodilator use, and/or a history of recurrent exacerbations. Not indicated for the initiation of bronchodilator therapy in COPD (October 2010).	• Cost-minimisation against budesonide/eformoterol FDC DPI (Symbicort Turbuhaler). • The PBAC noted that data were not presented in the current resubmission for the use of the Symbicort Rapihaler in COPD, but that such data had previously been presented to the PBAC in the November 2010 major submission [for Symbicort Turbuhaler DPI 400/12 µg] and the PBAC had recommended listing in COPD on this basis.	Restricted Benefit Asthma • Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids. • Patient must be aged 12 years or over. Note: Not recommended nor PBS-subsidised for use as 'maintenance and reliever' therapy.	As above.
Fluticasone propionate/ salmeterol (Seretide Accuhaler	1. Restricted Benefit COPD • Patient must have a FEV_1 less than 50% of predicted normal prior to therapy. • Patient must have a history of repeated	• Cost-minimisation against tiotropium. • The submission claimed that fluticasone propionate/ salmeterol is more effective than tiotropium with similar toxicity. • The choice of the cost-effectiveness approach	Restricted Benefit Asthma • Patient must have previously had frequent episodes of asthma while receiving treatment with OCS or	✓ GOLD: recommended as combination therapy. Notes from GOLD Strategy Report: • Long-term treatment with ICS is recommended for patients with severe and very severe COPD and

Name of active ingredient (brand name[a])	1. PBS prescribing restriction for COPD (listing date) 2. TGA indication for COPD (AusPAR date)	Intended use based on PSD and concerns of PBAC or sponsor	PBS or TGA restrictions for asthma, bronchospasm or mixed airways disease (October 2016)	Concordance between COPD PBS prescribing restrictions and clinical guidelines
500/50 µg actuations; Seretide MDI 250/25 µg actuations)	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 LABA. This product is not indicated for the initiation of bronchodilator therapy in COPD (August 2007 (for COPD)). 2. For the symptomatic treatment of patients with severe COPD (FEV_1 <50% predicted normal) and a history of repeated exacerbations who have significant symptoms despite regular beta-2 agonist bronchodilator therapy. Not indicated for the initiation of bronchodilator therapy in COPD (no AusPAR, first included on the ARTG February 2000).	was not considered valid as the PBAC did not accept the clinical claim of superior effectiveness.	optimal doses of ICS. • Patient must be aged 4 years or older.	frequent exacerbations that are not adequately controlled by long-acting bronchodilators. • Long-term treatment containing ICS should not be prescribed outside their indications, due to the risk of pneumonia and the possibility of an increased risk of fractures following long-term exposure. ✓ COPD-X: reduces the rate of exacerbations. AHRQ NGC: ×✓ ACCP, CTSG[f]: Fluticasone propionate/salmeterol not discussed. ICS/LABA recommended to prevent/decrease acute exacerbations of COPD. × BC Medical Services Commission (Canada): Fluticasone propionate/salmeterol not discussed. ICS/LABA not discussed, instead recommends triple therapy with LAMA/LABA/ICS. × Department of Veterans Affairs (US): Fluticasone propionate/salmeterol not discussed. ICS/LABA not discussed, instead recommends triple therapy with LAMA/LABA/ICS. × ACP, ACCP, ATS, ERS: Fluticasone propinate/salmeterol not discussed. ICS/LABA not discussed, instead recommends triple therapy with LAMA/LABA/ICS. ×✓ NICE PATHWAY: Fluticasone propionate/salmeterol not discussed. ICS recommended as combination therapy with a LABA.
Fluticasone furoate/ vilanterol (Breo Ellipta 100/25 µg actuations)	1. Restricted Benefit COPD [and asthma] • Patient must have a FEV_1 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 LABA. This	March 2014 PSD (rejected): • Cost-minimisation against fluticasone propionate/salmeterol FDC. • Safety concerns. • Clinical need concerns. July 2014 PSD (recommended): • Cost-minimisation against fluticasone propionate/salmeterol 500/50 µg. • The PBAC considered that the cost-effectiveness of fluticasone furoate/vilanterol would be acceptable if it were cost-minimised against aclidinium, which was recommended	Restricted Benefit Asthma • Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids. • Patient must be aged 12 years or over. Note: This drug is not recommended nor PBS-subsidised for use as 'maintenance and reliever' therapy.	✓ GOLD: recommended as combination therapy. Notes from GOLD Strategy Report: • Long-term treatment with ICS is recommended for patients with severe and very severe COPD and frequent exacerbations that are not adequately controlled by long-acting bronchodilators. • Long-term treatment containing ICS should not be prescribed outside their indications, due to the risk of pneumonia and the possibility of an increased risk of fractures following long-term exposure. ✓ COPD-X: recommended as combination therapy.

Name of active ingredient (brand name[a])	1. PBS prescribing restriction for COPD (listing date) 2. TGA indication for COPD (AusPAR date)	Intended use based on PSD and concerns of PBAC or sponsor	PBS or TGA restrictions for asthma, bronchospasm or mixed airways disease (October 2016)	Concordance between COPD PBS prescribing restrictions and clinical guidelines
	product is not indicated for the initiation of bronchodilator therapy in COPD (December 2014 (for COPD and asthma)). 2. Symptomatic treatment of patients with COPD with a FEV_1 <70% predicted normal (post-bronchodilator) in patients with an exacerbation history despite regular bronchodilator therapy. Not indicated for the initiation of bronchodilator therapy in COPD (June 2014).	for listing by PBAC in March 2014 for the same indication but at the lower price requested by the sponsor and which is, in turn, cost-minimised to the comparator via tiotropium.		AHRQ NGC: ×✓ ACCP, CTSG[f]: Fluticasone furoate/vilanterol not discussed. ICS/LABA recommended to prevent/decrease acute exacerbations of COPD. × BC Medical Services Commission (Canada): Fluticasone furoate/vilanterol not discussed. ICS/LABA not discussed, instead recommends triple therapy with LAMA/LABA/ICS. × Department of Veterans Affairs (US): Fluticasone furoate/vilanterol not discussed. ICS/LABA not discussed, instead recommends triple therapy with LAMA/LABA/ICS. × ACP, ACCP, ATS, ERS: Fluticasone/vilanterol not discussed. ICS/LABA not discussed, instead recommends triple therapy with LAMA/LABA/ICS. ×✓ NICE PATHWAY: Fluticasone furoate/vilanterol not discussed. ICS recommended as combination therapy with a LABA.

Abbreviations: ACCP, American College of Chest Physicians; ACP, American College of Physicians; AHRQ, Agency for Healthcare Research and Quality; ARTG, Australian Register of Therapeutic Goods; ATS, American Thoracic Society; AusPAR, Australian Public Assessment Reports for prescription medicines; BC, British Columbia; COPD, chronic obstructive pulmonary disease; CTS, Canadian Thoracic Society; DPI, dry powder inhaler; ERS, European Respiratory Society; FDC, fixed-dose combination; FEV, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; N/A, not applicable; NICE, National Institute of Health and Care Excellence; NGC, National Guidelines Clearinghouse; OCS, oral corticosteroid; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Schedule; PI, product information; SAMA, short-acting muscarinic antagonist; TGA, Therapeutic Goods Administration.

a Many agents have generic brands on the market; the brand listed in the Table is an example.

b COPD-X refers to the COPD-X Guidelines and/or the Lung Foundation of Australia.

c Formoterol and eformoterol are interchangeable.

d Stabilisation on a LAMA and LABA could refer to two separately administered products, or a [different] FDC.

e Key to recommendations: ✓ indicates that the agent is recommended for use. × indicates that the agent is not discussed either individually or as a class. ×✓ indicates that the agent is not discussed individually but is recommended for use as a class.

f The ACCP, CTSG guidelines are summarised for the OCS and ICS/LABA agents only, because this guideline refers to COPD exacerbations only; therefore, the LAMA, LABAs and LAMA/LABA combinations are less relevant to this patient population.

Budesonide monotherapy has an unrestricted PBS listing, with a TGA indication that includes 'Pulmicort may also be used when replacement or reduction in oral steroid therapy is desirable'. However, it is generally not recommended as long-term therapy in a chronic disease such as COPD. The general intention of COPD-X guideines and GOLD Strategy Report is to step up from LAMA/LABA combination to ICS/LABA, rather than introducing ICS as monotherapy (even for an exacerbation). Therefore, budesonide monotherapy does not appear in Table 1.7.

Notably, the COPD-X guidelines provide a table of allowable additions of combination therapy in their document, 'Stepwise Management of Stable COPD' (2016). The information is presented as both allowable classes of medications that can be combined, and specific medications available in Australia that belong to each class. Included in the schematic are possible additions to dual therapy, indicating which combinations of triple therapy are appropriate. Triple therapy combinations (for example, ICS + LABA + LAMA, which may be delivered as LAMA/LABA + ICS or ICS/LABA + LAMA) are mentioned in the reviewed guidelines; no triple therapy FDC has been considered by the PBAC at the time of this review. Conversely, the table illustrates combinations of COPD medicines that are considered inappropriate, such as LAMA/LABA + LABA or ICS/LABA + LAMA/LABA**Error! Reference source not found.** Section 5 documents that a variety of inappropriate combinations are in fact being used in a small but increasing number of patients.

Note that the PBAC considered evidence for triple therapy as part of the November 2013 submission for glycopyrronium, where it was evaluated as monotherapy and also as add-on to LABA or ICS/LABA (using direct comparison of glycopyrronium + ICS/LABA vs tiotropium + ICS/LABA). The November 2013 PSD states that glycopyrronium is non-inferior to tiotropium in terms of efficacy and safety, but noted that the studies that best supported the non-inferiority claim were the trials presented for monotherapy.

1.5.3 Doses of COPD medicines

The PBS-listed doses of COPD medications compared with the GOLD Strategy Report are itemised in Table 1.8. The PBS medications correspond well with the GOLD Strategy Report, in that the doses are either identical or very similar. In the GOLD Strategy Report, the frequency of dosing is not specified for the ICS/LABAs, although it is reported for the other agents. The frequency of dosing for all the PBS-listed medications are specified in their respective product information. In general, guidelines other than GOLD do not discuss dose, though they may mention doses *ad hoc*.

Table 1.8 Concordance between doses for PBS-listed medications and GOLD Strategy Report

Active ingredient	Dose specified on PBS (frequency in PI)	Doses specified in GOLD Strategy Report[a] (duration of action)	Concordance between PBS doses and GOLD Strategy Report
SAMA			
Ipratropium	N/A 250, 500 µg/mL inhalation solution (6 hourly)	20, 40 µg MDI 0.25-0.5 mg/mL (6-8 hrs)	N/A Identical
LAMA			
Aclidinium	400 µg actuations (BID)	Inhaler: 322 µg DPI (12 hrs)	Similar[b]
Glycopyrronium	50 µg inhalation capsules (QD)	Inhaler: 44 µg DPI (24 hrs)	Similar[b]
Tiotropium	18 µg inhalation capsules (QD)	Inhaler: 18 µg DPI (24 hrs)	Identical
Tiotropium	2.5 µg actuations (2 puffs QD)	Inhaler: 5 µg SMI (24 hrs)	Identical
Umeclidinium	62.5 µg actuations (QD)	Inhaler: 62.5 µg DPI (24 hrs)	Identical
LABA			
Indacaterol	150, 300 µg inhalation capsules (QD)	Inhaler: 75-300 µg DPI (24 hrs)	Similar[b]
LAMA/LABA FDC			
Aclidinium/eformoterol	340/12 µg actuations (BID)	Inhaler: 340/12 µg DPI (12 hrs)	Identical
Glycopyrronium/indacaterol	50/110 µg inhalation capsules (QD)	Inhaler: 43/85 µg DPI (24 hrs)	Similar[b]
Tiotropium/olodaterol	2.5/2.5 µg actuations (2 puffs QD)	Inhaler: 5/5 µg SMI (24 hrs)	Identical
Umeclidinium/vilanterol	62.5/25 µg actuations (QD)	Inhaler: 62.5/25 µg DPI (24 hrs)	Identical
OCS			
Prednisone	5 mg, 25 mg tablets (divided doses)	Oral: 5-60 mg (NR)	Similar[b]
ICS/LABA FDC			
Budesonide/eformoterol	400/12 µg actuations (1 puff BID)[d]	Inhaler: 320/9 µg DPI (NR)	N/A[c]
Budesonide/eformoterol	200/6 µg actuations (2 puffs BID)[d]	Inhaler: 160/4.5 µg MDI (NR)	N/A[c]
Fluticasone propionate/salmeterol	500/50 µg actuations (BID) 250/25 µg actuations (2 puffs BID)	Inhaler: 100/50, 250/50, 500/50 µg DPI (NR)	N/A[c]
Fluticasone furoate/vilanterol	100/25 µg actuations (QD)	Inhaler: 100/25 µg DPI (NR)	N/A[c]

Abbreviations: BID, twice daily; DPI, dry powder inhaler; FDC, fixed-dose combination; hrs, hours; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; MDI, metered dose inhaler; N/A, not applicable; NR, not reported; OCS, oral corticosteroid; PBS, Pharmaceutical Benefits Schedule; PI, product information; QD, once daily; SAMA, short-acting muscarinic antagonist; SMI, soft mist inhaler.

a GOLD Strategy 2016 Table 3.3 p22.

b Doses that appear similar may in fact be identical, but simply differ between PBS and GOLD as to whether the anion of the agent/s is included in the calculation of the administration weight.

c Duration of action is not reported in the GOLD guidelines for the ICS LABAs; therefore, concordance cannot be assessed.

d The maximum recommended daily dose in the PI is 800 µg budesonide/24 µg eformoterol.

1.5.4 Medications that are not PBS listed for COPD

COPD medications referred to in guidelines that are not PBS listed, or have an unrestricted PBS listing with a non-COPD TGA indication, are listed in Table 1.9. The content of the GOLD Strategy Report and COPD-X guidelines regarding these agents has been cross-referenced to determine why this has occurred. Of the agents that are PBS listed, they all either have a Restricted Benefit for asthma treatment, or they have an unrestricted PBS listing with a TGA indication for asthma. Several of the agents are PBS listed as part of a FDC for COPD, but are not approved or listed for monotherapy. Some agents are listed in the guidelines as possible COPD treatments, but the guidelines recommend against using them under certain circumstances; for example, long term ICS monotherapy. These agents may be being used off-label in COPD, or they could be being used in ACOS patients.

Table 1.9 COPD medications referred to in guidelines that are not PBS listed or have an unrestricted PBS listing with a non-COPD TGA indication

Name of active ingredient	Brand name	PBS listing date	PBS prescribing restriction or TGA indication	Source guideline/report and comments
LABA				
Arformoterol[a]	N/A	N/A	Not PBS listed.	GOLD
Olodaterol	Striverdi Respimat	N/A	Monotherapy is not PBS listed. Rejected for PBS listing July 2014.	GOLD
Formoterol or eformoterol	Foradile or Oxis Turbuhaler	Pre-2003	Restricted Benefit Asthma Patient must experience frequent episodes of the condition, AND Patient must be currently receiving treatment with OCS; OR Patient must be currently receiving treatment with optimal doses of ICS.	GOLD COPD-X: eformoterol used twice daily.
Salmeterol	Serevent Accuhaler	1992	Restricted Benefit Asthma Patient must experience frequent episodes of the condition, AND Patient must be currently receiving treatment with OCS; OR Patient must be currently receiving treatment with optimal doses of ICS.	GOLD COPD-X: salmeterol used twice daily.
Tulobuterol	N/A	N/A	Not PBS listed.	GOLD
ICS				
Beclomethasone	Unrestricted QVAR Restricted Benefit QVAR Autohaler	Pre-2003 Pre-2003	Unrestricted TGA indication: QVAR is indicated for the prophylactic management of asthma. Restricted Benefit Asthma Patient must be unable to achieve co-ordinated use of other metered dose inhalers containing this drug.	GOLD: beclomethasone mentioned. Notes from GOLD Strategy Report: Long-term monotherapy with ICS is not recommended in COPD because it is less effective than the combination of ICS with LABA.
Budesonide	Unrestricted Pulmicort Turbuhaler Authority Required (Streamlined) Pulmicort Respules	Pre-2003 Pre-2003	Unrestricted TGA indication: Authority Required (Streamlined) Severe chronic asthma Patient must require long-term steroid therapy, AND Patient must not be able to use other forms of ICS.	GOLD: budesonide mentioned. Notes from GOLD Strategy Report: Long-term monotherapy with ICS is not recommended in COPD because it is less effective than the combination of ICS with LABA. COPD-X: budesonide mentioned. Notes from COPD-X guidelines: ICS should be considered in patients with moderate to

Name of active ingredient	Brand name	PBS listing date	PBS prescribing restriction or TGA indication	Source guideline/report and comments
				severe COPD and frequent exacerbations. Budesonide is discussed. The guidelines state that any potential benefits of ICS should be weighed against the potential risks of local oropharyngeal adverse effects and pneumonia.
Fluticasone	Flixotide Junior Accuhaler Flixotide Accuhaler Flixotide Flixotide Junior	1996	Unrestricted TGA indication: For use in the prophylactic management of asthma in adults and children of ages 1 year and older.	GOLD: fluticasone mentioned. Notes from GOLD Strategy Report: Long-term monotherapy with ICS is not recommended in COPD because it is less effective than the combination of ICS with LABA. COPD-X: fluticasone mentioned. Notes from COPD-X guidelines: ICS should be considered in patients with moderate to severe COPD and frequent exacerbations. Fluticasone is discussed. The guidelines state that any potential benefits of ICS should be weighed against the potential risks of local oropharyngeal adverse effects and pneumonia.
ICS/LABA				
Beclomethasone/formoterol	N/A	N/A	Not PBS listed.	GOLD Notes from GOLD Strategy Report: Long-term treatment with ICS is recommended for patients with severe and very severe COPD and frequent exacerbations that are not adequately controlled by long-acting bronchodilators. Long-term treatment containing ICS should not be prescribed outside their indications, due to the risk of pneumonia and the possibility of an increased risk of fractures following long-term exposure.
Mometasone/formoterol	N/A	N/A	Not PBS listed.	GOLD Notes from GOLD Strategy Report: Long-term treatment with ICS is recommended for patients with severe and very severe COPD and frequent exacerbations that are not adequately controlled by long-acting bronchodilators. Long-term treatment containing ICS should not be prescribed outside their indications, due to the risk of pneumonia and the possibility of an increased risk of fractures following long-term exposure.

Name of active ingredient	Brand name	PBS listing date	PBS prescribing restriction or TGA indication	Source guideline/report and comments
OCS				
Prednisone or methylprednisolone	Sone	Prednisone: Pre-2003 Methylprednisolone: N/A	Prednisone: Unrestricted TGA indication: Wherever corticosteroid therapy is indicated. Methylprednisolone: Not PBS listed in oral formulation.	GOLD: Prednisone and methylprednisolone mentioned. Notes from GOLD Strategy Report: There is no evidence to recommend a short-term therapeutic trial with OCS in patients with COPD to identify those who will respond to ICS or other medications. Long-term monotherapy with OCS is not recommended in COPD.
Methylxanthine				
Aminophylline	N/A	N/A	Not PBS listed.	GOLD
Theophylline	Nuelin-SR	Pre-2003	Unrestricted TGA indication: For the relief and prophylaxis of reversible bronchospasm associated with bronchial asthma, bronchitis, emphysema and related conditions.	GOLD: theophylline mentioned as a possible treatment in several patient groups. Notes from GOLD Strategy Report: Based on evidence of relatively low efficacy and more side effects, treatment with theophylline is not recommended unless other LABA and LAMA are unavailable or unaffordable. NICE pathyway (2016): refers to theophylline. COPD-X: Severe symptoms Consider low-dose theophylline. Theophyllines have gone out of favour in many countries because of their narrow therapeutic index and potential for significant adverse effects.
PDE-4 inhibitor				
Roflumilast	N/A	N/A	Not PBS listed.	GOLD Notes from GOLD Strategy Report: The PDE-4 inhibitor, roflumilast, may also be used to reduce exacerbations for patients with chronic bronchitis, severe and very severe COPD, and frequent exacerbations that are not adequately controlled by LABA and LAMA. COPD-X Cilomilast and roflumilast are not currently available in Australia.

Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global initiative for chronic obstructive lung disease; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; N/A, not applicable; OCS, oral corticosteroid; PDE-4, phosphodiesterase-4; TGA, Therapeutic Goods Administration.
a Arformoterol is the R,R enantiomer of racemic formoterol

Attachment A: Bibliography

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