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

April 2016

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Boehringer Ingelheim welcomes the opportunity to comment on the Post-market Review of Chronic Obstructive Pulmonary Disease (COPD) Medicines. This submission addresses the following Terms of Reference:

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

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

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

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

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

6. Evaluate if the current utilisation of multiple therapies and the latest evidence relating to safety and efficacy justifies a review of cost-effectiveness for some or all medicines indicated for COPD.

Executive summary

Chronic obstructive pulmonary disease (COPD) is a serious, progressive and disabling condition that limits airflow in the lungs. COPD is a major cause of chronic morbidity and mortality; many people suffer from the disease for years, and die prematurely from it or its complications. The prevalence of COPD in Australians aged 55 years and older is estimated at 5.7%, which accounts for over 300,000 people [Australian Bureau of Statistics (ABS), 2012]. However, the prevalence of COPD is likely to be much higher, reflecting the widespread under-recognition and under-diagnosis of COPD (GOLD, 2015). COPD has a substantial impact on both individuals and the community and it is ranked as the third highest cause of disease burden in Australia. COPD is also the second leading cause of avoidable hospital admissions in Australia.

Boehringer Ingelheim has three products that are listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of COPD: tiotropium (Spiriva® and Spiriva® Respimat®), ipratropium (Atrovent®) and tiotropium/olodaterol (tio/olo) fixed dose combination (FDC) (Spiolto® Respimat®). This submission addresses the Terms of Reference (ToR) of the Review by reviewing the recent evidence on the clinical practice, efficacy, safety, cost-effectiveness and the appropriate use of tiotropium, ipratropium and tio/olo for the treatment of COPD.

Review of clinical practice guidelines and PBS prescribing restrictions

ToR 1 refers to whether the PBS prescribing restrictions are consistent with clinical practice guidelines. This submission presents a comprehensive review of the current clinical practice guidelines to establish the current treatment algorithm for COPD. The key Australian clinical practice guideline for COPD is the COPD-X Plan, which is an evidence-based guideline updated regularly and developed jointly by the Thoracic Society of Australia and New Zealand (TSANZ) and Lung Foundation Australia. The key international clinical practice guideline for COPD is the Global initiative for Chronic Obstructive Lung Disease (GOLD) Guideline; the treatment recommendations in the GOLD Guideline are consistent with those in the COPD-X Plan.

The treatment algorithm in the COPD-X Plan recommends a stepwise approach to pharmacological treatment of COPD, irrespective of disease severity, until adequate control has been achieved. The first step is treatment with a short acting bronchodilator [short acting muscarinic antagonist (SAMA e.g. ipratropium) or short acting β2 agonist (SABA)]. For patients who remain symptomatic, the next step is initiation of a long acting bronchodilator [long acting muscarinic antagonist (LAMA e.g. tiotropium) or long acting β2 agonist (LABA)]. A combination of long acting bronchodilators (LAMA plus LABA e.g. tio/olo) is recommended if additional control is required. The initiation of an inhaled corticosteroid (ICS) (in combination with a LABA) is recommended as one of the last steps in the treatment pathway, which is recommended by clinical practice guidelines and TSANZ. Specifically, this combination is recommended for moderate to severe COPD patients with a history of at least two exacerbations in the previous 12 months and forced expiratory volume in 1 second (FEV_1) <50%, despite current bronchodilator therapy. This is also consistent with the current PBS restriction for ICS/LABAs and concerns on the risk of adverse events (AEs) such as pneumonia. Recent analysis suggests that patients with severe COPD with a history of COPD exacerbations and a blood eosinophil count of 4% or greater may benefit from the addition of ICS therapy (Watz et al 2016).

The PBS prescribing criteria for tio/olo FDC exclude it from being used for the initiation of bronchodilator therapy, which is consistent with the stepwise approach recommended in the treatment guidelines. However, the PBS criteria require stabilisation on a combination of a LAMA and a LABA prior to commencing the FDC. This requirement is not consistent with the treatment guidelines which recommend the use of a LAMA/LABA FDC for patients who are not controlled on either monotherapy alone *or* for those patients who are stabilised on a LAMA and LABA.

ICS/LABAs are pharmacologically different from LAMAs with different clinical and adverse event profiles, in particular pneumonia, in addition to being used in a more severe COPD patient population. The PBS restriction criteria for ICS/LABAs are for symptomatic treatment of patients with severe COPD (FEV_1<50%) and a history of repeated exacerbations who have significant symptoms despite regular LABA use, which is in line with the clinical evidence and TGA indications. ICS/LABAs are not indicated to be used for initial bronchodilator therapy and the PBAC has considered that ICS/LABAs are more likely to be added to LAMA therapy rather than replace LAMAs (Indacaterol Public Summary Documents (PSDs) November 2010; July 2011). The TSANZ recommended that given the current practice to prescribe ICS/LABA FDC when stepping up therapy in persistently symptomatic patients, the LABA/LAMA FDC products are likely to provide an effective, convenient and potentially safer alternative to ICS/LABA FDCs (PSDs March 2014: glycopyrronium/indacaterol FDC; umeclidinium/vilanterol FDC; fluticasone/vilanterol FDC). Based on the comments from the TSANZ, the PBAC acknowledged the potential safety risks associated with ICS use and considered it appropriate to delay the introduction of ICS/LABA FDCs in favour of LAMA/LABA combinations in less severe disease. The PBAC also noted that delaying ICS use would be consistent with the Australian COPD-X Guidelines, where introduction of an ICS is recommended only for patients with more severe disease.

Therefore, ICS/LABA FDCs should not be considered interchangeable or a relevant comparator with other pharmacological classes such as LAMAs in the COPD treatment algorithm. The COPD Review should recognise this and there should not be any therapeutic relativity link between drugs of different classes, especially if further cost-effectiveness analyses are recommended by the Review.

Clinically important outcomes in COPD and their inclusion in previous PBAC assessments

ToR 2 refers to the inclusion of clinically important outcomes in previous PBAC assessments of COPD medicines. This submission summarises patient-relevant outcomes for COPD and the extent to which they were included in previous PBAC submissions for tiotropium and tio/olo FDC. The outcomes identified as most clinically relevant are:

- COPD Exacerbations
- Hospitalisations
- FEV_1
- Quality of life (QoL)
- Mortality
- Symptoms
- AEs

As detailed in the response to ToR 3, systematic reviews of tiotropium randomised controlled trials (RCTs) show that tiotropium has a treatment benefit for all clinical outcomes identified above. Tiotropium was listed on the PBS in 2003. Tiotropium was recommended by the PBAC based on superior efficacy and safety and acceptable cost-effectiveness compared with ipratropium. Tio/olo was listed on the PBS in December 2015 based on cost-minimisation to two LAMA/LABA FDCs which were listed on the PBS at the time of submission; glycopyrronium/indacaterol (gly/ind) and umeclidinium/vilanterol (ume/vil) FDCs. The PBAC submission for tiotropium and tio/olo considered ***all*** the clinical outcomes detailed above, and therefore, these outcomes remain clinically relevant for PBAC consideration.

Review of efficacy and safety of COPD medicines

ToR 3 refers to a review of the efficacy and safety of COPD medicines. This submission summarises the recent evidence on the efficacy and safety of tiotropium, ipratropium and tio/olo for the treatment of COPD.

Tiotropium evidence

The submission presents an overview of systematic reviews on the efficacy and safety of tiotropium compared with other LAMAs, usual care and ipratropium (ToR 3).

- Tiotropium has the most substantial body of evidence among the LAMAs, including long-term evidence demonstrating a reduction in exacerbations and hospitalisations, as well as improved lung function, QoL and symptoms compared with usual care therapy. Tiotropium is the only LAMA which has shown to reduce exacerbations, associated hospitalisations and mortality over the long-term compared with usual care (e.g. UPLIFT 4-years duration). Furthermore, tiotropium was the only LAMA to show a statistically significant reduction in severe exacerbations compared with usual care.
- In terms of FEV_1, St George respiratory questionnaire (SGRQ) and transition dyspnoea index (TDI), the results of the systematic reviews are consistent with recent PBAC assessments that tiotropium, aclidinium, glycopyrronium and umeclidinium are non-inferior in terms of efficacy and safety (equi-effective doses: tiotropium HandiHaler 18 µg once daily, tiotropium Respimat 5 µg once daily, glycopyrronium 50 µg once daily, aclidinium 400 µg twice daily, umeclidinium 62.5 µg once daily).
- Patients in many tiotropium RCTs were permitted access to usual-care respiratory medicines (including LABAs) which reflects real-life treatment practice whereas trials of other LAMAs were often more restricted in the background respiratory medicines permitted. Therefore, the results of tiotropium RCTs are directly applicable to patients likely to receive tiotropium in clinical practice.
- The effect of tiotropium and other LAMAs on all-cause and cardiovascular mortality was similar with no significant differences observed between the treatments. There was no difference in mortality between the different formulations of tiotropium (HandiHaler and Respimat). This is consistent with the PBAC's previous evaluation that tiotropium HandiHaler 18 µg and Respimat 5 µg are equivalent.

- Tiotropium has superior efficacy and safety compared with ipratropium, which is consistent with the PBAC's original recommendation of tiotropium on a cost-effectiveness basis compared with ipratropium.

Tiotropium with olodaterol evidence

A review of PSDs is conducted to summarise the clinical evidence considered by the PBAC in its recommendation of tio/olo and other LAMA/LABA FDCs.

- Tio/olo FDC has superior efficacy and comparable safety to tiotropium or olodaterol monotherapy.
- The RCT evidence presented in the PSDs demonstrates that tio/olo FDC is of comparable efficacy and safety to other PBS-listed LAMA/LABA FDCs, which is consistent with the PBAC's recent recommendations.

This submission also summarises relevant clinical evidence for tio/olo since it was recommended by the PBAC at the July 2015 meeting.

Ipratropium evidence

A summary of evidence supporting the use of ipratropium by the COPD-X Plan is presented.

- Ipratropium has a significantly greater effect on lung function compared to SABAs, in addition to improving quality of life and decreasing need for oral corticosteroid treatment.
- Ipratropium combined with SABA treatment reduces the number of patients experiencing exacerbations and the use of oral corticosteroids, without increasing drug related AEs.

Cost effectiveness of tiotropium

In addition to the clinical evidence, this submission presents a systematic review to summarise the published literature on the cost-effectiveness of tiotropium for the treatment of COPD compared with other LAMAs, usual care/placebo, ipratropium and in combination with ICS/LABAs.

- The economic evaluations indicate that tiotropium is similarly cost-effective to other LAMA therapies. Tiotropium is cost-effective compared with usual care and ipratropium.
- The cost effectiveness of tiotropium was driven primarily by its effectiveness in preventing exacerbations and hospitalisations; events associated with substantial decrease in QoL and increase in healthcare costs and mortality.
- The cost-effectiveness of tiotropium was consistent across different comparators and across different countries, despite differences in healthcare systems and costs.

Safety of prolonged ICS use

In response to ToR 4, this submission presents a brief discussion of safety issues associated with ICS use in relation to clinical practice guidelines and PBS prescribing criteria. The GOLD 2016 Guidelines state that ICS use is associated with higher prevalence of oral candidiasis, hoarse voice, skin bruising, increased risk of pneumonia and possible increased risk of fractures. Due to the potential of severe AEs, ICS/LABA combinations are recommended as one of the last options in the treatment algorithm

for patients with severe COPD and previous history of exacerbations (COPD-X 2015/2016, GOLD 2016). This is consistent with the PBS listing and intention of the PBAC to restrict their use to a specific COPD population. Given the place of ICS/LABA combinations in the COPD treatment algorithm and the different pharmacological class and safety profile, these combinations should not be linked to the LAMAs for the purposes of a therapeutic relativity.

Utilisation of COPD medicines

ToR 5 refers to use of COPD medicines that are inconsistent with PBS restrictions or clinical practice guidelines. The submission presents an analysis of prescribing patterns of tiotropium in Australia. A recent Medicare sample, obtained via an independent third party, included a random 10% PBS patient sample scaled up to national estimates (which was used for the recent tio/olo PBAC submission). Patients were tracked longitudinally using their Medicare number. All patients that had been prescribed tiotropium over the observation period were included, along with details of their concurrent medication use including LABA, ICS and ICS/LABA FDC. The Medicare data shows that there is appropriate prescribing of tiotropium as monotherapy and in combination with other long-acting COPD medications. In addition, Australian Medical Index (AMI) data from IMS Health further supports that tiotropium is used appropriately in accordance with clinical practice guidelines and PBS restrictions. Therefore, the current use of tiotropium is consistent with PBS restrictions and clinical practice guidelines. Boehringer Ingelheim supports the Quality Use of Medicines (QUM) with initiatives aimed at prescriber education to ensure appropriate use. A summary of QUM initiatives is presented in the submission

Assessment of the need for a review of cost-effectiveness of COPD medicine

ToR 6 refers to whether a review of the cost-effectiveness of COPD medicines is justified. This submission summarises the utilisation, clinical and economic evidence for tiotropium.

- The Medicare and IMS Health data show that there is appropriate prescribing of tiotropium as monotherapy or in combination with other long-acting COPD medications
- Tiotropium is the only LAMA which has shown to reduce exacerbations, associated hospitalisations and mortality over the long-term compared with usual care.
- The economic evaluations indicate that tiotropium is similarly cost-effective to other LAMA therapies. Tiotropium is cost-effective compared with usual care and ipratropium.
- The cost effectiveness of tiotropium was driven primarily by its effectiveness in preventing exacerbations and hospitalisations; events associated with substantial decrease in QoL and increase in healthcare costs and mortality.
- The cost-effectiveness of tiotropium was consistent across different comparators and across different countries, despite differences in healthcare systems and costs.

Based on the utilisation data, recent clinical evidence and economic evaluations presented in this submission, the clinical and cost-effectiveness of tiotropium in COPD remains unchanged to that originally recommended by the PBAC. Since the original PBAC recommendation there has been additional RCT evidence including long-term studies to support the use of tiotropium as a cost-effective treatment option as monotherapy and more recently, as a FDC with olodaterol.

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Abbreviations

Acl	aclidinium
Acl/efor	aclidinium/eformoterol FDC
AE	Adverse event
AIHW	Australian Institute of Health and Welfare
AMH	the Australian Medicines Handbook
AMSTAR	A Measurement Tool to Assess Systematic Reviews
ATS	American Thoracic Society
AUCx-x	area under the curve response from x to x hours
BDI	baseline dyspnoea index
BEACH	Bettering the Evaluation and Care of Health
BOLD	Burden of Obstructive Lung Disease
BTS	British Thoracic Society
Bud/for	budesonide/formoterol
CHEST	American College of Chest Physicians
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPG	clinical practice guideline
CrI	credible interval
CTS	Canadian Thoracic Society
EQ-5D	EuroQol five dimensions
FDC	fixed dose combination
FEV_1	forced expiratory volume in 1 second
Flu/sal	fluticasone/salmeterol FDC
FVC	forced vital capacity
Gly	glycopyrronium
Gly/ind	glycopyrronium/indacaterol FDC
GOLD	Global initiative for Chronic Obstructive Lung Disease
HR	hazard ratio
IC	incremental cost
ICS	inhaled corticosteroid
IHME	Institute for Health and Metrics Evaluation
Ipr	ipratropium
LABA	long acting β2 agonist
LAMA	long acting muscarinic antagonist
LY	life year
LYG	life year gained
MD	mean difference
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Care Excellence
NNT	number needed to treat
NS	non-significant
Olo	olodaterol
OR	odds ratio
PBAC	Pharmaceutical Benefits Advisory Committee

Pbo	placebo
PBS	Pharmaceutical Benefits Scheme
PPDE-4i	phosphodiesterase 4 inhibitor
PSA	probabilistic sensitivity analysis
PSD	Public Summary Document
QALY	quality adjusted life year
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
RTI	respiratory tract infection
SABA	short acting β2 agonist
SAE	serious adverse event
SAMA	short acting muscarinic antagonist
SGRQ	St George Respiratory Questionnaire
SR	systematic review
TDI	transition dyspnoea index
TG	Therapeutic Guidelines
Tio	tiotropium
Tio/olo	tiotropium/olodaterol FDC
TSANZ	Thoracic Society of Australia and New Zealand
UC	Usual care
Ume	umeclidinium
Ume/vil	umeclidinium/vilanterol FDC
WHO	World Health Organization
WTP	willingness to pay

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

Summary

Chronic obstructive pulmonary disease (COPD) is a serious, progressive and disabling condition that limits airflow in the lungs. COPD is a major cause of chronic morbidity and mortality; many people suffer from the disease for years, and die prematurely from it or its complications. Therefore, COPD has a substantial impact on both individuals and the community and it is ranked as the third highest cause of disease burden in Australia. COPD is also the second leading cause of avoidable hospital admissions in Australia and is one of the leading causes of death. As there is no cure for COPD, optimal treatment and management of the disease that is evidence-based and aligned with current clinical guidelines plays a critical role in improving health outcomes for patients and reducing the overall clinical and economic burden of the disease.

A comprehensive review of the current clinical practice guidelines has been undertaken in this section to establish the current treatment algorithm for COPD. The key Australian clinical practice guideline for COPD is the COPD-X Plan, which is an evidence-based guideline updated regularly and developed jointly by the Thoracic Society of Australia and New Zealand (TSANZ) and Lung Foundation Australia. The key international clinical practice guideline for COPD is the GOLD Guideline; the treatment recommendations in the GOLD Guideline are consistent with those in the COPD-X Plan.

The treatment algorithm in the COPD-X Plan recommends a stepwise approach to pharmacological treatment of COPD, irrespective of disease severity, until adequate control has been achieved. The first step is treatment with a short acting bronchodilator [short acting muscarinic antagonist (SAMA) or short acting β2 agonist (SABA)]. For patients who remain symptomatic, the next step is initiation of a long acting bronchodilator [long acting muscarinic antagonist (LAMA) or long acting β2 agonist (LABA)]. A combination of long acting bronchodilators (LAMA plus LABA) is recommended if additional control is required. The initiation of an inhaled corticosteroid (ICS) (in combination with a LABA) is recommended as one of the last steps in the treatment pathway. However, given the safety issues associated with ICS use such as pneumonia, addition of ICS/LABA to the treatment regimen is only recommended for moderate to severe COPD patients with a history of at least two exacerbations in the previous 12 months and forced expiratory volume in 1 second (FEV_1) <50%, despite current bronchodilator therapy. Concomitant use of drugs from the same class is not recommended at any stage of the treatment algorithm.

Boehringer Ingelheim has three products that are PBS-listed for the treatment of COPD: ipratropium, a SAMA; tiotropium, a LAMA; and tiotropium/olodaterol (tio/olo), a LAMA/LABA fixed dose combination (FDC).

The PBS prescribing criteria allow ipratropium and tiotropium to be used across all severities of COPD, from mild to severe, and in combination with drugs from other classes. These criteria are aligned with the treatment algorithm recommended in the current clinical guidelines, supporting appropriate use of these products on the PBS.

Recent PBS data also demonstrate that tiotropium is being used appropriately. A recent Medicare sample, obtained via an independent third party, included a random 10% PBS patient sample scaled up to national estimates. Patients were tracked longitudinally using their Medicare number. All patients that had been prescribed tiotropium over the observation period were included, along with details of their concurrent medication use including LABA, ICS and ICS/LABA FDC. The Medicare sample as well as more recent data from IMS Health indicate appropriate use of tiotropium; it was used either on its own or in combination with drugs from other classes.

The PBS prescribing criteria for tio/olo FDC exclude it from being used for the initiation of bronchodilator therapy, which is consistent with the stepwise approach recommended in the treatment guidelines. However, the PBS criteria require stabilisation on a combination of a LAMA and a LABA prior to commencing the FDC. This requirement is not consistent with the treatment guidelines which recommend the use of a LAMA/LABA FDC for patients who are not controlled on either monotherapy alone *or* for those patients who are stabilised on a LAMA and LABA. The current PBS criteria are likely to delay access for patients who are uncontrolled on a single long acting bronchodilator who would benefit from a LAMA/LABA FDC. Requiring patients to use additional inhalers may be unnecessarily burdensome and poses a quality use of medicines issue with an increased risk of patient confusion regarding correct device use and likely reduction in patient adherence resulting in adverse efficacy and safety related consequences. Reducing the complexity of the prescribed treatment regimen with simple, once daily inhaled combinations is likely to have a positive impact on patient adherence and device technique, which are essential for achieving good COPD symptom control (Rand, 2005). This could be achieved by amending the existing PBS listing for LAMA/LABA FDCs to also include patients who have symptoms that persist despite regular bronchodilator treatment with either a LAMA or LABA monotherapy.

In relation to the use of ICS/LABA FDCs, it is important to note that the current clinical guidelines, PBS restrictions and recent advice from the TSANZ indicate that this combination is now placed much later in the COPD treatment algorithm compared with all other therapies. The use of ICS/LABA FDCs is reserved for patients with moderate to severe COPD, with FEV_1 <50% and recent exacerbations, who remain uncontrolled despite current bronchodilator therapy. There is also recent evidence to use ICS/LABA therapy patients with a blood eosinophil count of 4% or greater (Watz et al 2016). ICS/LABAs are pharmacologically different from LAMAs with different clinical and adverse event profiles, in particular pneumonia, in addition to being used in a more severe COPD patient population. The PBS restriction criteria for ICS/LABAs are for symptomatic treatment of patients with severe COPD (FEV_1<50%) and a history of repeated exacerbations who have significant symptoms despite regular LABA use, which is in line with the clinical evidence and TGA indications. ICS/LABAs are not indicated to be used for initial bronchodilator therapy with the PBAC considering that ICS/LABAs are more likely to be added to LAMA therapy rather than replace LAMAs (Indacaterol PSDs November 2010; July 2011). The TSANZ recommended that given the current practice to prescribe ICS/LABA FDC when stepping up therapy in persistently symptomatic patients, the LABA/LAMA FDC products are likely to provide an effective, convenient and potentially safer alternative to ICS/LABA FDCs (PSDs March 2014: glycopyrronium/indacaterol FDC; umeclidinium/vilanterol FDC; fluticasone/vilanterol FDC). Based on the comments from the TSANZ, the PBAC acknowledged the potential safety risks associated with ICS use and considered it

appropriate to delay the introduction of ICS/LABA FDCs in favour of LAMA/LABA combinations in less severe disease. The PBAC also noted that delaying ICS use would be consistent with the Australian COPD-X Guidelines, where introduction of an ICS is recommended for patients with more severe disease.

Therefore, ICS/LABA FDCs should not be considered interchangeable or a relevant comparator with other pharmacological classes such as LAMAs in the COPD treatment algorithm. The COPD Review should recognise this and there should not be any therapeutic relativity link between drugs of different classes, especially if further cost-effectiveness analyses are recommended by the Review.

1.1 Introduction

Chronic Obstructive Pulmonary Disease (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 (COPD-X, 2015).

The development of COPD occurs over many years and therefore mainly affects middle aged and older people. Based on the most recent Australian Health Survey (AHS; 2011-2012), as indicated by self-reported emphysema and/or bronchitis, the prevalence of COPD in Australians aged 55 years and older is 5.7%, which accounts for over 300,000 people [Australian Bureau of Statistics (ABS), 2012]. 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, 2015). Other estimates based on lung function suggest that the prevalence of COPD in Australia is likely to be higher. A large international study (Burden of Obstructive Lung Disease (BOLD)) tested the lung function of nearly 10,000 people across 12 countries. In Australia, the prevalence of COPD was estimated to be 7.5% for people aged 40 years and over and 29.2% for people aged 75 and over, based on the Global initiative for Chronic Obstructive Lung Disease (GOLD) definition of Stage 2 or higher. That equates to over 770,000 Australians (2011 population) (Toelle et al. 2013). As the population ages over the coming years, the prevalence of COPD is expected to increase.

The health burden of COPD is significant. COPD is a major cause of chronic morbidity and mortality; many people suffer from the disease for years, and die prematurely from it or its complications (GOLD, 2015). COPD includes emphysema and chronic bronchitis and people with the disease are prone to severe episodes of shortness of breath, with fits of coughing. Therefore, COPD has a substantial impact on both individuals and the community (COPD-X, 2015). The Australian Institute of Health and Welfare (AIHW) is currently revising Australia's burden of disease estimates; in the interim, the AIHW has published the results of the Global Burden of Disease Study reported by the Institute for Health and Metrics Evaluation (IHME) (AIHW, 2015a; IHME, 2013). The IHME report includes estimates of the burden of disease from COPD and other respiratory conditions. Based on IHME 2013, the burden of disease for COPD was ranked the 9th highest in the world, when measured in terms of disability-adjusted life years (DALYs). However, COPD was ranked much higher in Australasia (includes Australia and New Zealand), being the 3rd highest cause of all health burden after ischaemic heart disease and low back pain (AIHW, 2015a; IHME, 2013).

COPD affects quality of life as it can interrupt daily activity, sleep patterns and the ability to exercise; therefore, Australians with COPD generally report their health as being worse than those without the condition (ABS, 2014a). According to the most recent AHS, 28% of Australians aged 55 years and over with COPD rated their health as poor, compared to 7% of those aged 55 years and over without it. At the same time, 3% of those with COPD rated their health as excellent compared to 15% of those without COPD (ABS, 2014a). The chronic systemic inflammation associated with COPD has also

been linked to increased risk of ongoing chronic lung damage, cardiovascular disease, increase mortality risk and muscle wasting (Hutchinson et al 2010).

Given the significant health burden of COPD, it is not surprising that COPD takes up a large proportion of general practice resources in Australia. According to the most recent *Bettering the Evaluation and Care of Health* (BEACH) report, COPD is one of the most frequently managed chronic problems in general practice and is one of the top ten health problems frequently referred to a hospital by a general practitioner (Britt et al, 2015). There are also a substantial number of hospitalisations each year due to COPD and it is the second leading cause of avoidable hospital admissions in Australia (Page et al 2007; Hutchinson et al 2010). 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 1,052 per 100,000 population (AIHW, 2015b).

COPD is a leading cause of mortality worldwide and is also a leading cause of death in Australia despite being a preventable and treatable disease. In 2012, 5,923 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 2014b; AIHW 2014a). Projections from the World Health Organization (WHO) Global Burden of Disease study estimate that total deaths from COPD could increase by more than 30% in the next 10 years which would result in COPD becoming the third leading cause of death worldwide (WHO, 2015).

COPD is associated with a substantial cost to government (with hospital costs contributing the largest share of health spending) and importantly, to those with COPD and their families and carers. A report prepared for the Lung Foundation Australia by Access Economics estimated that in 2008, the total economic impact in Australia was $98.2 billion, of which $8.8 billion was attributed to financial costs and $89.4 billion to the loss of wellbeing (Access Economics, 2008). Of the financial costs, a large proportion is due to the loss of productivity due to COPD, i.e. lower employment, absenteeism and the workplace impact of premature death of Australians with COPD. In 2008, the direct annual cost to the Australian health care system was estimated to be over $900 million, with hospital costs for admitted patients contributing the largest share of health spending. In addition, there are also costs due to lost wellbeing as a result of COPD. These are estimated to be at least $90 billion. In terms of overall costs, COPD is more costly per case than cardiovascular disease, osteoporosis or arthritis (Access Economics, 2008; AIHW, 2014b). Resource use for the treatment of COPD is high across all disease stages, with a trend for increasing resource use as the disease becomes more severe (GOLD, 2015). A retrospective Australian study found that costs associated with COPD increased with severity, mainly as a result of more frequent acute care hospital admissions; in very severe (GOLD 4) COPD patients the annual cost per patient per year was nearly double the cost observed in mild (GOLD 2) COPD patients (Hutchinson et al 2010).

As there is no cure for COPD, optimal treatment and management of the disease that is aligned with current clinical guidelines plays a critical role in improving health outcomes for patients and therefore reducing the overall clinical and economic burden of the disease. In response to Term of Reference (ToR) 1, a comprehensive review of the clinical practice guidelines has been undertaken

to establish the current treatment algorithm for COPD based on the best available evidence. A comparison between the current treatment algorithm for COPD as recommended in the clinical practice guidelines and the PBS prescribing restrictions for COPD medicines is then discussed.

1.1.1 Current clinical practice guidelines for the treatment of COPD

A comprehensive review of the current clinical practice guidelines for COPD involved a search of local and international clinical practice guideline databases as summarised in Table 1.1 below. A broad and sensitive strategy was employed using the terms 'chronic obstructive pulmonary disease' or 'COPD' or 'respiratory' to search these databases. For the purposes of this submission, clinical practice guidelines were only considered 'current' and included for discussion if they were published from 2011 onwards. This approach is consistent with the recommendations of the National Health and Medical Research Council (NHMRC) who advise that clinical practice guidelines should be revised and the evidence updated every five years[1].

Table 1.1 Comprehensive review of CPGs for COPD

CPG database	Description
NHMRC CPG Portal[1]	A database of CPGs developed for use in Australian health care settings produced by or endorsed by the NHMRC, which is the leading body of experts in Australia to ensure health standards for individuals and the public.
National Guidelines Clearinghouse[2]	An initiative of the Agency for Healthcare Research and Quality of the United States of America. It is a public resource that publishes structured summaries of evidence-based practice guidelines.
Canadian Medical Association Infobase: CPG[3]	A CPG database that is maintained by the Canadian Medical Association, containing those that have been produced or endorsed in Canada by a medical, health or government organisation/agency at a national, provincial or territorial level.
Scottish Intercollegiate Guidelines Network[4]	A guideline development group that produces evidence-based guidelines for the National Health Service in Scotland.
eGuidelines[5]	A UK-based database that provides access to guidance documents from a variety of national and professional body's online evidence-based guidelines and publications.
Guidelines International Network (G-I-N)[6]	An international and not-for-profit association of organisations and individuals involved in the development and application of CPGs. G-I-N's International Guideline Library is the world's largest international CPG database.

Abbreviations: COPD, chronic obstructive pulmonary disease; CPG, clinical practice guideline; NHMRC, National Health and Medical Research Council

[1] www.clinicalguidelines.gov.au
[2] www.guideline.gov
[3] www.cma.ca/En/Pages/clinical-practice-guidelines.aspx
[4] www.sign.ac.uk/guidelines/index.html
[5] www.guidelines.co.uk/guidelinessummaries
[6] www.g-i-n.net

The comprehensive search and review of local and international clinical practice guideline databases retrieved three current and relevant guidelines, including:

[1] https://www.nhmrc.gov.au/guidelines-publications/how-nhmrc-develops-its-guidelines

i. *COPD-X Plan (2015/2016)*: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease;

ii. *Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines (2016)*: Global Strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease; and

iii. *Prevention of Acute Exacerbations of COPD (AECOPD) Guideline (2015):* published by the American College of Chest Physicians (CHEST) and Canadian Thoracic Society (CTS).

Two additional clinical guidance resources that are commonly referred to in Australian clinical practice were also retrieved through hand searching. These are the Australian Medicines Handbook (AMH) and the Therapeutic Guidelines (TGs), which will also be given consideration in response to ToR 1.

A COPD clinical practice guideline published by the National Institute for Health and Care Excellence (NICE) was also retrieved; however since it was published in 2010, the guideline was not considered to be current. Although an Evidence Update to the guideline is available (2012), which provides a summary of selected new evidence published since the literature search was last conducted, NICE Evidence Updates are not intended to replace current accredited guidance and do not provide formal practice recommendations. Therefore, this document is not discussed any further in response to ToR 1. An update to the NICE COPD Guideline is scheduled for later in 2016.

The Public Summary Documents (PSDs) for all COPD medicines were also reviewed to determine if there are any specific clinical practice guidelines for COPD that the Pharmaceutical Benefits Advisory Committee (PBAC) considers to be most relevant to the Australian healthcare context. A review of the PSDs for COPD medicines indicates that the clinical practice guideline that is accepted by the PBAC as being the most applicable to the Australian health care context is the COPD-X Plan [PSDs: aclidinium/eformoterol, July 2015; aclidinium, March 2014; fluticasone/vilanterol, March 2014; indacaterol/glycopyrronium, March 2014; umeclidinium/vilanterol, March 2014; glycopyrronium, November 2013]. The PBAC has also given consideration to the treatment algorithm recommended in the GOLD International Guidelines [PSDs: glycopyrronium/indacaterol, March 2014; umeclidinium/vilanterol, March 2014; glycopyrronium, November 2013].

As the PBAC has previously accepted the COPD-X and GOLD Guidelines as being the most applicable to the Australian healthcare context, these will be reviewed in detail below and used to establish the current treatment algorithm for COPD in Australia, against which the PBS prescribing criteria for COPD medicines will be compared. Consideration will also be given to the AMH, Therapeutic Guidelines and the CHEST/CTS Guideline to determine whether there is broad local and international consensus for the treatment of COPD.

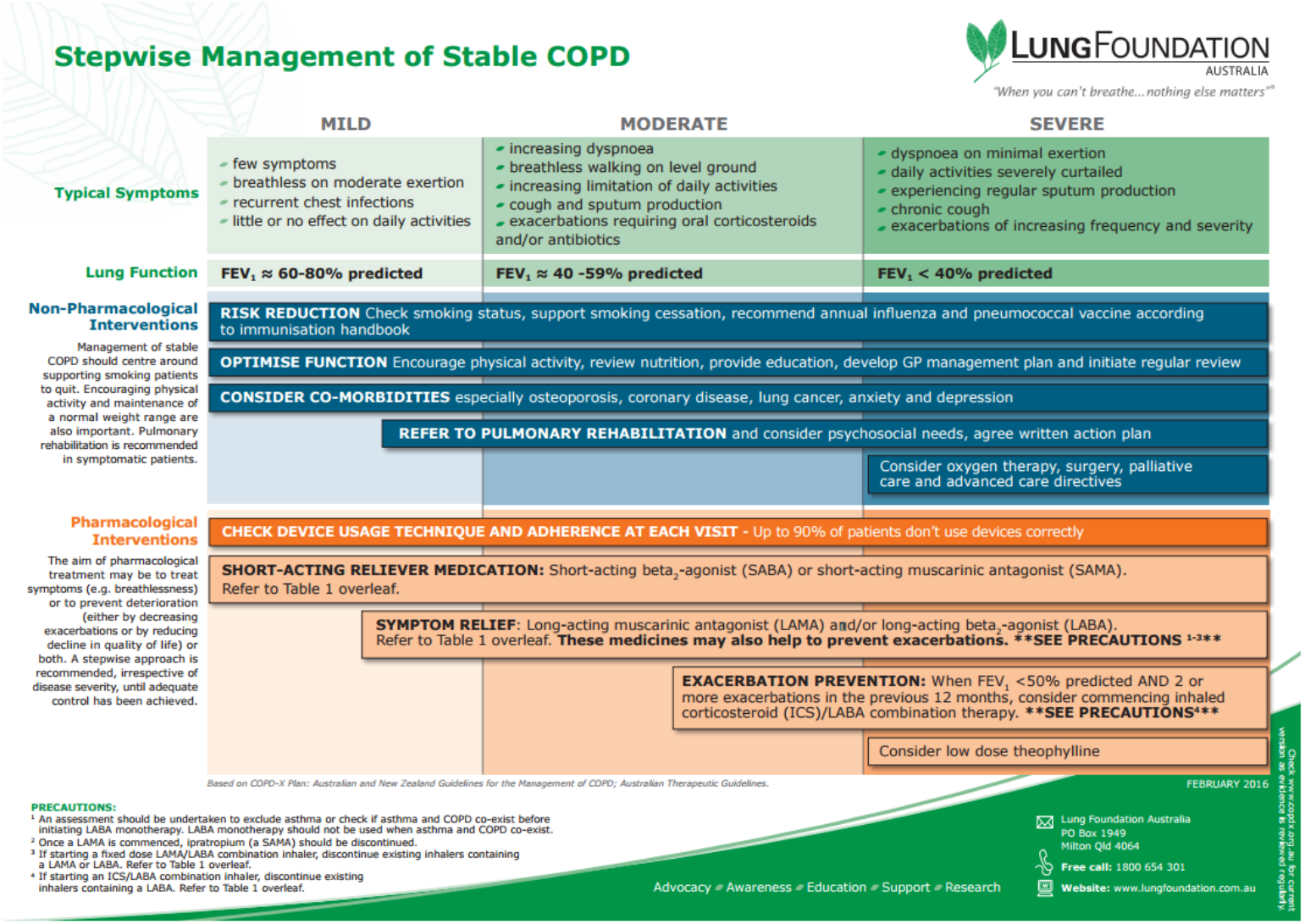
COPD-X Plan, 2015/2016

The COPD-X Plan is the Australian and New Zealand Guideline for the management of COPD published by Lung Foundation Australia and Thoracic Society of Australia and New Zealand (TSANZ) and is updated regularly throughout the year. A '*Concise Guide for Primary Care*' is also available,

which summarises the key recommendations made in the full COPD-X Guideline to provide short and concise guidance on COPD management during daily practice.

As noted in the COPD-X Plan, the Guideline aims to effect changes in clinical practice using an evidence-based approach. The aims of drug treatment in COPD are to relieve symptoms and to prevent deterioration, either by reducing frequency of exacerbations or by reducing decline in quality of life, or both. Overall, the COPD-X Plan recommends a stepwise approach to pharmacological treatment, irrespective of disease severity, until adequate control has been achieved. The treatment algorithm is summarised in Figure 1.1 below. The COPD-X Plan also includes a guide to the addition of multiple pharmacological therapies in combination to help prevent inappropriate prescribing, which is summarised in Figure 1.2 below.

Figure 1.1 COPD-X Plan Clinical Practice Guideline - Stepwise management of stable COPD



Source: COPD-X Plan 2015/2016 (LFA-Stepwise-Management-of-COPD_0216.pdf)

Figure 1.2 COPD-X Plan Clinical Practice Guideline - Guide to addition of therapies

Table 1: Guide to addition of therapies

Green tick indicates therapies that can be used together

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

Source: COPD-X Plan 2015/2016 (LFA-Stepwise-Management-of-COPD_0216.pdf)

The COPD-X Plan recommends that for all symptomatic patients with COPD, a stepwise approach to pharmacological treatment should be followed until adequate control of breathlessness, functional capacity, and exacerbation frequency is achieved. Each step in the treatment algorithm is described in more detail below.

Step 1: Use short-acting inhaled bronchodilator therapy for short-term relief of breathlessness

The COPD-X Plan recommends the use of either a short acting β2 agonist (SABA) (salbutamol and terbutaline) or a short acting muscarinic antagonist (SAMA) (ipratropium bromide) to improve lung function and daily breathlessness scores. These medications are usually prescribed for use as 'rescue' medication, for the short-term relief of breakthrough COPD symptoms such as breathlessness, rather than for regular use. They may be used on an as-required basis by patients with all levels of disease severity from mild to severe COPD. As these medications provide short-term symptom relief only, their use does not substitute for maintenance bronchodilator treatments such as tiotropium.

- The COPD-X Plan notes that ipratropium bromide has a significantly greater effect on lung function compared to SABAs, in addition to improving quality of life and decreasing need for oral corticosteroid treatment. These benefits occur with a decreased risk of adverse drug effects.
- It is also noted that combining two classes of short-acting bronchodilator (SAMA plus SABA) may provide added benefits without compounding adverse effects.

Step 2: Add a regular long acting bronchodilator

The COPD-X Plan recommends that for patients receiving short-acting bronchodilators who have persistent troublesome dyspnoea, that a long-acting bronchodilator should be initiated. This includes either a long acting muscarinic antagonist (LAMA) or a long acting β2 agonist (LABA). Long-acting bronchodilators can be used in mild to severe disease and produce significant improvements in lung function, symptoms and quality of life, as well as decreasing exacerbations but do have an increased risk of adverse effects, which are generally of mild to moderate severity.

- LAMAs cause bronchodilation with duration of action over 24 hours and are used once daily (tiotropium, glycopyrronium, umeclidinium) or duration of approximately 12 hours and used twice daily (e.g. aclidinium). Of the four LAMAs noted in the COPD-X Plan (tiotropium, glycopyrronium, umeclidinium, aclidinium), tiotropium has the largest body of evidence over the longest period of time to support its use. The evidence for tiotropium is addressed in further detail in response to ToR 3.
- LABAs induce prolonged bronchodilation and can be administered once daily (indacaterol) or twice daily (salmeterol, eformoterol). Of the single agent LABAs, only indacaterol is PBS-listed for use in COPD.

Step 3: Combination long acting bronchodilator treatment

The COPD-X Plan recommends a combination of a LAMA and a LABA if monotherapy with either treatment is not adequate. For COPD patients who remain symptomatic despite long-acting bronchodilator monotherapy, LAMA/LABA fixed-dose combination (FDC) treatments are available, including tiotropium with olodaterol FDC (COPD-X Concise Guidance, p 9).

- Prior use of both single agents before initiating the FDC is not required or recommended in the COPD-X Plan.

The guide to addition of therapies (Figure 1.2) indicates that if LABA/LAMA FDC treatments are used, they should not be used concurrently with SAMAs, other LAMAs, LABAs or inhaled corticosteroid (ICS)/LABA FDC treatments.

Step 4: Addition of inhaled corticosteroid treatment

For patients with forced expiratory volume in 1 second (FEV_1) <50% predicted and $\geq$2 exacerbations in 12 months, the COPD-X Plan recommends initiation of an ICS/LABA FDC (and discontinuation of any concurrent LABA therapy).

- The COPD-X Plan notes that there is evidence for an increased risk of pneumonia for patients treated with ICS/LABA.
- Safety concerns should be balanced against the benefits of reduced rate of exacerbations and reduced decline in quality of life.

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 FDC. For severe COPD (FEV1 < 40% predicted), consider adding low-dose theophylline (100 mg twice daily). Avoid long-term (> 2 weeks) use of systemic corticosteroids.

The GOLD guideline, 2016

The GOLD Guideline is an international evidence-based strategy document for health care professionals to use as a tool to implement effective COPD diagnosis, management, and prevention programs. Consistent with COPD-X Plan, the recommendations for pharmacologic management of stable COPD also follow a stepwise approach depending on disease severity, as summarised in Table 1.2 below. The current GOLD strategy classifies COPD patients according to an assessment of lung function (spirometry), current symptoms, and future exacerbation risks, into one of four groups: Group A, B, C, and D (with A being the mildest and D being the most severe).

Appropriate pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Each pharmacological treatment regimen needs to be patient-specific, guided by severity of symptoms, risk of exacerbations, drug availability, and the patient's response.

Overall, short acting bronchodilators are recommended as first line treatment, followed by long acting bronchodilators. Long-term treatment with ICS is only recommended for patients with severe and very severe COPD with frequent exacerbations that are not adequately controlled by long-acting bronchodilators, given the risk of adverse events including pneumonia and the possibility of an increased risk of fractures. The stepwise approach to treatment recommended in the GOLD Guidelines is discussed in more detail below.

Table 1.2 GOLD Guidelines - Recommendations for Pharmacologic Management of Stable COPD

Patient Group	First choice	Alternative choice	Other treatment(s)[a]
Group A	SAMA prn or SABA prn	LAMA or LABA or SAMA and SABA	Theophylline
Group B	LAMA or LABA	LAMA and LABA	SABA and/or SAMA Theophylline
Group C	ICS/LABA or LAMA	LAMA and LABA or LAMA and PPDE-4i or LABA and PPDE-4i	SABA and/or SAMA Theophylline
Group D	ICS/LABA and/or LAMA	ICS/LABA and LAMA or ICS/LABA and PPDE-4i or LAMA and LABA or LAMA and PPDE-4i	Carbocysteine SABA and/or SAMA Theophylline

Source: GOLD Guidelines 2016 Table 4.4
Abbreviations: ICS, inhaled corticosteroid; LABA, long acting β2 agonist; LAMA, long acting muscarinic antagonist; PPDE-4i; phosphodiesterase 4 inhibitor; prn, pro re nata (as necessary); SABA, short acting β2 agonist; SAMA, short acting muscarinic antagonist;
a Used alone or in combination with first or alternative choice options.

Group A patients are classified as those at low risk of exacerbations with few symptoms; GOLD 1 or 2 (mild-moderate airflow limitation); and/or 0-1 exacerbations per year (and no hospitalisation); and modified British Medical Research Council questionnaire (mMRC) grade 0-1 or COPD Assessment Test (CAT) score <10.

- A short acting bronchodilator (SAMA or SABA) is recommended as the first choice based on their effect on lung function and breathlessness.

Group B patients are classified as those at low risk of exacerbations but more significant symptoms. Patients are typically GOLD 1 or 2; and/or 0-1 exacerbations per year (and no hospitalisation); and mMRC grade ≥ 2 or CAT score ≥10.

- Long acting bronchodilators (LAMA or LABA) are recommended as they are superior to short acting bronchodilators (taken as needed, or prn)
- For patients with severe breathlessness the alternative choice is a combination of long acting bronchodilators (LAMA plus LABA).

Group C patients are at high risk of exacerbations but few symptoms. Patients are typically GOLD 3 or 4 (severe or very severe airflow limitation); and/or ≥ 2 exacerbations per year (or ≥ 1 with hospitalisation); and mMRC grade 0-1 or CAT score <10.

- LAMA monotherapy (but not LABA monotherapy) is a first-choice treatment option for patients at high risk of exacerbations.
- The FDC of ICS/LABA is also a first choice option.
- An alternative choice includes two long acting bronchodilators (LAMA plus LABA).
- A phosphodiesterase-4 inhibitor used in combination with at least one long acting bronchodilator could be considered if the patient has chronic bronchitis.

Group D patients are at high risk of exacerbations with more symptoms. Patients are typically GOLD 3 or 4 (severe or very severe airflow limitation); and/or ≥ 2 exacerbations per year (or ≥ 1 with hospitalisation); and mMRC grade ≥ 2 or CAT score ≥10.

- LAMA monotherapy (but not LABA monotherapy) is a first-choice treatment option for patients at high risk of exacerbations.
- The FDC of ICS/LABA is also a first choice option.
- As a second choice, a combination of all three classes of drugs (ICS/LABA plus LAMA) or two long acting bronchodilators (LAMA plus LABA) is recommended.
- It is also possible to add a phosphodiesterase-4 inhibitor to the first choice treatment if the patient has chronic bronchitis.

Overall, the GOLD Guideline is consistent with the recommendations made in the COPD-X Plan regarding pharmacological treatment of COPD. Patients should follow a stepwise approach to therapy starting with short acting bronchodilators, followed by long acting bronchodilators. Importantly, LAMA monotherapy (but not LABA monotherapy) is a first-choice treatment option for patients at high risk of exacerbations. Similar to the COPD-X Plan, use of ICS/LABA should be limited to severe or very severe COPD (Group C and Group D patients).

American College of Chest Physicians and Canadian Thoracic Society (CHEST/CTS) 2015

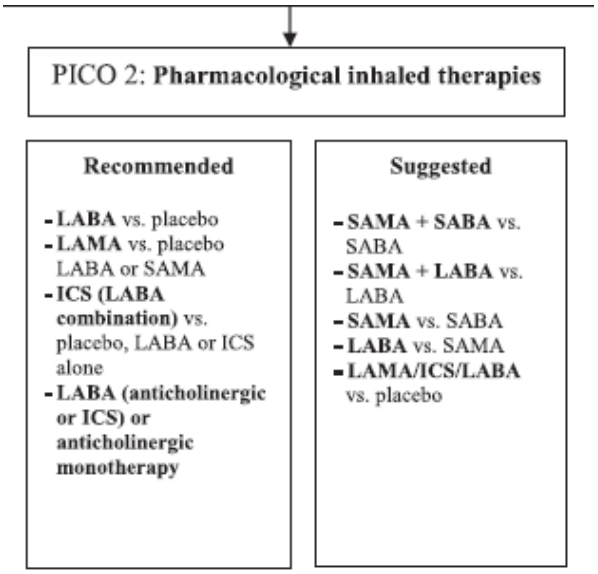
The CHEST/CTS joint evidence-based Guideline (AECOPD Guideline) was developed to provide an up-to-date, rigorous, evidence-based analysis of current randomised controlled trial data regarding the prevention of COPD exacerbations. The Guideline addresses three clinical questions around the prevention of acute exacerbations of COPD in patients with moderate to severe COPD using: i) nonpharmacologic therapies; ii) inhaled therapies; and iii) oral therapies. As mentioned above, the PBAC has previously accepted the COPD-X and GOLD Guidelines as being the most applicable to the Australian healthcare context; however, consideration is also given to the CHEST/CTS Guideline to determine whether there is broad international consensus for the treatment of COPD.

A summary of the recommendations for the clinical question addressing inhaled therapies is presented in Figure 1.3 below (PICO 2). Although a specific treatment algorithm is not provided, recommendations are made between alternative treatment options. Note that the wording used was “recommended” when the evidence was strong or “suggested” when the evidence was weak.

Based on a systematic review of the evidence in adults with COPD at risk of an acute exacerbation, the CHEST/CTS Guideline recommends the use of a LAMA (e.g. tiotropium) over the use of placebo, a LABA or a SAMA to prevent moderate to severe acute exacerbations. This recommendation places high value on the LAMAs for reducing the risk of acute exacerbations of COPD and having a lower rate of nonfatal serious adverse events compared with LABAs.

A specific preference is not provided between LABA/LAMA, LABA/ICS, or LAMA monotherapy by CHEST/CTS for preventing exacerbations in moderate to severe COPD. This is slightly different to the COPD-X Plan and GOLD Guidelines, which recommend a step wise approach to treatment that includes long acting bronchodilator monotherapy, followed by long acting bronchodilator combination therapy for symptomatic relief. In the COPD-X Plan and GOLD guideline, ICS/LABA combination therapy is only recommended for exacerbation prevention later in the treatment algorithm in moderate to severe COPD for patients who are already on optimal bronchodilator therapy. However, the CHEST/CTS Guidelines ‘*place a relatively lower value on the risks and consequences of pneumonia*’ regarding ICS use in patients with moderate to severe COPD.

Figure 1.3 Pharmacological inhaled therapies



Source: CHEST/CTS: AECOPD Guideline 2015

Additional clinical guidance

Two additional clinical guidance resources that are commonly referred to in Australian clinical practice are the Australian Medicines Handbook (AMH) and the Therapeutic Guidelines (TGs).

The AMH is an independent, evidence-based national drug reference developed jointly by the Royal Australian College of General Practitioners, the Pharmaceutical Society of Australia and the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (Rossi, 2016). In reference to COPD, the AMH recommends a stepwise approach to drug treatment that is consistent with the COPD-X Plan and GOLD Guidelines. That is: i) initial treatment with a short acting bronchodilator (SAMA or SABA), followed by ii) a long acting bronchodilator (LAMA or LABA) as monotherapy, followed by iii) addition of a second long acting bronchodilator (LAMA+LABA) as dual therapy. The final recommended step, only for patients with FEV_1<50% and more than 2 exacerbations annually, is the addition of ICS to the treatment regimen (LAMA+LABA+ICS) (Rossi, 2016).

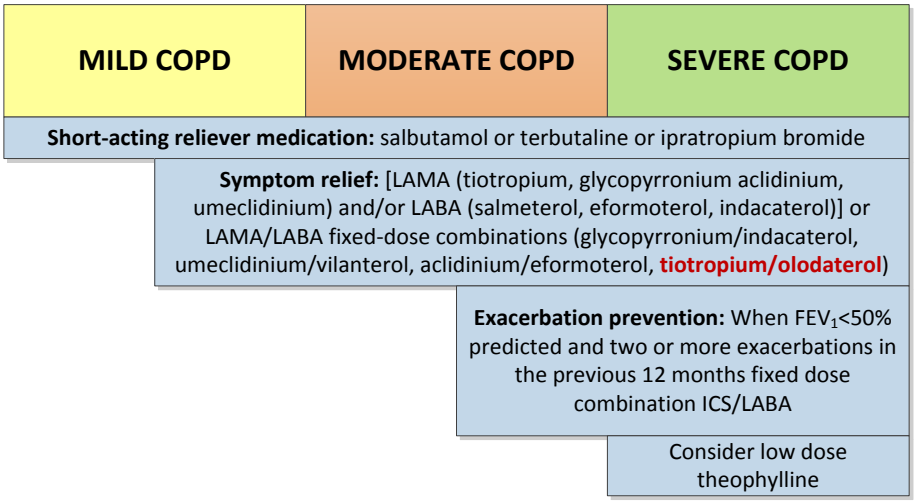
The TGs are written principally for prescribers (general practitioners and trainee physicians in particular) to provide clear, practical, succinct and up-to-date therapeutic information that has undergone extensive peer-review, to guide the management of patients with specific conditions. In reference to COPD, the recommendations in the TGs for pharmacological treatment are based on the stepwise COPD-X algorithm. The TGs recommend short acting bronchodilator therapy, followed by long acting bronchodilator therapy. If combination therapy with a LABA and a LAMA is indicated, a FDC inhaler is suggested to be more convenient for patients rather than single-drug inhalers. Consistent with the recommendations in the COPD-X and GOLD Guidelines, ICS are indicated at the end of the treatment algorithm, as add-on therapy only for patients already taking bronchodilator therapy and who have FEV_1 ≤50% and have experienced at least two recent exacerbations (eTG complete, 2015).

1.1.2 Current COPD clinical management algorithm

The current COPD clinical management algorithm is shown in Figure 1.4 and is derived from the COPD-X Plan for the Stepwise Management of Stable COPD as this is most closely aligned with Australian treatment practices. The first step in the treatment algorithm includes the use of short-acting reliever medications, as required, from mild to severe disease. Initiation of long-acting bronchodilator therapy can occur from mild stage disease with a LAMA, such as tiotropium, or a LABA. If adequate control has still not been achieved with one long acting bronchodilator, the guidelines recommend long-acting bronchodilators can be combined in the next step, as a LAMA and a LABA used concurrently, or as a combination product, such as tiotropium/olodaterol (tio/olo) FDC. A LAMA/LABA FDC should not be used concurrently with a LAMA single agent, a LABA single agent or a LABA/ICS FDC.

From moderate to severe disease, LABA/ICS FDC treatments (fluticasone/salmeterol, fluticasone/vilanterol or budesonide/eformoterol) can be used. A LABA/ICS FDC should not be used concurrently with any other LABA-containing therapy. In severe patients, low dose theophylline could be added.

Figure 1.4 Current COPD clinical management algorithm



Public Summary Documents

The PSDs for recent submissions to the PBAC for COPD medicines were also reviewed to compare the current COPD management algorithm described above, with the clinical place of COPD medicines as considered by the PBAC.

Of note, PSDs for recent LAMA submissions to the PBAC (March 2014: aclidinium; July 2014: umeclidinium) described a staged approach to the treatment of COPD. The LAMAs are positioned in the treatment algorithm for patients with mild COPD who may be experiencing high levels of breathlessness and also for patients with moderate, severe and very severe COPD. LAMAs can be used either as monotherapy or in combination with a LABA as patients experience more breathlessness. For patients who experience frequent exacerbations, an ICS can be added on to bronchodilator therapy. The PBAC accepted the stepwise treatment algorithm described above, which is also consistent with the recommendations of the COPD-X Plan and GOLD Guidelines and consistent with the treatment algorithm shown in Figure 1.4.

PSDs for recent LAMA/LABA and ICS/LABA submissions to the PBAC (March 2014: glycopyrronium/indacaterol FDC; umeclidinium/vilanterol FDC; fluticasone/vilanterol FDC) contained statements from the TSANZ in relation to the COPD treatment algorithm. The TSANZ recommended that given the current practice to prescribe ICS/LABA FDC when stepping up therapy in persistently symptomatic patients, the LABA/LAMA FDC products are likely to provide an effective, convenient and potentially safer alternative to ICS/LABA FDCs. Based on the comments from the TSANZ, the PBAC noted that the treatment algorithm for COPD is changing and considered it appropriate to delay the introduction of ICS/LABA FDCs in favour of LAMA/LABA combinations in less severe disease. The PBAC acknowledged the potential safety risks associated with ICS use and considered that combination of LAMA and LABA (given concurrently or as a FDC treatment) was preferred to earlier introduction of an ICS/LABA FDC. The PBAC also noted that delaying ICS use would be consistent with the Australian COPD-X Guidelines, where introduction of an ICS is recommended for patients with more severe disease. The view of the PBAC with respect to delaying the use of ICS in favour of bronchodilators is consistent with the treatment algorithm shown in Figure 1.4.

1.1.3 Prescribing restrictions for PBS-listed COPD medicines

The current version of the Schedule of Pharmaceutical Benefits (April 2016) was reviewed and a summary of Boehringer Ingelheim's PBS-listed medicines that are available for the treatment of COPD, along with their prescribing restrictions, are presented in Table 1.3 below. The prescribing restrictions for ICS/LABA combinations are also included, for comparison with the treatment algorithm as discussed above.

Table 1.3 PBS-listed COPD medicines

Drug	Summary of prescribing restrictions
SAMA	
Ipratropium	Unrestricted
LAMA	
Tiotropium	Restricted benefit: COPD (Spiriva Handihaler); or Bronchospasm and dyspnoea associated with COPD for long term maintenance treatment (Spiriva Respimat).
LAMA/LABA	
Tiotropium/olodaterol	Authority required (STREAMLINED): COPD; and Previously stabilised on combination of LAMA and LABA. Must not be used in combination with an ICS/LABA, or LAMA or LABA monotherapy. Not PBS-subsidised for the treatment of asthma and not indicated for the initiation of bronchodilator therapy in COPD.
ICS/LABA[a]	
Budesonide/eformoterol Fluticasone[b]/salmeterol Fluticasone[c]/vilanterol	Restricted benefit: COPD; and FEV_1 <50% of predicted normal prior to therapy; and History of repeated exacerbations with significant symptoms despite regular LABA; and The treatment must be for symptomatic treatment. Must not be on a concomitant single agent LABA. Not indicated for the initiation of bronchodilator therapy in COPD.

Abbreviations: ICS, inhaled corticosteroid; LABA, long acting β2 agonist; LAMA, long acting muscarinic antagonist; SABA, short acting β2 agonist; SAMA, short acting muscarinic antagonist; TGA, Therapeutic Goods Administration

a The low dose ICS/LABA formulations are not PBS listed for use in COPD.

b Fluticasone propionate

c Fluticasone furoate

SAMA - PBS prescribing restrictions (ipratropium)

The unrestricted PBS prescribing criterion for ipratropium, a SAMA, allows it to be initiated as early as first line therapy, which is consistent with the current treatment guidelines for short acting bronchodilators.

As discussed above, the COPD-X Plan and GOLD Guidelines recommend that a SAMA can be used in COPD patients for symptomatic relief either as monotherapy for mild disease or as an add-on combination therapy for moderate to severe disease. Therefore, the PBS prescribing criterion for

ipratropium is aligned with the recommendations of the current treatment guidelines, supporting appropriate use on the PBS.

LAMA - PBS prescribing restrictions (tiotropium)

Tiotropium, as a single agent, is PBS listed as a Restricted Benefit for use in COPD. The prescribing criteria allow the LAMA to be used for mild to severe COPD and in combination with other agents, such as a SABA, LABA (indacaterol) or ICS/LABA FDC. The prescribing criteria are therefore consistent with the treatment guidelines as described above, and as such, support appropriate use of tiotropium on the PBS.

Recent Medicare data demonstrate that tiotropium is being used appropriately on the PBS. A Medicare data sample, obtained via an independent third party (Hi Connections), included a random 10% PBS patient sample scaled up to national estimates. Longitudinal tracking was applied over the period January 2011 to May 2013, which linked patients using Medicare numbers. All patients that had been prescribed tiotropium over the observation period were included, along with details of their concurrent medication use including LABA, ICS and ICS/LABA FDC. No data was available for LAMA/LABA FDCs at the time as none were PBS listed. The Medicare sample as well as more recent data from IMS Health indicate appropriate use of tiotropium; it was used either on its own or in combination with drugs from other classes, which is consistent with the clinical guidelines and PBS prescribing criteria.

LAMA/LABA - PBS prescribing restrictions (tiotropium/olodaterol)

The LAMA/LABA FDC of tio/olo is PBS-listed as an Authority required (STREAMLINED) benefit. The prescribing criteria require patients to have COPD and patients must have been previously stabilised on a combination of a LAMA and a LABA prior to commencing the FDC. Therefore, tio/olo is not PBS-listed for the initiation of bronchodilator therapy in COPD. The LAMA/LABA combinations must not be taken concurrently with an ICS/LABA, or LAMA or LABA monotherapy. Although the PBS prescribing criteria for tio/olo FDC is broadly consistent with the stepwise approach to treatment recommended in the clinical practice guidelines, the requirement for patients to have used a LAMA and a LABA prior to commencing the FDC limits access for patients compared with recommendations in the current clinical practice guidelines. Both the COPD-X and GOLD Guidelines recommend the use of a LAMA/LABA FDC for patients who are not controlled on either therapy alone *or* for those patients who are stabilised on a LAMA and LABA.

The inconsistency of the LAMA/LABA PBS prescribing criteria with the current clinical practice guidelines has been raised in a recent submission to the PBAC. A PBAC submission for the LAMA/LABA FDC, umeclidinium/vilanterol, was considered at the November 2014 meeting seeking a revision of the prescribing criteria that would more closely align the LAMA/LABA FDC use with the treatment guidelines (umeclidinium/vilanterol PSD, November 2014). The submission proposed an amendment to expand the existing listing to also include patients who have symptoms that persist despite regular bronchodilator treatment with either a LAMA *or* LABA monotherapy. In consideration of the submission, the PBAC noted the advice received from the TSANZ describing the benefits for patients in having fewer inhaler devices in order to limit technique errors. Nevertheless,

the PBAC rejected the submission and considered that the individual components should be prescribed prior to prescribing a FDC to determine whether the two therapies are beneficial.

As noted above, the PBS restrictions requiring patients to start with monotherapy before stepping up to combination bronchodilator therapy is consistent with the treatment guidelines. However, requiring stabilisation on a combination of a LAMA and a LABA prior to commencing the FDC is not consistent with the treatment guidelines. As for the ICS/LABA combinations, an assessment of whether the two therapies are beneficial can be made irrespective of whether the patient is using one combined inhaler. Medication regimens for patients with COPD are particularly vulnerable to adherence problems because of the chronic nature of the disease, the use of multiple medications and devices, and periods of symptom remission (Restrepo et al, 2008). Requiring patients to use additional inhalers complicates therapy and is unnecessarily burdensome. It is reported that an average of 60% of patients with COPD do not adhere to prescribed therapy and up to 90% of patients use their devices incorrectly (eTG complete, 2015; Restrepo et al, 2008); requiring patients to use additional inhalers is likely to reduce adherence further and may lead to added confusion for patients regarding correct device technique, resulting in adverse efficacy and safety related consequences.

The TGs recommend avoiding the prescribing of multiple different inhaler devices if possible, to reduce confusion (eTG complete, 2015). Reducing the complexity of the prescribed treatment regimen with simple, once daily inhaled combinations is likely to have a positive impact on patient adherence and device technique, which are essential for achieving good COPD symptom control (Rand, 2005). This could be achieved by amending the existing PBS listing for LAMA/LABA FDCs to also include patients who have symptoms that persist despite regular bronchodilator treatment with either a LAMA *or* LABA monotherapy.

ICS/LABA PBS prescribing restrictions

There are several ICS/LABA FDCs that are PBS listed for use in COPD as restricted benefits. The prescribing criteria place the ICS/LABA FDCs much later in the treatment algorithm compared with all other COPD treatment options. Not only do the prescribing criteria require patients to have COPD, but the ICS/LABA must be for symptomatic treatment and patients must meet spirometry requirements (FEV1 <50%), and also have a history of repeated exacerbations with significant symptoms despite regular LABA use. Therefore, ICS/LABA FDC use is recommended as one of the last options in the treatment algorithm, which is also in line with the clinical evidence and TGA indications.

The PBS prescribing restrictions for ICS/LABA FDCs as discussed above are consistent with recent recommendations made by the TSANZ who advised the PBAC that the LABA/LAMA FDC products are likely to provide an effective, convenient and potentially safer alternative to ICS/LABA FDC products (PSDs March 2014: glycopyrronium/indacaterol FDC; umeclidinium/vilanterol FDC). Based on the comments from TSANZ, the PBAC noted that the treatment algorithm for COPD is changing and considered it appropriate to delay the introduction of ICS/LABA FDCs in favour of LAMA/LABA FDCs in less severe disease, acknowledging the potential safety risks associated with ICS use and

considered that a combination of LAMA and LABA (given concurrently or as a FDC treatment) was preferred to earlier introduction of ICS/LABA.

ICS/LABAs are pharmacologically different from LAMAs with different clinical and adverse event profiles, in particular pneumonia, in addition to being used in a more severe patient population. ICS/LABAs are not indicated to be used for initial bronchodilator therapy with the PBAC considering that ICS/LABAs are more likely to be added to LAMA therapy rather than replace LAMAs (Indacaterol PSDs November 2010; July 2011). Therefore, ICS/LABA FDCs should not be considered interchangeable or a relevant comparator with other pharmacological classes such as LAMAs in the COPD treatment algorithm. The COPD Review should recognise this and there should not be any therapeutic relativity link between drugs of different classes, especially if further cost-effectiveness analyses are recommended by the Review.

1.1.4 Importance of Quality use of Medicine (QUM)

QUM is one of the central objectives of Australia's National Medicines Policy. The goal of the National Strategy for QUM is to make the best possible use of medicines to improve health outcomes for all Australians. QUM includes selecting management options wisely, choosing suitable medicines if a medicine is considered necessary and using medicines safely and effectively (Department of Health, 2015).

Boehringer Ingelheim supports a number of QUM initiatives for patients and health care professionals, including prescribers and pharmacists, to ensure the appropriate use of tiotropium, tio/olo and ipratropium in the clinical setting and correct inhaler technique with the HandiHaler® and Respimat® devices.

Educational support

Boehringer Ingelheim promotes educational grants to support prescriber education, guideline development and patient education.

- High level of support of the Lung Foundation Australia via an unrestricted grant to support the National COPD Program activities which support COPD research, guidelines, committees and patient support.
- Support of the Thoracic Society of Australia and New Zealand (TSANZ) education activities.
- Education of health professionals at various national health conferences.
- Education of GPs via face-to-face evening education meetings including RACGP accredited programmes.
- A dedicated pharmacy education team to correctly train pharmacists in inhaler technique and patient training with the Respimat® Soft Mist Inhaler.
- Sponsorship of Pharmacy Guild Guildlink program to provide Inhaler education to patients new to HandiHaler® or Respimat® inhalers.

Online education

Lung Learning' (www.lunglearning.com.au) is a freely accessible website with content personalised based on whether the user is a health care professional, COPD patients and the general public. The website includes numerous RACGP accredited Quality Improvement and Continuing Professional Development education modules.

Consumer Medicines Information

Consumer Medicines Information (CMI) is designed to inform consumers about prescription and pharmacist-only medicines. The CMI provides patients with clear instruction on what each medicine is used for in reducing COPD symptoms, how to use each medicine, and which other medicines should be continued or avoided.

2 Term of Reference 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

Summary

This submission presents a summary of patient-relevant outcomes which are also important for assessing the clinical and cost-effectiveness of different treatments for COPD and the extent to which they were included in previous PBAC submissions for tiotropium and tio/olo FDC. The outcomes identified as most clinically relevant are:

- Exacerbations
- Hospitalisations
- FEV_1
- Quality of life (QoL)
- Mortality
- Symptoms
- Adverse Events (AEs)

As detailed in the response to ToR 3, systematic reviews of tiotropium RCTs show that tiotropium has a treatment benefit for all clinical outcomes identified above. Tiotropium was listed on the PBS in 2003. Tiotropium was recommended by the PBAC based on superior efficacy and safety and acceptable cost-effectiveness compared with ipratropium. Tio/olo was listed on the PBS in 2015 based on cost-minimisation to two LAMA/LABA FDCs which were listed on the PBS at the time of submission; glycopyrronium/indacaterol (gly/ind) and umeclidinium/vilanterol (ume/vil) FDCs. The PBAC submission for tiotropium and tio/olo considered ***all*** the clinical outcomes detailed above, and therefore, these outcomes remain clinically relevant for PBAC consideration.

2.1 Clinical outcomes in COPD

COPD is a major cause of chronic morbidity and mortality; many people suffer from the disease for years, and die prematurely from it or its complications (GOLD, 2016). As there is no cure for COPD, optimal treatment and management of the disease plays a critical role in improving health outcomes for patients and therefore reducing the overall clinical and economic burden of the disease. COPD is associated with many different patient-relevant symptoms which cause increased morbidity and mortality as well as decreased quality of life (QoL). This submission presents a summary of patient-relevant outcomes which are also important for assessing the clinical and cost-effectiveness of different treatments for COPD.

2.1.1 COPD exacerbations

Acute exacerbations of COPD are characterised by clinically worsening dyspnoea, cough, sputum production, and airflow obstruction. As detailed in the GOLD 2016, exacerbations of COPD are important events in the course of the disease because they:

- Negatively affect a patient's QoL
- Have effects on symptoms and lung function that take several weeks to recover from
- Accelerate the rate of decline of lung function
- Are associated with significant mortality, particularly in those requiring hospitalisation
- Have high socioeconomic costs

2.1.2 Hospitalisations

Severe exacerbations require hospitalisation and are associated with a poor prognosis with increased risk of death (Soler-Cataluna et al 2005). COPD is the second leading cause of avoidable hospital admissions in Australia (Page et al 2007; Hutchinson et al 2010). 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 1,052 per 100,000 population (AIHW, 2015b). As such, prevention, early detection, and prompt treatment of exacerbations are vital to reduce the burden of COPD (GOLD 2016).

2.1.3 Lung function: Trough FEV_1

FEV_1 is the most commonly used measure of lung function for the diagnosis of COPD and determination of disease severity. FEV1 is a strong predictor of mortality and morbidity in COPD (COPD-X 2015/2016) and therefore, is used for the evaluation of treatment effect in COPD. As detailed in the COPD-X Plan, the five-year survival rate was only about 10% for those with an FEV_1 <20% predicted, 30% for those with FEV_1 of 20%–29% predicted and about 50% for those with an FEV_1 of 30%–39% predicted (Connors et al 1996). The effect of treatments on COPD is commonly assessed using *trough* FEV_1. Trough FEV_1 (also called pre-dose FEV_1) is the mean volume of air that can be forced out in one second approximately 24 hours after the last administration of a bronchodilator treatment.

2.1.4 Health-related quality of life

COPD affects QoL as it can interrupt daily activity, sleep patterns and the ability to exercise. Therefore, Australians with COPD generally report their health as being worse than those without the condition (ABS, 2014a). As discussed in the COPD-X Plan, QoL, as measured by the St George Respiratory Questionnaire (SGRQ), deteriorates faster in patients with more severe disease. The SGRQ is designed to measure health-related QoL specifically in patients with asthma or COPD and is widely used in clinical trials to assess the effects of treatment on health-related QoL in patients with COPD (Glaab et al., 2010). The SGRQ covers the domains of symptoms (frequency and severity of respiratory symptoms), activity (effects on and adjustment of everyday activities), and psycho-social impact, from which a total score with a possible maximum of 100 points is calculated. Higher scores indicate worsening health-related QoL. The SGRQ responder analysis is based on a patient's total SGRQ score at the specified time point.

One aspect of QoL which is particularly impacted by COPD is capacity for everyday activities that require exertion and exercise capacity. A number of tests are used to assess the impact of COPD on exertion. These include measuring inspiratory capacity, exercise endurance time and the six-minute walk test.

2.1.5 Mortality

COPD is a leading cause of mortality worldwide and is also a leading cause of death in Australia despite being a preventable and treatable disease. In 2012, 5,923 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 2014b; AIHW 2014a). Projections from the WHO Global Burden of Disease study estimate that total deaths from COPD could increase by more than 30% in the next 10 years which would result in COPD becoming the third leading cause of death worldwide (WHO, 2015). As discussed above, COPD exacerbations, hospitalisations and decline in lung function are predictors of increased mortality in COPD. As such, it is a primary goal of treatment to improve mortality by reducing exacerbations and associated hospitalisations as well as by improving the risk of lung function.

2.1.6 Symptoms (dyspnoea)

Dyspnoea is a key symptom of COPD and is a major cause of disability and anxiety associated with the disease (GOLD 2016). Typical COPD patients describe their dyspnoea as a sense of increased effort to breathe, heaviness, air hunger, or gasping (GOLD, 2016). The Transition Dyspnoea Index (TDI) (also called the Mahler Dyspnoea Indices) is designed to measure the severity of dyspnoea, or pathologic breathlessness (Mahler et al., 1984). The TDI measures the transitions or changes in a patient's dyspnoea compared to the baseline state (measured by the baseline dyspnoea index [BDI](Mahler et al., 1984). The TDI ranges from -3 (major deterioration) to 3 (major improvement) including a 0 score to indicate "no change".

2.1.7 Treatment-related adverse events

The GOLD 2016 Guidelines emphasise the importance of monitoring disease progress and pharmacotherapy, including monitoring adverse events (AEs) and avoiding unnecessary polypharmacy. The GOLD 2016 Guidelines highlight the following adverse events associated with different pharmacological classes.

- Anticholinergics (e.g. SAMAs, LAMAs)- Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of the mouth.
- β2-agonists (e.g. SABAs, LABAs)- Stimulation of β2-adrenergic receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in susceptible patients
- ICS- ICS use is associated with higher prevalence of oral candidiasis, hoarse voice, skin bruising, increased risk of pneumonia and possible increased risk of fractures. Due to the potential of severe AEs, ICS/LABA combinations are only recommended for patients with severe COPD and previous history of exacerbations (COPD-X 2015/2016, GOLD 2016).

2.2 Inclusion of clinical outcomes in previous PBAC assessment on the cost-effectiveness of tiotropium

Tiotropium was listed on the PBS in 2003. Tiotropium was the first LAMA listed on the PBS. Tiotropium was recommended by the PBAC based on superior efficacy and safety and acceptable

cost-effectiveness compared with ipratropium. The PBAC submission for tiotropium considered ***all*** the clinical outcomes detailed above.

Tio/olo was listed on the PBS in 2015 based on cost-minimisation to two LAMA/LABA FDCs which were listed on the PBS at the time of submission; glycopyrronium/indacaterol (gly/ind) and umeclidinium/vilanterol (ume/vil) FDCs. The PBAC submission for tio/olo considered ***all*** the clinical outcomes detailed above, and therefore, these outcomes remain clinically relevant for PBAC consideration.

Since the PBS listing of tiotropium, there has been new published evidence, including long-term RCTs, which continue to demonstrate the clinical and economic effectiveness of tiotropium compared with ipratropium as well as more recent PBS-listed treatment options for COPD. As detailed in the response to ToR 3 below, systematic reviews of tiotropium RCTs show that tiotropium has a treatment benefit for all clinical outcomes identified above.

3 Term of Reference 3. Review the published literature on the efficacy and safety of monotherapy and combinations of LABA/LAMA, ICS/LABA and LAMA + ICS/LABA (separate items or fixed dose combinations) for treatment of COPD that PBAC has not previously considered.

Summary

Boehringer Ingelheim has three products that are listed on the PBS for the treatment of COPD: tiotropium (Spiriva® and Spiriva® Respimat®), ipratropium (Atrovent®) and tio/olo FDC (Spiolto® Respimat®). In response to ToR 3, the recent evidence on the efficacy, safety and cost-effectiveness of tiotropium, ipratropium and tio/olo for the treatment of COPD is summarised and discussed.

Tiotropium evidence

To summarise the clinical evidence for tiotropium an overview of systematic reviews on the efficacy and safety of tiotropium is presented. Three different treatments were considered as comparators to tiotropium:

- Other LAMAs- Consistent with the PBAC Guidelines, other LAMAs are the most relevant comparator in terms of treatments that tiotropium would most likely replace in clinical practice as they are pharmacological analogues and have the same reimbursed indication as tiotropium
- Usual care- The efficacy and safety of tiotropium can be assessed in real-world conditions representative of Australian clinical practice
- Ipratropium- Tiotropium was listed on the PBS for the treatment of COPD based on superior efficacy and safety compared with ipratropium

LABA monotherapy and ICS/LABA were not considered as relevant comparators to tiotropium as the PBAC has previously considered that LABA monotherapy and ICS/LABA be used as an add-on therapy to tiotropium rather than replace tiotropium. Furthermore, as recommended by clinical practice guidelines and consistent with PBS restrictions, ICS/LABA is intended for a different population of use: ICS/LABA is a treatment option in a subgroup of severe COPD patients with FEV1 <50% predicted and two or more previous exacerbations whereas tiotropium is a long-term maintenance treatment option for patients with moderate to severe COPD, providing symptom relief and exacerbation protection.

Based on the response to ToR 2, the following outcomes were included:

- Exacerbations
- FEV_1
- QoL
- Mortality
- Hospitalisations
- Symptoms
- AEs

Key findings

- Tiotropium has the most substantial body of evidence among the LAMAs, demonstrating a reduction in exacerbations and hospitalisations, as well as improved lung function, QoL and symptoms compared with usual care therapy. Tiotropium is the only LAMA which has shown

to reduce exacerbations, associated hospitalisations and mortality over the long-term compared with usual care (e.g. UPLIFT 4-years duration). Furthermore, tiotropium was the only LAMA to show a statistically significant reduction in severe exacerbations compared with usual care.

- In terms of FEV_1, SGRQ and TDI, the results of the systematic reviews presented in this Response to ToR 3 are consistent with recent PBAC assessments that tiotropium, aclidinium, glycopyrronium and umeclidinium are non-inferior in terms of efficacy and safety based on (equi-effective doses: tiotropium HandiHaler 18 µg once daily, tiotropium Respimat 5 µg once daily, glycopyrronium 50 µg once daily, aclidinium 400 µg twice daily, umeclidinium 62.5 µg once daily).
- Patients in many tiotropium RCTs were permitted access to usual-care respiratory medicines (including LABAs) which reflects real-life treatment practice whereas trials of other LAMAs were often more restricted in the background respiratory medicines permitted. Therefore, the results of tiotropium RCTs are directly applicable to patients likely to receive tiotropium in clinical practice.
- The effect of tiotropium and other LAMAs on all-cause and cardiovascular mortality was similar with no significant differences observed between the treatments. There was no difference in mortality between the different formulations of tiotropium (HandiHaler and Respimat). This is consistent with the PBAC's previous evaluation that tiotropium HandiHaler 18 µg and Respimat 5 µg are equivalent.
- Tiotropium has superior efficacy and safety compared with ipratropium, which is consistent with the PBAC's original recommendation of tiotropium on a cost-effectiveness basis compared with ipratropium.

Tiotropium/olodaterol evidence

A review of PSDs was conducted to summarise the clinical evidence considered by the PBAC in its recommendation of tio/olo and other LAMA/LABA FDCs.

- Tio/olo FDC has superior efficacy and comparable safety to tiotropium or olodaterol monotherapy.
- The RCT evidence presented in the PSDs demonstrates that tio/olo FDC is of comparable efficacy and safety to other PBS-listed LAMA/LABA FDCs, which is consistent with the PBAC's recent recommendations.

Ipratropium evidence

A summary of evidence supporting ipratropium's use by the COPD-X Plan is presented.

- Ipratropium has a significantly greater effect on lung function compared to SABAs, in addition to improving QoL and decreasing need for oral corticosteroid treatment.
- Ipratropium combined with SABA treatment reduces the number of patients experiencing exacerbations and the use of oral corticosteroids, without increasing drug related AEs.

Tiotropium economic evaluations

A systematic review was also undertaken to summarise the published literature on the cost-effectiveness of tiotropium for the treatment of COPD compared with other LAMA's, usual care/placebo, ipratropium and in combination with ICS/LABAs.

Key findings

- The economic evaluations indicate that tiotropium is similarly cost-effective to other LAMA therapies. Tiotropium is cost-effective compared with usual care and ipratropium.

- The cost effectiveness of tiotropium was driven primarily by its effectiveness in preventing exacerbations and hospitalisations. This is supported by the clinical evidence which shows that tiotropium is the only LAMA which has demonstrated to reduce exacerbations, associated hospitalisations and mortality over the long term.

The addition of ICS/LABA *add-on* to tiotropium therapy may be a cost-effective option in patients with severe COPD and a history of exacerbations.

3.1 Outline

Boehringer Ingelheim has three products that are listed on the PBS for the treatment of COPD: tiotropium (Spiriva® and Spiriva® Respimat®), ipratropium (Atrovent®) and tio/olo FDC (Spiolto® Respimat®). In response to ToR 3, the recent evidence on the efficacy and safety of tiotropium, ipratropium and tio/olo for the treatment of COPD is summarised and discussed. The submission to ToR 3 is structured in three sections:

- **Tiotropium evidence**. There is a large body of high level evidence for tiotropium, including recent systematic reviews (SRs) of randomised controlled trials (RCTs). Therefore, an overview of SRs (of RCTs) on the efficacy and safety of tiotropium is undertaken.
- **Tio/olo FDC evidence**. Tio/olo and other LAMA/LABA FDCs were recently reviewed by PBAC. Therefore, this submission summarises the recent evidence considered by the PBAC and provides an update of recent tio/olo RCTs.
- **Ipratropium evidence**. Summary of ipratropium efficacy and safety

3.2 Tiotropium evidence

3.2.1 Aim

Tiotropium was listed on the PBS in 2003. Tiotropium was the first LAMA listed on the PBS. Tiotropium was recommended by the PBAC based on superior efficacy and safety compared with ipratropium. Since the PBS listing of tiotropium, there has been new published evidence, including long-term RCTs, which continue to demonstrate the clinical effectiveness and safety of tiotropium. In addition, there are now more treatment options for the treatment of COPD.

In this submission to ToR 3, we summarise the efficacy and safety of tiotropium for the treatment of COPD. Specifically, the aims of the submission are to:

- Review the RCT evidence for tiotropium published since tiotropium was last evaluated by the PBAC.
- Demonstrate the efficacy and safety of tiotropium as measured by clinically important outcomes.
- Examine the efficacy and safety of tiotropium over the longer-term.
- Compare the efficacy and safety of tiotropium with other comparable treatment options currently listed on the PBS.

3.2.2 Methodology

The search strategy and eligibility criteria for the overview are informed by the 'PICOS' criteria discussed below.

Population

All patients with a diagnosis of COPD of any severity were considered which is consistent with the broad population defined in the scope of the Review, as well as the treatment algorithm recommended in the COPD-X Plan and the PBS prescribing criteria for COPD medicines (see ToR 1).

Intervention

Tiotropium is available as a dry powder for inhalation (HandiHaler) and as a solution for inhalation (Respimat). The recommended daily doses are HandiHaler 18 µg and Respimat 5 µg. The PBAC has previously assessed HandiHaler 18 µg and Respimat 5 µg to be equi-effective doses.

Comparators

As discussed in ToR 1, there are multiple treatment options for COPD. The choice of treatment is dependent on multiple factors including disease progression, symptoms, comorbidities and physician and patient preference. Therefore, it is important to consider treatments intended for use in the same treatment population as tiotropium. Consistent with PBAC Guidelines, this submission considers relevant comparators as treatments which tiotropium would be most likely to *replace* in Australian clinical practice. This submission includes comparators that are informative to real-world clinical practice and provides long-term evidence consistent with ToR 2 on the clinically relevant COPD outcomes such as exacerbations, hospitalisations and mortality. The following provides a summary and rationale for inclusion or exclusion of different treatments as comparators for tiotropium based on the approach recommended in the PBAC Guidelines (v4.4, Section A.4).

Other LAMAs

Since the listing of Tiotropium on the PBS, three other LAMAs (glycopyrronium, aclidinium and umeclidinium) have been listed on the PBS for the treatment of COPD. All three LAMAs were PBS-listed on a cost minimisation basis with tiotropium (equi-effective doses: tiotropium 18 µg once daily, glycopyrronium 50 µg once daily, aclidinium 400 µg twice daily, umeclidinium 62.5 µg once daily). Consistent with the PBAC Guidelines, other LAMAs are the most relevant comparator in terms of treatments that tiotropium would most likely replace in clinical practice as they are pharmacological analogues and have the same reimbursed indication as tiotropium. Therefore, this submission summarises the comparative efficacy and safety of tiotropium with other LAMAs.

Add-on to usual care

COPD-X Plan recommends that multiple different treatment options be available to patients depending on disease progression and patient symptoms. As such, it is important to assess the efficacy and safety of tiotropium in real-world conditions applicable to Australian clinical practice. Many tiotropium RCTs are designed with tiotropium as *add-on* to usual care therapy, with patients permitted access to other therapies (e.g. LABAs, ICS and theophylline) during the trial. This trial design enhances the applicability of tiotropium RCTs to real-world treatment practice. This is important as RCTs of tiotropium add-on to usual care therapy are used to inform cost-effectiveness over the long term (see Section 3.5). It is also important to take into account background medication in indirect comparisons of tiotropium with other LAMA RCTs which are more restrictive in the background medications allowed.

Ipratropium

COPD-X Plan recommends SAMAs (e.g. ipratropium) as an initial treatment option in patients with COPD. In patients with persistent symptoms, it is recommended that SAMA treatment be replaced with a LAMA such as tiotropium. Tiotropium was listed on the PBS for the treatment of COPD based

on superior efficacy and safety compared with ipratropium. As such, it is necessary to identify any new evidence confirming that tiotropium is still an effective option compared with ipratropium.

LABA monotherapy

LABA monotherapy is *not* considered a relevant comparator consistent with PBAC Guidelines and previous PBAC decision making. As described above, there are now other LAMAs listed on the PBS which are the most relevant comparator in terms of pharmacological analogues that tiotropium would most likely replace in clinical practice. Furthermore, the PBAC has previously considered indacaterol (the only LABA PBS-listed for COPD) to be more likely used as add-on therapy to tiotropium than replace tiotropium (Indacaterol PSDs November 2010; July 2011).

The COPD-X Plan lists LABA monotherapy as a treatment alternative to tiotropium. GOLD Guidelines also recommend LABA monotherapy as a treatment alternative to LAMA monotherapy in patients at low risk of exacerbations whereas only LAMA monotherapy (but not LABA monotherapy) is a first-choice treatment option for patients at high risk of exacerbations. Indacaterol is the only LABA monotherapy listed on the PBS for the treatment of COPD. Recent SRs show that tiotropium provides similar benefits to indacaterol in terms of lung function and QoL, however, tiotropium is superior in preventing exacerbations (Kim et al 2015; Tricco et al 2015), which is consistent with the recommendations in the GOLD Guidelines.

Indacaterol was recommended in 2011 on a cost minimisation basis with fluticasone/salmeterol (an ICS/LABA) (equi-effective doses: indacaterol 150 µg daily, fluticasone 500 µg/salmeterol 50 µg twice daily). In consideration of the clinical place of indacaterol in Australian clinical practice, the PBAC stated that tiotropium was not an appropriate comparator for indacaterol. The PBAC considered fluticasone/salmeterol to be the most appropriate comparator for indacaterol as both therapies are more likely to be *added* to existing tiotropium therapy rather than replace tiotropium (Indacaterol PSDs November 2010; July 2011). Therefore, a comparison of tiotropium and indacaterol is not presented in this submission as indacaterol has been considered by the PBAC as an add-on treatment to tiotropium in the majority of patients. Other LABAs (not listed for COPD) are also not included as comparators given the PBAC's view of indacaterol as discussed above and no other LABAs have been considered for cost-effectiveness by the PBAC for the treatment of COPD.

LAMA/LABA FDC

The COPD-X Plan recommends LAMA/LABA combination therapy in patients who remain symptomatic despite treatment with monotherapy (LAMA or LABA). The comparative efficacy of tiotropium vs LABA/LAMAs are not presented in this section of the submission. The PBAC has recently considered the efficacy and safety of LABA/LAMAs compared with tiotropium in the recent listing of LAMA/LABA FDCs. A summary of the evidence considered by the PBAC for LAMA/LABA FDCs as well as an update of recently published SRs and RCTs comparing tio/olo FDC and tiotropium is provided in Section 3.3 demonstrating an additive benefit when olodaterol is added on to tiotropium.

ICS/LABA

ICS/LABA dual therapy is *not* considered a relevant comparator as ICS/LABA is intended for use in a different population compared with tiotropium and is not an appropriate comparator in Australian clinical practice. ICS/LABA is a treatment option in a subgroup of severe COPD patients with FEV1 <50% predicted and two or more exacerbations in the previous 12 months. In contrast, tiotropium is a long-term maintenance treatment option for patients with moderate to severe COPD, providing symptom relief *and* exacerbation protection. As discussed in ToR 1, this is consistent with PBS restrictions.

Since the PBAC recommendation of ICS/LABAs in 2007, the PBAC has noted that the treatment algorithm regarding the use of ICS/LABA treatments in COPD is changing. Based on comments from the TSANZ, the PBAC considered it appropriate to delay the introduction of ICS/LABA combinations in favour of LAMA/LABA combinations (PSDs March 2014: glycopyrronium/indacaterol FDC; umeclidinium/vilanterol FDC). Safety concerns associated with ICS/LABAs (e.g. increased risk of pneumonia) may limit the use of ICS/LABA as a long-term treatment option. Furthermore, as discussed above, the PBAC considered indacaterol and ICS/LABAs are more likely to be added to tiotropium therapy rather than replace tiotropium (Indacaterol PSDs November 2010; July 2011). The use of ICS/LABA as add-on therapy is reflected in recent Cochrane reviews (Welsh et al 2013) and economic analyses comparing ICS/LABA *add-on* to tiotropium therapy with tiotropium monotherapy (see Section 3.5.6). Therefore, given that ICS/LABA is not a pharmacological analogue of tiotropium and the different intended COPD populations of use, changing treatment algorithm, and insufficient evidence regarding the comparative effectiveness (Welsh et al 2013), the original therapeutic relativity between ICS/LABA and tiotropium is not considered relevant. ICS/LABA is not considered a relevant comparator for tiotropium in the Australian context. This approach is consistent with the recommendations for comparator selection as recommended in the PBAC Guidelines (v4.4, Section A.4).

Outcomes

The following clinically relevant outcomes are included in this submission. The clinical relevance of each outcome is discussed in response to ToR 2

- Exacerbations
- FEV_1
- QoL
- Mortality
- Hospitalisations
- Symptoms
- AEs

Study type

There is a large volume of RCT evidence for tiotropium. Due to the constrained deadline prompted by the Review, we have briefly summarised all individual tiotropium RCTs in Appendix 3. Many SRs of tiotropium RCTs have recently been published. Therefore, SRs on the efficacy and safety of tiotropium were considered in this submission. This approach is considered appropriate as SRs of

RCTs are considered to provide the highest level of evidence for interventional questions (NHMRC 2009). In addition, a search was performed to identify any recent tiotropium RCTs published since the publication of the included SRs.

Literature review

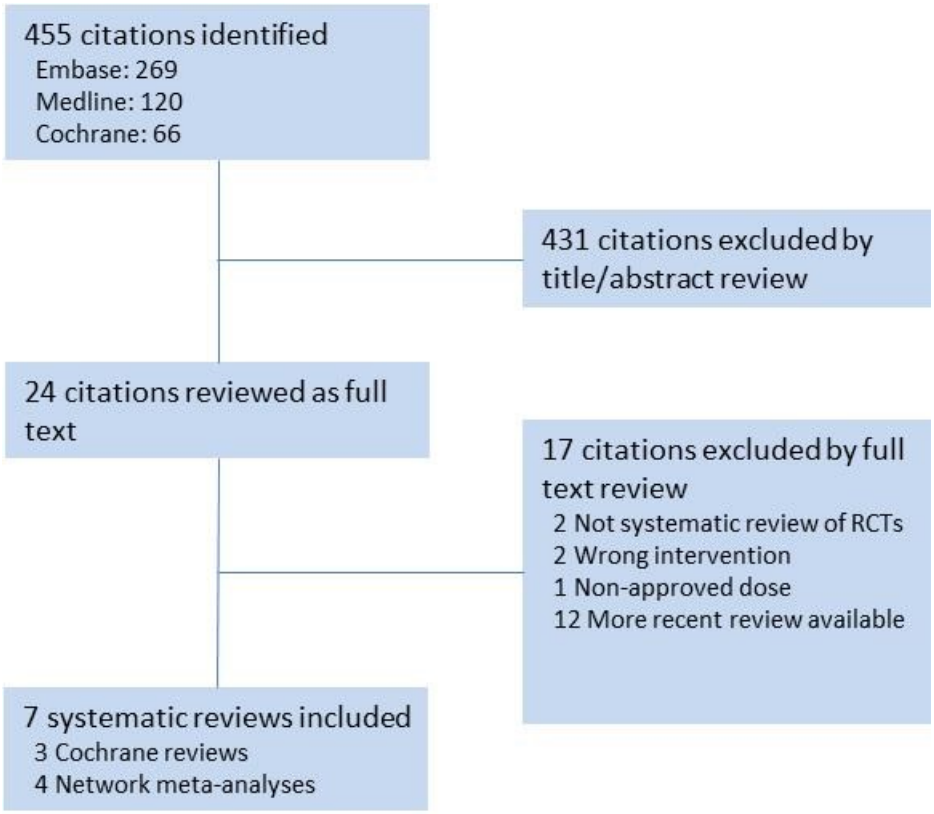
A full review of the literature was undertaken in order to identify the most relevant SRs evaluating the efficacy and safety of tiotropium in patients with COPD. To ensure that all relevant SRs were identified, a comprehensive search of the published literature was conducted. The following approaches were used to search for relevant data:

- A search of published literature via OvidSP, to search Embase and MEDLINE
- A search of the Cochrane Library via Wiley Online Library

The search strategies are summarised in Appendix 1. In order to consider the most up-to-date evidence, the literature search was limited to SRs published since 2011. The literature searches conducted within each of these SRs could be conducted at any time period. The results of the literature search are summarised in Figure 3.1. A total of 455 citations were identified. All citations were reviewed by title and abstract. Studies were considered eligible for initial inclusion in the current review based on the following criteria:

- Population: patients with COPD
- Intervention: tiotropium
- Comparator: placebo/usual care, ipratropium, other LAMAs
- Outcomes: Exacerbations, FEV_1, QoL, mortality, hospitalisations, symptoms, AEs
- Study type: SR of RCTs published since 2011

Figure 3.1 Flow diagram of study selection.



A total of 24 SRs were identified for initial inclusion. There was substantial overlap in the RCTs included as well as variation in the quality in each SR. Therefore, to avoid duplication and present only the high-quality and the most recent reviews, the following reviews were considered for further analysis:

- Cochrane reviews which represent the highest quality reviews
- Recent network meta-analyses which provide the most up-to-date evidence for each outcome

Table 3.1 provides the citations of the SRs included for further analysis. Five SRs were identified which compared tiotropium with other LAMAs (Ismaila 2015; Karabis et al 2013; Tricco et al 2015; Oba and Lorne 2015; Ni et al 2014). One Cochrane review was identified (Ni et al 2014), however, the focus of the Cochrane review was on aclidinium and only two small head-to-head trials comparing the efficacy and safety of aclidinium and tiotropium were presented. Therefore, it was necessary to consider other recent SRs. The four most recent network meta-analyses (NMAs) for each outcome of interest were included as they provided the most up-to-date RCT evidence. Two of the NMAs (Ismaila 2015 and Karabis 2013) examined lung function (trough FEV_1), QoL (SGRQ) and symptoms (TDI). Ismaila et al 2015 is the most recent SR and network meta-analysis comparing relative lung function, QoL and symptoms, of all four PBS-listed LAMAs. Notably, only dry powder formulations were included and as such, tiotropium Respimat was excluded in the analysis. The authors did not explain why soft mist inhalers available at the time of analysis were not included. Therefore, to assess the relative efficacy of tiotropium Respimat for lung function, QoL and symptoms, the NMA by Karabis et al 2013 (which included tiotropium Respimat) is also presented.

Oba and Lorne 2015 was the most recent NMA which assessed exacerbations. Tricco et al 2015 is the most recent meta-analysis to compare LAMAs for mortality and AEs. In addition, Tricco et al 2015 presented comparisons for different long-acting classes, however, only the relevant tiotropium comparisons vs other LAMAs are presented in this submission.

The literature search identified two recent Cochrane reviews for the comparisons of tiotropium vs usual care (Karner et al 2014) and tiotropium vs ipratropium (Cheyne et al 2015). The Cochrane reviews represent the best quality, recent evidence summaries for these comparisons

Table 3.1 List of included systematic reviews

Study	Citation	Reason for inclusion
Tiotropium vs other LAMAs		
Oba and Lone 2015	Oba Y, Lone NA. Comparative efficacy of long-acting muscarinic antagonists in preventing COPD exacerbations: a network meta-analysis and meta-regression. Therapeutic advances in respiratory disease. 2015 1753465814565624.	Most recent exacerbation evidence
Ismaila et al 2015	Ismaila AS, Huisman EL, Punekar YS, Karabis A. Comparative efficacy of long-acting muscarinic antagonist monotherapies in COPD: a systematic review and network meta-analysis. International journal of chronic obstructive pulmonary disease. 2015;10:2495.	Most recent FEV_1, QoL and Symptoms evidence including tiotropium HandiHaler
Karabis et al 2013	Karabis A, Lindner L, Mocarski M, Huisman E, Greening A. Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: a systematic review and network meta-analysis. Int J Chron Obstruct Pulmon Dis 2013;8:405-23.	Most recent FEV_1, QoL and Symptoms evidence including tiotropium Respimat
Ni et al 2014	Ni H, Soe Z, Moe S. Aclidinium bromide for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2014;9:CD010509.	Cochrane review. Head to head trials of aclidinium and tiotropium only
Tricco et al 2015	Tricco AC, Strifler L, Veroniki AA, Yazdi F, Khan PA, Scott A, Ng C, Antony J, Mrklas K, D'Souza J, Cardoso R. Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis. BMJ open. 2015 Oct 1;5:e009183.	Most recent mortality and exacerbation evidence
Tiotropium vs usual care		
Karner et al 2014	Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2014;7:CD009285.	Most recent Cochrane review
Tiotropium vs ipratropium		
Cheyne et al 2015	Cheyne L, Irvin-Sellers MJ, White J. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2015;9:CD009552	Most recent Cochrane review

Table 3.2 lists SRs identified in the literature search which are not considered for further analysis. SRs were excluded as there are more recent Cochrane reviews or NMAs for each outcome of interest. In order to avoid duplication and only consider high-quality, up-to-date evidence for tiotropium, these SRs are not considered for further analysis.

Table 3.2 List of identified systematic not considered for further analysis

Study	Citation	Outcomes presented	Reason for exclusion
Tiotropium vs other LAMAs			
Cope et al 2013	Cope S, Donohue JF, Jansen JP, Kraemer M, Capkun-Niggli G, Baldwin M et al. Comparative efficacy of long-acting bronchodilators for COPD: a network meta-analysis. Respir Res 2013;14:100.	FEV_1 QoL TDI	More recent NMAs available (Ismaila et al 2015; Karabis et al 2013)
Dong et al 2013	Dong Y-H, Lin H-H, Shau W-Y, Wu Y-C, Chang C-H, Lai M-S. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: Systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. Thorax 2013;68:48-56.	Mortality	More recent SR available (Tricco et al 2015)
Suppli Ulrik et al 2012	Suppli Ulrik C. Aclidinium Bromide: Clinical Benefit in Patients with Moderate to Severe COPD. Open Respir Med J 2012;6:150-4.	FEV_1 QoL Exacerbations	Recent Cochrane review available (Ni et al 2014)
Tiotropium vs placebo (usual care)			
IQWiG 2012	IQWiG. Tiotropium bromide in the treatment of chronic obstructive pulmonary disease. Health Technology Assessment Database 2012	TDI Exacerbations Hospitalisations QoL Mortality AEs	Recent Cochrane review available (Karner et al 2014)
Karner et al 2012	Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. Cochrane database of systematic reviews (Online) 2012;7:CD009285.	See Karner et al 2014	More recent version available (Karner et al 2014)
Mathioudakis et al 2014a	Mathioudakis AG, Kanavidis P, Chatzimavridou-Grigoriadou V, Gialmanidis IP, Amanetopoulou SG, Christopoulou E et al. Tiotropium HandiHaler improves the survival of patients with COPD: A systematic review and meta-analysis. J Aerosol Med Pulm Drug Deliv 2014;27:43-50.	Mortality	Recent Cochrane review (Karner et al 2014) and NMA (Tricco et al 2015) available
Mathioudakis et al 2014b	Mathioudakis AG, Chatzimavridou-Grigoriadou V, Evangelopoulou E, Mathioudakis GA, Siafakas NM. Comparative mortality risk of	Mortality	More recent NMAs available comparing HandiHaler to Respimat

Study	Citation	Outcomes presented	Reason for exclusion
	tiotropium administered via HandiHaler or Respimat in COPD patients: Are they equivalent? Pulm Pharmacol Ther 2014;28:91-97.		(Karabis et al 2013; Tricco et al 2015; Oba and Lorne et al 2015)
Mills et al 2011	Mills EJ, Druyts E, Ghement I, Puhan MA. Pharmacotherapies for chronic obstructive pulmonary disease: A multiple treatment comparison meta-analysis. Clin Epidemiol 2011;3:107-129.	Exacerbations	Recent Cochrane review available (Karner et al 2014)
Ram et al 2011	Ram FSF, Carvallho CR, White J. Clinical effectiveness of the respimat inhaler device in managing chronic obstructive pulmonary disease: Evidence when compared with other handheld inhaler devices. Int J COPD 2011;6:129-139	FEV_1 Exacerbations AEs	More recent NMAs available comparing HandiHaler to Respimat (Karabis et al 2013; Tricco et al 2015; Oba and Lorne et al 2015)
Singh et al 2011	Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. BMJ (Clinical research ed) 2011;342:d3215.	Mortality	More recent NMA available comparing mortality of HandiHaler to Respimat (Tricco et al 2015)
Yohannes et al 2011	Yohannes AM, Willgoss TG, Vestbo J. Tiotropium for treatment of stable COPD: A meta-analysis of clinically relevant outcomes. Respir Care 2011;56:477-487.	QoL Exacerbations Hospitalisations Symptoms AEs	Recent Cochrane reviews available (Karner et al 2014; Cheyne et al 2015)
Tiotropium vs ipratropium			
Cheyne et al 2013	Cheyne L, Irvin-Sellers MJ, White J. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2013;9:CD009552.	See Cheyne et al 2015	More recent version available (Cheyne et al 2015)

Abbreviations: AE, adverse event; FEV_1, forced expiratory volume in 1 second; LAMA, long-acting muscarinic antagonist; NMA, network meta-analysis; QoL, quality of life; TDI, transition dyspnoea index;

3.2.3 Tiotropium vs other LAMAs

Tiotropium was the first LAMA PBS-listed in 2003. Three other LAMAs have since been PBS-listed on a cost minimisation basis with tiotropium (equi-effective doses: tiotropium 18 µg once daily, glycopyrronium 50 µg once daily, aclidinium 400 µg twice daily, umeclidinium 62.5 µg once daily). Consistent with the PBAC Guidelines, other LAMAs are the most relevant comparator in terms of treatments that tiotropium would most likely replace in clinical practice as they are pharmacological analogues and have the same reimbursed indication as tiotropium. Therefore, the aim of this section is to summarise the most recent SRs comparing the efficacy and safety of tiotropium with other LAMAs, and to determine whether recent evidence is consistent with PBAC's assessment that tiotropium and other LAMAs have non-inferior efficacy and safety.

3.2.3.1 Study characteristics

As described above, the literature search identified four recent NMAs and one Cochrane review describing the relative efficacy and safety of LAMAs. The study characteristics of the included SRs are summarised in Table 3.3.

Of note, tiotropium is the most studied LAMA. Studies which included tiotropium accounted for 86% to 91% of patients included in the NMAs. As discussed above, the Cochrane review by Ni et al 2014 only presented two small trials of four to six weeks duration comparing tiotropium and aclidinium. Three NMAs included RCTs with both the tiotropium HandiHaler and Respimat formulations whereas the NMA by Ismaila et al 2015 and Ni et al 2014 only presented results for tiotropium HandiHaler. Umeclidinium was only included in two SRs reflecting it being the most recently approved LAMA. The SRs by Ismaila et al 2015, Karabis et al 2013 and Ni et al 2014 considered approved doses only (e.g. daily doses aclidinium 800 µg, glycopyrronium 50 µg, tiotropium 18 µg (HandiHaler) or 5 µg (Respimat), umeclidinium 62.5 µg OD) whereas the studies by Oba and Lorne 2015 and Tricco et al 2015 included any dose. All SRs included RCTs in patients with COPD at any severity.

The duration of RCTs included in the analyses varied. Ismaila et al 2015 and Karabis et al 2013 considered outcomes at 12 and 24 weeks only whereas Oba and Lorne 2015 and Tricco et al 2015 reported studies up to 4 years duration (e.g. UPLIFT study). The reviews were assessed as medium to high quality (AMSTAR rating range: 7 to 11, see Appendix 2).

Three NMAs employed Bayesian methodology. Each study (with the exception of Ismaila et al 2015) explored heterogeneity using meta-regression, sensitivity, subgroup or scenario analyses. Ismaila et al 2015 stated that scenario analysis was used to test the impact of certain studies on the relative treatment estimates. However, neither the scenario analyses, nor any other measure of heterogeneity were presented.

Table 3.3 Characteristics of included tiotropium vs other LAMA reviews

Citation	Treatments evaluated (dose/day)	No. of trials/sample size included in the analysis	Summary of main population characteristics	Duration of included RCTs	Outcomes	AMSTAR quality rating (0 to 11)	Analysis
Ismaila et al 2015	Tiotropium (HandiHaler 18 µg) Aclidinium (800 µg) Glycopyrronium (50 µg) Umeclidinium (62.5 µg)	Overall 24/21,311 Tio HandiHaler vs placebo 14/13,998 Tio HandiHaler vs glycopyrronium 4/4,379 Glycopyrronium vs placebo 1/822 Aclidinium vs placebo 3/1,277 Umeclidinium vs placebo 2/835	COPD	12 and 24 week data analysed	Trough FEV_1 QoL (SGRQ) Symptoms (TDI)	7	Bayesian fixed- and random-effects NMA Sensitivity analyses performed but not presented
Karabis et al 2013[a]	Tiotropium (Respimat 5 µg, HandiHaler 18 mg) Aclidinium (800 µg) Glycopyrronium (50 µg)	Overall 21/22,542 Tio HandiHaler vs placebo 13/13,774 Tio Respimat vs placebo 3/5,601 Tio HandiHaler vs glycopyrronium 1/1,066 Glycopyrronium vs placebo 1/832 Aclidinium vs placebo 3/1,279	COPD	12 and 24 week data analysed	Trough FEV_1 QoL (SGRQ) Symptoms (TDI)	8	Bayesian fixed- and random-effects NMA the results of the Meta-regression analysis to explore the effect of baseline FEV1% predicted and concomitant the ICS use Scenario analyses with studies allowing LABA use excluded and ACCORD II study included
Ni et al 2014[a]	Tiotropium (HandiHaler	Tiotropium vs aclidinium	COPD	4 to 6 weeks	Trough FEV_1	11	Fixed and random effects

Citation	Treatments evaluated (dose/day)	No. of trials/sample size included in the analysis	Summary of main population characteristics	Duration of included RCTs	Outcomes	AMSTAR quality rating (0 to 11)	Analysis
	18 mg) Aclidinium (800 µg)	2/729			SAEs Exacerbations Hospitalisations Mortality Withdrawals		meta-analysis Planned subgroup analysis for dose, duration, disease severity, concomitant theophylline therapy
Oba and Lone 2015	Tiotropium (Respimat 5, 10 µg; HandiHaler 18 µg) Aclidinium (200, 400, 800 µg) Glycopyrronium (50 µg)	Overall 27/48,140 Tio HandiHaler vs placebo 14/16,192 Tio Respimat vs placebo 2/5,907 Tio HandiHaler vs Tio Respimat 1/17,116 Tio HandiHaler vs glycopyrronium 5/4,542 Glycopyrronium vs placebo 1/817 Aclidinium vs placebo 4/3,566	COPD	12 weeks to 4 years	Exacerbations	8	Bayesian fixed- and random-effects NMA Meta-regression analysis to explore the effect of study duration, smoking status, baseline disease severity (FEV_1), concomitant ICS or LABA use
Tricco et al 2015[b]	Tiotropium (Respimat 5, 10 µg; HandiHaler 18 µg) Glycopyrronium Aclidinium Umeclidinium	Overall[c] 208/134,692 Tio HandiHaler vs placebo 13/13,408 Tio Respimat vs placebo 2/4,773	COPD	9 hours to 4 years	Exacerbations Mortality CV mortality Pneumonia Arrhythmia	10	Random-effects NMA. Meta-regression analysis to explore the effect of study duration. Sensitivity analyses with high or unclear risk of

Citation	Treatments evaluated (dose/day)	No. of trials/sample size included in the analysis	Summary of main population characteristics	Duration of included RCTs	Outcomes	AMSTAR quality rating (0 to 11)	Analysis
		Tio HandiHaler vs Tio Respimat 1/11,405 Tio HandiHaler vs glycopyrronium 3/3,385 Tio HandiHaler vs umeclidinium 1/437					bias studies excluded

Abbreviations: AMSTAR, A Measurement Tool to Assess Systematic Reviews; ATS, American Thoracic Society; BDI, baseline dyspnoea index; BTS, British Thoracic Society; COPD, chronic obstructive pulmonary disease; EQ-5D, EuroQol five dimensions; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; QoL, quality of life; SGRQ, St George Respiratory Questionnaire; SAE, serious adverse event; TDI, transition dyspnoea index; tio, tiotropium; TSANZ, Thoracic Society of Australia and New Zealand

Notes: a Karabis et al 2013 only presented comparisons with aclidinium. b Tricco et al 2015 included other drug classes in the indirect comparisons (e.g. LABA, ICS/LABA). Only results for LAMAs are reported here. c Reported for head-to-head trials with tiotropium.

Source: Ismail et al 2015 Text 2497, Table 1 pg 2499 ; Karabis et al 2013 Text 407-408, Table 1 pg 410 ; Ni et al 2014 Text pg 9, 20; Oba and Lorne 2015 Text pg 2-3, Table 1 pg 5 ; Tricco et al 2015 text pg 2-3 and Appendix 10

3.2.3.2 Patient characteristics

Patient characteristics of RCTs included in the SRs are summarised in Table 3.4. Patient characteristics have been summarised for each intervention to investigate whether there were any differences in baseline patient characteristics and concomitant medications for RCTs of different LAMAs. Comparisons of patient characteristics for different interventions are important considering the indirect NMA methodology used to compare interventions. Further details of patient and study characteristics of tiotropium RCTs included in the SRs are presented in Appendix 3.

The mean age and percentage of males was broadly similar between studies comparing different interventions. The mean age of participants in the included RCTs was 60 to 67 years and the majority male (range 49% to 98%).

Mean baseline disease severity of included RCTs was reported in two SRs (Ismaila et al 2015; Karabis et al 2013). Patient disease severity varied between RCTs of different interventions. RCTs comparing tiotropium vs placebo and glycopyrronium vs placebo or tiotropium included patients with a broad range of COPD disease severity with RCTs reporting mean FEV_1 %predicted of 35 to 37% (i.e. severe COPD) to 55 to 56% (i.e. moderate COPD). Ismaila et al (2015) noted that more tiotropium RCTs were in a more severe patient population compared with glycopyrronium trials. RCTs of aclidinium and umeclidinium and placebo were in a more restricted patient population with RCTs reporting mean FEV_1%predicted in the moderate severity range (aclidinium vs placebo: 47 to 56%; umeclidinium vs placebo: 45 to 48%).

Background medications allowed in RCTs was reported in three SRs (Ismaila et al 2015; Karabis et al 2013; Ni et al 2014). Due to the limited information reported in the SRs, only the extent of concomitant ICS, LABA and theophylline is summarised in Table 3.4. All RCTs permitted concomitant ICS use (two tiotropium vs placebo trials did not report concomitant medication use). However, only placebo-controlled tiotropium trials allowed background use of LABAs (5 RCTs including 9,224 patients) and theophylline (9 to 11 RCTs). RCTs of glycopyrronium, aclidinium and umeclidinium were much more restrictive in the background treatments allowed during the trials. In this regard, many placebo-controlled tiotropium studies investigated tiotropium as add-on to *usual care* therapy and can be considered more applicable to real-world clinical practice. Further discussion of background medications allowed and study design of placebo-controlled tiotropium RCTs is presented in Section 3.2.4 (tiotropium vs usual care therapy).

Table 3.4 Patient characteristics of RCTs included in tiotropium vs other LAMA systematic reviews

Study	N trials	Age (years, mean)	Gender (% male, range)	COPD severity (FEV_1 %predicted mean)	Background medications allowed (N trials)
Ismaila et al 2015					
Tiotropium 18 µg vs placebo	14	60 to 67	49 to 98	35% to 55%	ICS (12[a]) LABA (5) Theophylline (9)
Aclidinium v placebo	3	62 to 65	50 to 69	50% to 56%	ICS (3) Theophylline (3)
Glycopyrronium vs placebo and/or tiotropium 18 µg	5	63 to 64	63 to 83	37% to 56%	ICS (5)
Umeclidinium vs placebo	2	62 to 64	64 to 71	45% to 48%	ICS (2)
Karabis 2013					
Tiotropium 18 µg vs placebo	13	60 to 68	49 to 99	35% to 56%	ICS (11[a]) LABA (5) Theophylline (8)
Tiotropium Respimat vs placebo	3	63 to 65	69 to 78	38 to 42%	ICS (3) LABA (1) Theophylline (3)
Glycopyrronium vs placebo and/or tiotropium 18 µg	2	64	63 to 83	NR	ICS (2)
Aclidinium vs placebo	3	62 to 65	50 to 69	48 to 52%	ICS (3)
Ni 2014					
Tiotropium 18 µg vs aclidinium	2	62 to 63	67 to 88	NR	ICS (2)
Oba and Lorne 2015					
Tiotropium 18 µg vs placebo	14	62 to 67	54 to 99	36% to 55%	NR
Tiotropium Respimat vs placebo and/or tiotropium 18 µg	3	65	72 to 78	38 to 48	NR
Aclidinium v placebo	4	62 to 64	53 to 71	47% to 53%	NR
Glycopyrronium vs placebo and/or tiotropium 18 µg	6	63 to 69	64 to 98	37% to 56%	NR
Tricco et al 2015					
All comparators		≥18 years (93.8) 18 to 64 years (1.9) NR (4.3)	42% to 100%	Mild to moderate (4.8) Mild to severe (4.3) Mild to very severe (3.8) Moderate (3.4) Moderate to severe (28.9) Moderate to very severe (32.2) Severe (2.4)	NR

Study	N trials	Age (years, mean)	Gender (% male, range)	COPD severity (FEV_1 %predicted mean)	Background medications allowed (N trials)
				Severe to very severe (2.9) Stable (2.4) NR (14.9)	

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; NR, not reported; tio, tiotropium

Source: Ismail et al 2015 Table 1 pg 2499, Table 2 pg 2501 ; Karabis et al 2013 Table 1 pg 410, Table 2 pg 413 ; Ni et al 2014 Text pg 57, 60; Oba and Lorne 2015 Table 1 pg 5 ; Tricco et al 2015 Table 2 pg 5

a Two studies did not report ICS use

3.2.3.3 Results

Lung function, QoL and Symptoms

Base case meta-analyses for trough FEV_1, SGRQ and TDI are presented in Table 3.5, Table 3.6 and Table 3.7. Results of Tiotropium RCTs included in the meta-analyses are presented in Appendix 3. Two NMAs specifically examined the relative efficacy of different LAMAs on lung function (trough FEV_1), QoL (SGRQ) and symptoms (TDI) (Ismaila et al 2015; Karabis et al 2013). Both NMAs only presented results at 12 and 24 weeks as these were the most frequently reported timepoints for these outcomes. While Ismaila et al 2015 is the most recent study, the results of the analysis are limited as the study did not include trials of tiotropium Respimat. Therefore, the results of an older NMA (Karabis et al 2013) which included both tiotropium HandiHaler 18 µg and Respimat 5 µg are also presented. Note, however, that Karabis et al 2013 only presented results of tiotropium vs aclidinium. Similarly, the Cochrane review by Ni et al 2014 also presented meta-analysis of two head-to-head tiotropium vs aclidinium trials for the outcome of trough FEV_1.

Overall, results of the NMAs showed that tiotropium HandiHaler and Respimat were similar to other LAMAs in terms of trough FEV_1, overall SGRQ score and overall TDI score. There were no statistical differences between tiotropium and other LAMAs for most comparisons presented. In the SR by Ismaila et al 2015, the authors reported a small but statistically significant improvement in trough FEV_1 and overall SGRQ at 24 weeks, and overall TDI score at 12 and 24 weeks for glycopyrronium compared with tiotropium HandiHaler 18 µg. The authors suggested that this difference may be due to patients in glycopyrronium RCTs having less severe COPD disease at baseline compared with patients in tiotropium RCTs, however, the authors did not present any sensitivity or regression analysis to test this (see discussion below). For the SR by Karabis et al 2013, base case results showed aclidinium had a small but statistically significantly improvement in SGRQ score at 24 weeks compared with tiotropium Respimat 5 µg. This result was not statistically significant in scenario analysis which excluded tiotropium studies allowing concomitant LABA use. Tiotropium and aclidinium also showed similar improvements in SGRQ in analysis with the aclidinium ACCORD II trial included in the analysis.

Table 3.5 Tiotropium vs other LAMAs base case results: trough FEV_1

Outcome/comparator	Result mL, MD (95%CrI) [a]	Systematic review interpretation
Ismaila et al 2015		
12 weeks		
Aclidinium vs Tiotropium 18 µg	-12.80 (-39.39, 13.93)	NS
Glycopyrronium vs Tiotropium 18 µg	3.08 (-7.58, 13.69)	NS
Umeclidinium vs Tiotropium 18 µg	22.58 (-11.58, 56.97)	NS
24 weeks		
Aclidinium vs Tiotropium 18 µg	21.74 (-23.43, 66.88)	NS
Glycopyrronium vs Tiotropium 18 µg	29.46 (19.75, 38.96)	Significant for comparator [b]
Umeclidinium vs Tiotropium 18 µg	8.59 (-33.33, 50.45)	NS
Karabis et al 2013		
12 weeks		
Aclidinium vs Tiotropium 5 µg	-10 (-60, 50)	NS
Aclidinium vs Tiotropium 18 µg	0 (-30, 30)	NS
24 weeks		
Aclidinium vs Tiotropium 5 µg	20 (-50, 90)	NS
Aclidinium vs Tiotropium 18 µg	20 (-50, 80)	NS
Ni et al 2014		
6 weeks		
Aclidinium vs Tiotropium 18 µg	40 (-10, 90)	NS

Abbreviations: CrI, credible interval; FEV_1, forced expiratory volume in 1 second; LAMA, long-acting muscarinic antagonist; MD, mean difference; NS, non-significant

Source: Ismail et al 2015 Figure 3 pg 2505; Karabis et al 2013 Figure 3 pg 418; Ni et al 2014 Text pg 21

a Confidence interval for results reported in Ni et al 2014

b Differences in baseline disease severity and background medication use, in placebo-controlled trials, and use of open-label tiotropium in head-to-head trials are likely to bias the result. See discussion.

Table 3.6 Tiotropium vs other LAMAs base case results: SGRQ

Outcome/comparator	Result MD (95%CrI)	Systematic review interpretation
Ismaila et al 2015		
12 weeks		
Aclidinium vs Tiotropium 18 µg	-0.19 (-1.76, 1.36)	NS
Glycopyrronium vs Tiotropium 18 µg	-0.25 (-1.07, 0.56)	NS
Umeclidinium vs Tiotropium 18 µg	-1.92 (-4.08, 0.24)	NS
24 weeks		
Aclidinium vs Tiotropium 18 µg	-2.17 (-4.38, 0.03)	NS
Glycopyrronium vs Tiotropium 18 µg	-0.71 (-1.28, -0.15)	Significant for comparator [a]
Umeclidinium vs Tiotropium 18 µg	-2.26 (-4.68, 0.17)	NS
Karabis et al 2013		
12 weeks		
Aclidinium vs Tiotropium 5 µg	NA	NA
Aclidinium vs Tiotropium 18 µg	-1.02 (-2.84, 0.80)	NS
24 weeks		
Aclidinium vs Tiotropium 5 µg	-2.44 (-4.82, -0.05)	Significant for comparator [a]
Aclidinium vs Tiotropium 18 µg	-1.80 (-4.52, 0.14)	NS

Abbreviations: CrI, credible interval; LAMA, long-acting muscarinic antagonist; MD, mean difference; NA, not applicable; NS, non-significant; SGRQ, St George Respiratory Questionnaire

Source: Ismail et al 2015 Figure 3 pg 2505, Table S6 pg 2516; Karabis et al 2013 Figure 3 pg 418

a Differences in baseline disease severity and background medication use, in placebo-controlled trials, and use of open-label tiotropium in head-to-head trials are likely to bias the result. See discussion.

Table 3.7 Tiotropium vs other LAMAs base case results: TDI

Outcome/comparator	Result MD (95%CrI)	Systematic review interpretation
Ismaila et al 2015		
12 weeks		
Aclidinium vs Tiotropium 18 µg	0.21 (-0.16, 0.59)	NS
Glycopyrronium vs Tiotropium 18 µg	0.18 (0.04, 0.33)	Significant for comparator [a]
Umeclidinium vs Tiotropium 18 µg	0.16 (-0.30, 0.63)	NS
24 weeks		
Aclidinium vs Tiotropium 18 µg	0.18 (-0.44, 0.80)	NS
Glycopyrronium vs Tiotropium 18 µg	0.19 (0.03, 0.35)	Significant for comparator [a]
Umeclidinium vs Tiotropium 18 µg	0.18 (-0.36, 0.73)	NS
Karabis et al 2013		
12 weeks		
Aclidinium vs Tiotropium 5 µg	NA	NA
Aclidinium vs Tiotropium 18 µg	0.16 (-0.31, 0.63)	NS
24 weeks		
Aclidinium vs Tiotropium 5 µg	NA	NA
Aclidinium vs Tiotropium 18 µg	0.08 (-0.53, 0.68)	NS

Abbreviations: CrI, credible interval; LAMA, long-acting muscarinic antagonist; MD, mean difference; NA, not applicable; NS, non-significant; TDI, transition dyspnoea index

Source: Ismail et al 2015 Figure 3 pg 2505, Table S6 pg 2516; Karabis et al 2013 Figure 3 pg 418

a Differences in baseline disease severity and background medication use, in placebo-controlled trials, and use of open-label tiotropium in head-to-head trials are likely to bias the result. See discussion.

Exacerbations

Two NMAs reported the comparative efficacy of different LAMAs on exacerbations (Oba and Lorne 2015; Tricco et al 2015). The SR by Oba and Lorne 2015 compared Tiotropium (HandiHaler and Respimat), and other LAMAs (glycopyrronium and aclidinium) in reducing moderate to severe and severe exacerbations. There were no significant differences between tiotropium and other LAMAs in preventing exacerbations (Table 3.8). However, the authors noted that tiotropium was the only LAMA to show a statistically significant reduction in severe exacerbations compared with placebo. Meta-regression adjusting for the percentage of concomitant use of ICS, proportion of active smokers, FEV_1 at baseline, concomitant use of LABA showed similar results. However, the authors found that the relative reduction in exacerbations by LAMAs was greater in studies which prohibited concomitant use of LABA as compared with those that allowed it.

Tricco et al 2015 did not present a network meta-analysis for patients with moderate to severe exacerbations due to inconsistency observed between direct and indirect evidence. A subgroup analysis was presented for RCTs which only included patients that had experienced exacerbations within the past year. Data was not available for this subgroup for aclidinium and umeclidinium and so only a comparison of tiotropium (HandiHaler and Respimat) and glycopyrronium was presented. There were no significant differences between tiotropium HandiHaler, Respimat and glycopyrronium in preventing moderate to severe exacerbations (Table 3.8).

Table 3.8 Tiotropium vs other LAMAs base case results: COPD Exacerbations

Outcome/comparator	Result Estimate (95%CI) [a]	Systematic review interpretation
Oba and Lorne 2015		
Moderate to severe exacerbations (HR)		
Aclidinium vs Tiotropium 18 µg	1.05 (0.81, 1.34)	NS
Glycopyrronium vs Tiotropium 18 µg	0.96 (0.80, 1.16)	NS
Tiotropium 5 µg vs Tiotropium 18 µg	0.90 (0.71, 1.13)	NS
Aclidinium vs Tiotropium 5 µg	1.17 (0.85, 1.60)	NS
Glycopyrronium vs Tiotropium 5 µg	1.07 (0.80, 1.43)	NS
Severe exacerbations (HR)		
Aclidinium vs Tiotropium 18 µg	0.80 (0.40, 1.64)	NS
Glycopyrronium vs Tiotropium 18 µg	1.11 (0.78, 1.54)	NS
Tiotropium 5 µg vs Tiotropium 18 µg	1.06 (0.81, 1.41)	NS
Aclidinium vs Tiotropium 5 µg	0.75 (0.37, 1.58)	NS
Glycopyrronium vs Tiotropium 5 µg	1.05 (0.67, 1.58)	NS
Tricco et al 2015		
Moderate to severe exacerbations (OR)		
Tiotropium 5/18 µg vs Aclidinium	NA	NA
Tiotropium 5/18 µg vs Glycopyrronium	0.85 (0.68, 1.05)	NS
Tiotropium 5/18 µg vs Umeclidinium	NA	NA
Ni et al 2014		
Exacerbations requiring medication (OR)		
Aclidinium vs Tiotropium 18 µg	2.64 (0.31, 22.18)	NS
Exacerbation hospitalisations (OR)		
Aclidinium vs Tiotropium 18 µg	0.54 (0.07, 4.11)	NS

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LAMA, long-acting muscarinic antagonist; NA, not applicable; NS, non-significant; OR, odds ratio

Source: Ni et al 2014 text pg 20-21; Oba and Lorne 2015 Table 2 pg 8; Tricco et al 2015 Appendix 10

a Credible interval for Oba and Lorne 2015

Mortality and Adverse events

Mortality

Tricco et al 2015 compared the effect of different LAMAs on mortality (Table 3.9). Comparisons were reported separately for HandiHaler and Respimat formulations. The SR reported no statistically significant differences between tiotropium (HandiHaler or Respimat) and other LAMAs for all-cause mortality or cardiovascular mortality. There was also no statistically significant difference between tiotropium HandiHaler compared with tiotropium Respimat for all-cause mortality (OR 1.01; 95%CI: 0.82, 1.24) and cardiovascular mortality (OR 1.16; 95%CI: 0.89, 1.50). Sensitivity analyses, in which only trials with a low risk of bias were included, showed similar results.

Adverse events

AEs were reported by Tricco et al 2015 and Ni et al 2014 (Table 3.9). Tricco et al 2015 found no statistically significant difference between tiotropium and other LAMAs for pneumonia or cardiac arrhythmia. Ni et al 2014 also reported no statistically significant differences between tiotropium and aclidinium for SAEs and withdrawals due to AEs.

Table 3.9 Tiotropium vs other LAMAs: Mortality and AEs

Outcome	Result OR (95%CI)	Interpretation
Tricco et al 2015		
All-cause mortality		
Tiotropium 18 µg vs Aclidinium	1.31 (0.55, 3.11)	NS
Tiotropium 5 µg vs Aclidinium	1.32 (0.54, 3.22)	NS
Tiotropium 18 µg vs Glycopyrronium	1.28 (0.78, 2.11)	NS
Tiotropium 5 µg vs Glycopyrronium	1.30 (0.75, 2.23)	NS
Tiotropium 5 µg vs Tiotropium 18 µg	1.01 (0.82, 1.24)	NS
Umeclidinium vs Tio 18 µg	1.17 (0.28, 4.87)	NS
Umeclidinium vs Tiotropium 5 µg	1.16 (0.28, 4.90)	NS
Cardiovascular mortality		
Tiotropium 18 µg vs Aclidinium	0.41 (0.02, 10.43)	NS
Tiotropium 5 µg vs Aclidinium	0.48 (0.02, 12.12)	NS
Tiotropium 18 µg vs Glycopyrronium	5.36 (0.44, 65.17)	NS
Tiotropium 5 µg vs Glycopyrronium	6.21 (0.51, 76.08)	NS
Tiotropium 5 µg vs Tiotropium 18 µg	1.16 (0.89, 1.50)	NS
Umeclidinium vs Tiotropium 18 µg	0.89 (0.07, 10.81)	NS
Umeclidinium vs Tiotropium 5 µg	0.77 (0.06, 9.41)	NS
Pneumonia		
Tiotropium 5/18 µg vs Aclidinium	1.40 (0.65, 3.01)	NS
Tiotropium 5/18 µg vs Glycopyrronium	1.15 (0.80, 1.67)	NS
Umeclidinium vs Tiotropium 5/18 µg	0.78 (0.12, 5.23)	NS
Cardiac arrhythmia		
Tiotropium 5/18 µg vs Aclidinium	1.04 (0.36, 3.00)	NS
Tiotropium 5/18 µg vs Glycopyrronium	0.77 (0.36, 1.68)	NS
Umeclidinium vs Tiotropium 5/18 µg	NA	
Ni et al 2014		
All-cause mortality		
Aclidinium vs Tiotropium 18 µg	No deaths reported	Not estimable
Serious AEs		
Aclidinium vs Tiotropium 18 µg	0.67 (0.17 to 2.65)	NS
Withdrawals due to AEs		
Aclidinium vs Tiotropium 18 µg	0.94 (0.26 to 3.42)	NS

Abbreviations: AE, adverse event; CI, confidence interval; LAMA, long-acting muscarinic antagonist; NS, non-significant; OR, odds ratio

Source: Ni et al 2014 summary pg 22-23; Tricco et al 2015 Appendix 10

3.2.3.4 Discussion

Results of the SRs presented in this submission showed that tiotropium had similar efficacy and safety to other LAMAs in terms of trough FEV_1, overall SGRQ score, overall TDI score, exacerbations, mortality and adverse events. In terms of FEV_1, SGRQ and TDI, the results of the NMAs are consistent with the PBAC's assessment that the LAMAs are non-inferior in terms of efficacy and safety.

Overall, results of the NMAs by Ismaila et al 2015 and Karabis et al 2013 showed that tiotropium HandiHaler 18 µg and Respimat 5 µg were similar to other LAMAs in terms of trough FEV_1, overall SGRQ score and overall TDI score for most comparisons. However, in the NMA by Ismaila et al 2015, the authors reported a small but statistically significant improvement in trough FEV_1, mean SGRQ score and TDI favouring glycopyrronium compared with tiotropium HandiHaler. There are several reasons for this finding. The authors suggested that tiotropium RCTs were in a more severe patient population compared with glycopyrronium trials. As such, the magnitude of improvement in patients with more severe disease is lower compared with patients with moderate disease (Tashkin 2013). As noted above, patients in many placebo-controlled tiotropium trials were permitted access to usual-care respiratory medicines which reflects real-life treatment practice whereas trials of other LAMAs were often more restricted in the background respiratory medicines permitted. Subgroup analysis of UPLIFT (a 4-year RCT comparing tiotropium with usual care (Tashkin et al 2008)) showed that patients that were naïve to maintenance treatment at baseline had higher rates of trough FEV_1 decline compared with the overall cohort (Troosters et al 2010). Consequently, tiotropium had a greater effect in reducing trough FEV_1 decline and improving QoL compared with placebo in patients that were treatment naïve at baseline (Troosters et al 2010). This demonstrates that permitting usual-care background medication impacts the relative efficacy of tiotropium due to a slower rate of disease progression in the placebo arm. Ismaila et al 2015 did not present any sensitivity or regression analysis to explore the impact of disease severity or concomitant medications on the base case results. Furthermore, pair-wise meta-analyses from the head-to-head trials of tiotropium and glycopyrronium were not presented so the consistency between the head-to-head trials and the NMA was unclear. It should also be noted that in most head-to-head trials with glycopyrronium, the tiotropium arm was open-label (e.g. GLOW2, GLOW4, SHINE) and have a higher risk of bias, particularly for patient-reported outcomes such as QoL. The only trial with a blinded comparison between tiotropium and glycopyrronium (GLOW5, Chapman et al 2014) showed no difference in lung function (MD 4 mL (SE 15.1) see Appendix 3). In addition, for the only trial to compare tiotropium and glycopyrronium with severe exacerbations requiring hospitalisations as a primary outcome (SPARK, Wedzicha et al 2013), patients treated with glycopyrronium had significantly increased severe exacerbations compared with tiotropium (RR 1.43; 95%CI: 1.05, 1.97). This suggests that tiotropium has additional benefits in preventing exacerbations. Finally, recent meta-analyses assessed by the PBAC of the same head-to head trials of tiotropium and glycopyrronium showed no significant differences for trough FEV_1 (Glycopyrronium PSD November 2013). Overall, the NMAs demonstrated similar efficacy of tiotropium and other LAMAs in terms of trough FEV_1, overall SGRQ score and overall TDI score. This is consistent with previous PBAC evaluations of LAMA therapies (Glycopyrronium PSD November 2013; Aclidinium PSD March 2014; Umeclidinium PSD July 2014).

The NMAs by Oba and Lorne 2015 and Tricco et al 2015 showed no significant differences between tiotropium and other LAMAs in preventing moderate to severe or severe exacerbations. However,

Oba and Lorne 2015 noted that tiotropium was the only LAMA to show a statistically significant reduction in severe exacerbations compared with placebo. As noted above, patients treated with tiotropium had significantly fewer severe exacerbations compared with glycopyrronium (Wedzicha et al 2013). Furthermore, as described in Table 3.3, trials including tiotropium accounted for 86% to 91% of patients included in the NMAs. As such, there is greater confidence in the treatment benefit of tiotropium in preventing exacerbations compared with other LAMAs. Furthermore, tiotropium was the only LAMA with RCTs included in the NMAs demonstrating a reduction in COPD exacerbation over duration greater than 18 months (e.g. UPLIFT 4-years duration (Tashkin et al 2008). In contrast, the long-term efficacy of other LAMAs is uncertain. Oba and Lorne 2015 also noted that the relative reduction in exacerbations by tiotropium was greater in RCTs which prohibited concomitant use of LABA as compared with those that allowed it. As highlighted above, this is expected as trials permitting concomitant LABA are able to more aggressively prevent exacerbations and there is a slower rate of disease progression in the placebo arm.

The effect of tiotropium and other LAMAs on all-cause and cardiovascular mortality was also similar with no significant differences observed between the treatments. Importantly, there was no difference in mortality between the different formulations of tiotropium (HandiHaler and Respimat). This finding was primarily driven by the TIOSPIR trial (Wise 2013), which followed 17,135 patients over mean 2.3 years and showed that patients treated with tiotropium HandiHaler 18 µg and Respimat 5 µg have a similar risk of all-cause mortality. The results of the NMA by Tricco et al 2015 confirms the PBAC's previous evaluation that tiotropium HandiHaler 18 µg and Respimat 5 µg are equivalent.

Tricco et al 2015 also investigated pneumonia and cardiac arrhythmia; AEs more associated with LABA and ICS treatment. No significant differences observed between tiotropium and other LAMAs, which suggests that the LAMAs have a similar safety profile.

In summary, results of NMAs show similar efficacy and safety for tiotropium compared with other LAMAs. The clinical evidence in consistent with the economic evaluations which indicate that overall, tiotropium is similarly cost-effective to comparator LAMA therapies (see Section 3.5). Tiotropium had the most substantial body of evidence among the LAMAs, demonstrating a reduction in exacerbations, as well as improved lung function, QoL and symptoms. In terms of FEV_1, SGRQ and TDI, the results of the NMAs are consistent with recent PBAC assessments that aclidinium, glycopyrronium and umeclidinium are non-inferior to tiotropium (equi-effective doses: tiotropium HandiHaler 18 µg once daily, tiotropium Respimat 5 µg once daily, glycopyrronium 50 µg once daily, aclidinium 400 µg twice daily, umeclidinium 62.5 µg once daily).

3.2.4 Tiotropium vs usual care

The aim of this section is to summarise the most recent evidence comparing tiotropium with usual care. As discussed above, usual care is an important comparator as the efficacy and safety of tiotropium can be assessed in real-world conditions representative of Australian clinical practice. Furthermore, RCTs of tiotropium add-on to usual care therapy are used to inform cost-effectiveness over the long term (see Section 3.5) as well as the indirect comparisons with other LAMAs. The literature search identified the recent Cochrane review by Karner et al 2014 comparing tiotropium and placebo. As discussed further below, most tiotropium RCTs identified in the Karner et al 2014 were designed with tiotropium as add-on to *usual-care* therapy. Therefore, the Cochrane review by Karner et al 2014 is the most recent, high quality SR of RCTs directly comparing tiotropium with usual-care and provides the primary evidence comparing tiotropium with usual-care.

3.2.4.1 Study characteristics

The study characteristics of Karner et al 2014 are summarised in Table 3.10. Karner et al 2014 aimed to assess the RCT evidence comparing the efficacy and safety of tiotropium (HandiHaler 18 µg or Respimat 5 or 10 µg) with placebo in patients with COPD, using clinically important endpoints (e.g. QoL, exacerbations, hospitalisations, mortality, trough FEV_1, SAEs, withdrawals). The SR identified 22 RCTs of three months or longer, which included 23,309 participants with COPD. All included studies were meta-analysed where possible. Subgroup analyses were also presented by disease severity at baseline, formulation (HandiHaler or Respimat), concomitant medication and study duration. The SR was rated as high quality (AMSTAR rating 11).

Table 3.10 Study characteristics of Karner et al 2014

Citation	Treatments evaluated (dose/day)	No. of trials/sample size included in the analysis	Summary of main population characteristics	Duration of included trials	Outcomes	AMSTAR quality rating (0 to 11)	Analysis
Karner et al 2014	Tiotropium (Respimat 5 mg and 10 mg; HandiHaler 18 mg) Placebo/usual care	22/23,309	COPD External set of criteria used to screen participants (e.g. GOLD, ATS, BTS, TSANZ)	12 weeks to 4 years	QoL (SGRQ and EQ-5D) Exacerbations Hospitalisations Mortality Trough FEV_1 SAEs Withdrawals	11	Meta-analysis, fixed-effects. Subgroup analysis by disease severity at baseline, formulation (HandiHaler or Respimat), concomitant medication and study duration

Abbreviations: ATS, American Thoracic Society; BTS, British Thoracic Society; COPD, chronic obstructive pulmonary disease; EQ-5D, EuroQol five dimensions; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; QoL, quality of life; SGRQ, St George Respiratory Questionnaire; SAE, serious adverse event; TSANZ, Thoracic Society of Australia and New Zealand

Source: Karner et al 2014 Text pg 6, 10

3.2.4.2 Patient characteristics

Patient characteristics of the included RCTs in Karner et al 2014 are summarised in Table 3.11. Further details of patient and study characteristics of tiotropium RCTs are presented in Appendix 3. The majority of included trials were assessed as having a low risk of bias and the authors noted that included studies were of high methodological quality. The duration of studies ranged from 12 weeks to 4 years (UPLIFT, Tashkin et al 2008). The mean age of participants in the included trials was 60 to 68 years and the majority were male (range 60% to 98%) (Table 3.11). Mean baseline severity varied between trials from FEV_1 less than 50% (i.e. severe COPD) to 66% (moderate COPD). The majority of studies permitted access to other respiratory medications, with the exception of other anticholinergics. As discussed above, the majority of RCTs included in Karner et al 2014 are designed with tiotropium as add-on to *usual-care* therapy. Among the 22 studies included in the meta-analyses, eight studies specified that they *did not* allow LABAs, three did not allow antileukotrienes and two did not allow ICS or ICS/LABA combination inhalers.

Table 3.11 Summary of population characteristics from Karner et al 2014

Age (years, mean)	Gender (% male, range)	COPD severity (mean FEV_1 %predicted)	Concomitant medications allowed (N trials) a
60 to 68	60% to 98%	<50% to 66%	SABA: 22 LABA: 14 ICS: 20 Antileukotriene: 19

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; SABA, short-acting β2-agonist

Source: Karner et al 2014 Text pg 10

Notes: a Karner et al 2014 reported medications that were not allowed

3.2.4.3 Results

The results of the base case meta-analyses comparing tiotropium to usual-care therapy are summarised in Table 3.12. Results of Tiotropium RCTs included in the meta-analyses are presented in Appendix 3.

QoL

QoL was assessed using the SGRQ in nine studies. Treatment with tiotropium significantly improved QoL compared with usual care (mean difference (MD) -2.89; 95%CI: -3.35, -2.44). Significantly more patients treated with tiotropium experienced a clinically significant improvement in QoL (greater than 4 units) compared with usual care (OR 1.52; 95%CI: 1.38, 1.68) whereas significantly fewer patients experienced a decline in QoL (OR 0.65; 95%CI: 0.59, 0.72). Subgroup analysis showed that there was a similar treatment benefit in patients with different disease severity (i.e. FEV_1 more or less than 50%), and patients with and without background ICS use.

Exacerbations and hospitalisations

All included studies reported COPD exacerbations. Treatment with tiotropium significantly reduced the number of patients experiencing exacerbations compared with usual care (OR 0.78; 95%CI: 0.70, 0.87). In addition, tiotropium significantly reduced the number of patients experiencing

exacerbations leading to hospitalisation compared with usual care (OR 0.85; 95%CI: 0.72, 1.00). There was no statistically significant difference between tiotropium and usual care for all-cause hospitalisations (OR 1.00; 95%CI: 0.88, 1.13).

Subgroup analysis showed that tiotropium had a similar treatment benefit in preventing exacerbations in patients with different disease severity (i.e. FEV_1 more or less than 50%), background ICS use, different formulations (HandiHaler or Respimat), study duration (greater or less than one year). This demonstrates that the treatment benefit of tiotropium in preventing exacerbations is applicable to a wide patient population likely to use tiotropium in clinical practice and is maintained over the longer term.

Mortality

All included studies reported mortality. The meta-analysis showed no statistically significant difference in all-cause mortality between tiotropium and usual care (Peto OR 0.98; 95%CI 0.86, 1.11). Subgroup analysis showed that patients treated with HandiHaler had a lower risk of death compared with usual care (Peto OR 0.92; 95%CI: 0.80, 1.05) whereas patients treated with Respimat were reported to have a higher risk of all-cause mortality (Peto OR 1.47; 95%CI: 1.04, 2.08). The authors noted that this result should be interpreted carefully in light of the results of the TIOSPIR study (Wise et al 2013). Results of the TIOSPIR study demonstrated that patients treated with Respimat and HandiHaler have a similar risk of all-cause mortality. Karner et al 2014 noted that TIOSPIR provides the *least* biased evidence available and has allayed some of the concerns of differences in mortality between the delivery devices.

Trough FEV_1

All included studies reported change from baseline in trough FEV_1. Treatment with tiotropium significantly improved trough FEV_1compared with usual care (MD 118.92 mL; 95%CI 113.07, 124.77).

SAEs and withdrawals

All included studies reported SAEs and withdrawals. There was no statistically significant difference in SAEs between tiotropium and usual care groups (OR 1.03; 95%CI: 0.97, 1.10). There were significantly fewer withdrawals in patients treated with tiotropium compared with usual care (OR 0.66; 95%CI: 0.59, 0.73).

Table 3.12 Summary of results from Karner et al 2014

Outcome	N trials	Result (Tiotropium vs usual care) Estimate (95%CI)	Systematic review interpretation
QoL (SGRQ)			
Mean QoL (MD)	9	-2.89 (-3.35, -2.44)	Tiotropium superior
N clinically significant improvement (OR)	9	1.52 (1.38, 1.68)	Tiotropium superior
N clinically significant deterioration (OR)	9	0.65 (0.59, 0.72)	Tiotropium superior
Exacerbations			
Overall (OR)	22	0.78 (0.70, 0.87)	Tiotropium superior
Exacerbation hospitalisations (OR)	21	0.85 (0.72, 1.00)	Tiotropium superior
Trough FEV_1, mL (MD)	22	118.92 (113.07, 124.77)	Tiotropium superior
All-cause hospitalisations(OR)	19	1.00 (0.88, 1.13)	NS
All-cause mortality (OR)	22	0.98 (0.86, 1.11)	NS
SAEs (OR)	22	1.03 (0.97, 1.10)	NS
Withdrawals (OR)	22	0.66 (0.59, 0.73)	Tiotropium superior

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; MD, mean difference; NS, non-significant; OR, odds ratio; QoL, quality of life; SGRQ, St George Respiratory Questionnaire; SAE, serious adverse event

Source: Karner et al 2014 Summary pg 3-4

3.2.4.4 Discussion

The aim of this section was to assess the efficacy and safety of tiotropium compared with usual care therapy. The majority of RCTs included in Karner et al 2014 were designed with tiotropium as add-on to usual-care therapy, with patients permitted access to other respiratory medicines including ICS and LABAs. The results of Karner et al 2014 showed that tiotropium was superior to usual care in preventing exacerbations and hospitalisations due to exacerbations as wells as improving QoL, FEV_1 and symptoms. These results demonstrate the benefits of tiotropium in settings which are representative of real-world clinical practice.

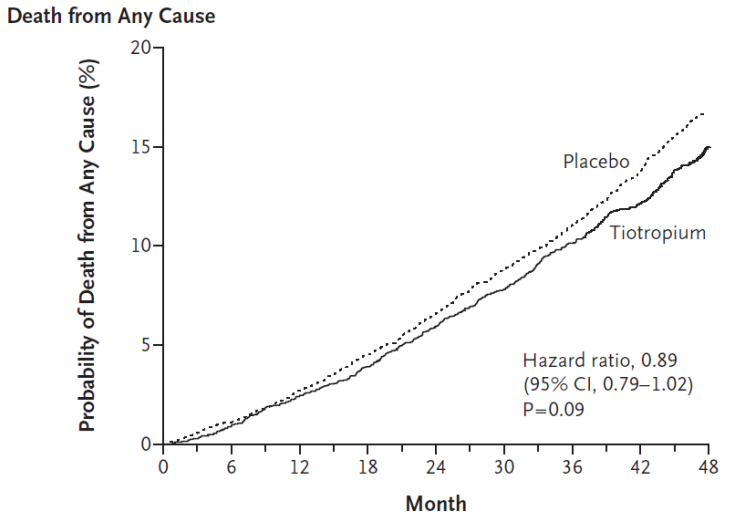
The results of Karner et al 2014 also demonstrate that tiotropium has efficacy in a wide patient population with COPD. Subgroup analysis consistently showed that tiotropium had a similar treatment benefit in patients with different disease severity, background medication, different formulations (HandiHaler or Respimat), and study duration (greater or less than one year). This demonstrates that the treatment benefit of tiotropium is applicable to a wide patient population likely to use tiotropium in clinical practice. The results of Karner et al 2014 are consistent with the recommendations of clinical practice guidelines for the use of tiotropium in COPD. As discussed in ToR 1, COPD-X Plan recommends tiotropium as maintenance treatment as well as for exacerbation prevention. GOLD Guidelines also recommend tiotropium as a first choice treatment for patients with moderate COPD at low risk of exacerbation and patients with more severe disease at high risk of exacerbations.

The meta-analyses presented by Karner et al 2014 showed that tiotropium was superior to usual care in preventing exacerbations and hospitalisations due to exacerbations. Exacerbations and

associated hospitalisations are associated with a substantial decrease in QoL and increase in healthcare costs. Therefore, the results of Karner et al 2014 support the economic evaluations presented in the Section 3.5 which demonstrate that tiotropium is a cost-effective treatment for COPD. The results presented in Karner et al 2014 are consistent with a very recent review that specifically examined the efficacy of tiotropium on COPD exacerbations (Halpin et al 2016). Halpin et al 2016 presented a descriptive analysis of tiotropium RCTs for which exacerbations were a *prespecified endpoint* (meta-analyses were not included due to differences in the definitions of exacerbation events used). Halpin et al 2016 showed that tiotropium consistently reduced exacerbations and associated hospitalisations compared with usual care. In addition, treatment with tiotropium prolonged the time to first exacerbation and first hospitalisation.

As highlighted above, subgroup analysis showed that tiotropium had a treatment benefit in trials with duration greater than one year. The meta-analysis by Karner et al 2014 included the UPLIFT trial; a 4-year multicentre, double-blind trial comparing tiotropium with placebo (usual care) in patients with moderate to severe COPD (Tashkin et al 2008). Over 4 years, tiotropium significantly delayed the time to first exacerbation (HR 0.86, 95%CI: 0.81, 0.91), first hospitalisation due to exacerbations (HR 0.86, 95%CI: 0.78, 0.95), as well as the overall mean number of exacerbations (RR 0.86, 95%CI: 0.81, 0.91). Tiotropium also reduced the risk of mortality compared with usual care over 4 years. Among patients with vital status information, fewer patients in the tiotropium group died (14.4%) compared with the placebo group (16.3%; HR 0.87; 95%CI: 0.76, 0.99). In the intent-to-treat analysis, 14.9% in the tiotropium group died compared with 16.5% receiving usual care (HR 0.89; 95%CI: 0.79, 1.02; Figure 3.2).

Figure 3.2 Kaplan-Meier estimate of probabilities of all-cause mortality over 4 years



No. at Risk									
Tiotropium	2986	2948	2899	2851	2785	2721	2646	2574	2306
Placebo	3006	2961	2903	2836	2772	2696	2624	2523	2249

Abbreviations: CI, confidence interval

Source: Tashkin et al 2008

UPLIFT is the only trial to assess LAMA therapy over a 4-year timeframe in patients with COPD. UPLIFT provides the best evidence that tiotropium prevents exacerbations over the long term.

Patients in UPLIFT were permitted access to all respiratory medications, except other inhaled anticholinergic drugs, during the trial. As discussed above, the results of the trial are therefore representative of medical care in real-world practice, particularly in the event of an exacerbation where patients are likely to be more aggressively treated. Furthermore, as discussed in Section 3.5, results from UPLIFT demonstrate that tiotropium is a cost-effective treatment in preventing exacerbations over the long-term.

Overall, the results of the meta-analysis showed that patients treated with tiotropium had a similar risk of mortality to patients on a background of usual care. However the authors noted that UPLIFT (Tashkin et al 2008) was the only study to have mortality as a specified outcome, with a mortality adjudication committee evaluating the primary cause of death from blinded data. As discussed above, results from UPLIFT show that there were fewer deaths in patients treated with tiotropium compared with usual care. In addition, TIOSPIR, a large head-to-head RCT comparing tiotropium Respimat and HandiHaler showed comparable risk of mortality between the two delivery devices (Wise et al 2013). In TIOSPIR, 17,135 patients treated with tiotropium Respimat (2.5 µg or 5 µg) or HandiHaler 18 µg were followed-up for a mean of 2.3 years. Results of the TIOSPIR study demonstrated that patients treated with Respimat (2.5 µg or 5 µg) and HandiHaler 18 µg have a similar risk of all-cause mortality (HR 0.96; 95%CI: 0.84, 1.09). Karner et al 2014 noted that TIOSPIR provides the *least* biased evidence available that the risk of mortality is similar between the two devices.

TIOSPIR and UPLIFT included patients with a history of cardiac disease and stable heart failure, however, patients with recent and significant cardiac events were excluded. Subsequent post-hoc analysis from TIOSPIR also demonstrated that for patients with a cardiac event during the trial (cardiac arrhythmia, heart failure or myocardial infarction), there was no difference in mortality or serious cardiac events for patients treated with Respimat 5 µg and Tiotropium 18 µg (Wise et al 2015). Similarly, post-hoc analysis from UPLIFT showed that the risk of subsequent cardiac events, mortality or SAEs was not increased by tiotropium compared with placebo in patients experiencing an initial cardiac event during the trial (Tashkin et al 2015). Together, the results support the cardiac safety of tiotropium HandiHaler and Respimat and the applicability of the trial data to a broad patient population likely to receive tiotropium in clinical practice. The results are consistent with the PBAC's previous evaluation that tiotropium HandiHaler 18 µg and Respimat 5 µg are equivalent.

Results of the Cochrane review by Karner et al 2014 demonstrate that tiotropium has superior efficacy and similar safety compared with usual care. These results are applicable to patients likely to receive tiotropium in clinical practice. Importantly, tiotropium prevents exacerbations, associated hospitalisations and mortality over the long-term; events associated with substantial decrease in QoL and increase in healthcare costs. Therefore, the results support tiotropium as a cost-effective treatment option over the long-term (see Section 3.5).

3.2.5 Tiotropium vs ipratropium

Tiotropium was listed on the PBS in 2003 for the treatment of COPD based on superior efficacy and safety compared with ipratropium. As such, it is necessary to identify any new evidence confirming that tiotropium is still an effective option compared with ipratropium. The literature search identified the recent Cochrane review by Cheyne et al 2015 comparing tiotropium and ipratropium. This is the most recent, high quality SR of RCTs directly comparing tiotropium with ipratropium.

3.2.5.1 Study characteristics

Study characteristic of Cheyne et al 2015 are summarised in Table 3.13. Cheyne et al 2015 identified two RCTs for inclusion in the meta-analysis: Vincken et al 2002 compared HandiHaler 18 µg with ipratropium over 12 months; and Voshaar 2008 compared Respimat 5µg and 10µg with ipratropium over 12 weeks. Data were combined using meta-analysis, with subgroup analysis for different formulations used (HandiHaler or Respimat). The SR was rated as high quality (AMSTAR rating 11).

Table 3.13 Study characteristics of Cheyne et al 2015

Citation (Date of literature search)	Treatments evaluated (dose/day)	No. of trials/sample size included in the analysis	Summary of main population characteristics	Duration of included trials	Outcomes	AMSTAR quality rating (0 to 11)	Analysis
Cheyne et al 2015	Tiotropium (Respimat 5, 10 µg; HandiHaler 18 mg) Ipratropium MDI	2/1073	COPD External set of criteria used to screen participants (e.g. GOLD, ATS, BTS, TSANZ)	3 to 12 months	Trough FEV_1 SAEs Exacerbations Hospitalisations Mortality QoL (SGRQ) Symptoms (BDI, TDI) Withdrawals	11	Meta-analysis, fixed effects. Subgroup analysis for different formulations used (HandiHaler or Respimat)

Abbreviations: ATS, American Thoracic Society; BDI, baseline dyspnoea index; BTS, British Thoracic Society; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; QoL, quality of life; SGRQ, St George Respiratory Questionnaire; SAE, serious adverse event; TDI, transition dyspnoea index; TSANZ, Thoracic Society of Australia and New Zealand

Source: Cheyne et al 2015 Text pg 7, 10

3.2.5.2 Patient characteristics

Patient characteristics of the included studies in Cheyne et al 2015 are summarised in Table 3.14. Further details of patient and study characteristics of tiotropium RCTs are presented in Appendix 3. Both RCTs included patients with moderate to severe COPD, the mean age was 65 years and gender predominantly male (67 to 86%). ICS use was allowed whereas β2 agonists and other anticholinergics were disallowed. Both RCTs were assessed as having a low risk of bias.

Table 3.14 Summary of population characteristics of Cheyne et al 2015

Age (years, mean)	Gender (% male, range)	COPD severity (mean FEV_1 %predicted)	Concomitant medications allowed (N trials)
65	67 to 86	39 to 41	SABA (2) ICS (2)

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; SABA, short-acting β2-agonist

Source: Cheyne et al 2015 Text pg 10-11

3.2.5.3 Results

The results of the meta-analyses are summarised in Table 3.15. Results of Tiotropium RCTs included in the meta-analyses are presented in Appendix 3.

Trough FEV_1

Both RCTs reported change from baseline in trough FEV_1. Treatment with tiotropium significantly improved trough FEV_1 compared with ipratropium after three months treatment (MD 109 mL; 95%CI: 81, 137). The treatment effect was maintained over 12 months (MD 150 mL; 95%CI: 111, 190).

Exacerbations and hospitalisations

Both RCTs reported COPD exacerbations. Treatment with tiotropium significantly reduced the number of patients experiencing exacerbations compared with ipratropium (OR 0.71; 95%CI: 0.52, 0.95). In addition, tiotropium significantly reduced the number of patients experiencing exacerbations leading to hospitalisation compared with ipratropium (OR 0.56; 95%CI: 0.31, 0.99) as well as the number of patients requiring hospitalisation for any cause (OR 0.34; 95%CI: 0.15, 0.76).

QoL

QoL as measured by the SGRQ was reported in one study (Vincken et al 2002). Treatment with tiotropium significantly improved QoL compared with ipratropium (MD -3.30; 95%CI: -5.63, -0.97).

Mortality

Both RCTs reported all-cause mortality. There was no statistically significant difference in all-cause mortality between tiotropium and ipratropium (OR 1.39; 95%CI: 0.44, 4.39).

Symptoms

One RCT (Vincken et al 2002) reported the baseline dyspnoea index (BDI) and transition dyspnoea index (TDI). Treatment with tiotropium significantly improved TDI compared with ipratropium (0.90;

95%CI: 0.39, 1.41). There was no statistically significant difference between tiotropium and placebo for BDI (MD -0.28; 95%CI: -0.74, 0.18).

AEs and Withdrawals

Both RCTs reported SAEs and withdrawals. Treatment with tiotropium significantly reduced the number of patients experiencing SAEs compared with ipratropium (OR 0.50; 95%CI 0.34, 0.73). There were significantly fewer withdrawals in patients treated with tiotropium compared with ipratropium (OR 0.58; 95%CI: 0.41, 0.83).

Table 3.15 Summary of results from Cheyne et al 2015

Outcome	N trials	Result (Tiotropium vs ipratropium) Estimate (95%CI)	Systematic review interpretation
Trough FEV_1, mL (MD)			
3 months	2	109 (81, 137)	Tiotropium superior
12 months	1	150 (111, 190)	Tiotropium superior
Exacerbations, Overall (OR)	2	0.71 (0.52, 0.95)	Tiotropium superior
Exacerbation hospitalisations (OR)	2	0.56 (0.31, 0.99)	Tiotropium superior
All-cause hospitalisations(OR)	1	0.34 (0.15, 0.76)	Tiotropium superior
All-cause mortality (OR)	2	1.39 (0.44, 4.39)	NS
QoL (SGRQ) (MD)	1	-3.30 (-0.97, -5.63)	Tiotropium superior
TDI (MD)	1	0.90 (0.39, 1.41)	Tiotropium superior
BDI (MD)	1	-0.28 (-0.74, 0.18)	NS
Serious AEs (OR)	2	0.50 (0.34, 0.73)	Tiotropium superior
Withdrawals (OR)	2	0.58 (0.41, 0.83)	Tiotropium superior

Abbreviations: BDI, baseline dyspnoea index; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; MD, mean difference; NS, non-significant; OR, odds ratio; QoL, quality of life; SGRQ, St George Respiratory Questionnaire; SAE, serious adverse event; TDI, transition dyspnoea index

Source: Cheyne et al 2015 Summary pg 4-5, text pg 12-13

3.2.5.4 Summary

The review by Cheyne et al 2015 shows that tiotropium has superior efficacy compared with ipratropium in preventing exacerbations and hospitalisations as well as improved QoL, FEV_1 and symptoms. Patients treated with tiotropium also experience significantly fewer SAEs and a lower rate of withdrawal compared with patients treated with ipratropium. The results reported by Cheyne et al 2015 are consistent with the PBAC's original recommendation of tiotropium on a cost-effectiveness basis compared with ipratropium and support published models demonstrating that tiotropium is a cost-effective treatment compared with ipratropium (see Section 3.5).

3.2.6 Tiotropium RCT update

An additional search of tiotropium RCTs was performed to identify any recent tiotropium RCTs published since the publication of the included SRs. The search was limited to studies published from 2014 (the search date of the most recent SR (Tricco et al 2015)). The search strategy and results of the literature search are presented in Appendix 1. The literature search identified five recent RCTs comparing tiotropium with placebo and one RCT comparing tiotropium with umeclidinium (Table 3.16).

Table 3.16 List of RCTs identified in the literature search

Trial ID	Citation
Beck 2015	NCT01663987 and NCT01662986 Beck B, Clerisme-Beaty E, Liu D, Thomashow BM, Wise RA, ZuWallack RL, Make BJ, Ferguson GT. Difficulties Of Enrolling Patients With An Acute Exacerbation Of COPD Into A Hospitalization Discharge Study. Am J Respir Crit Care Med. 2015;191:A2826.
Leidy 2014	NCT01483625 Leidy NK, Mannino DM, Franceschina J, Ting N, Clerisme-Beaty E. Efficacy And Safety Of Tiotropium In Patients With Chronic Obstructive Pulmonary Disease (COPD) Experiencing An Acute Respiratory Tract Infection. Am J Respir Crit Care Med. 2014;189:A6005.
OTEMTO 1/ OTEMTO 2	NCT01964352 and NCT02006732 Singh D, Ferguson GT, Bolitschek J, Grönke L, Hallmann C, Bennett N, Abrahams R, Schmidt O, Bjermer L. Tiotropium+ olodaterol shows clinically meaningful improvements in quality of life. Respiratory medicine. 2015; 109:1312-9.
Feldman et al 2016	NCT02207829 Feldman G, Maltais F, Khindri S, Vahdati-Bolouri M, Church A, Fahy WA, Trivedi R. A randomized, blinded study to evaluate the efficacy and safety of umeclidinium 62.5 µg compared with tiotropium 18 µg in patients with COPD. Int J COPD. 2016:11 719-30

Study characteristics and results of recent tiotropium RCTs are summarised in Table 3.17.

3.2.6.1 OTEMTO 1/2

OTEMTO 1/2 (Singh et al 2015) are two replicate, double-blind, parallel-group, placebo-controlled trials designed to evaluate the effects of tio/olo FDC compared with tiotropium 5 µg or placebo on lung-function improvement and QoL after 12 weeks of treatment in patients with moderate to severe COPD. Patients were randomised to receive tio/olo 5/5 µg, 2.5/5 µg, tiotropium 5 µg or placebo for 12 weeks, via the Respimat® inhaler. The results of the tiotropium and placebo arms are discussed here (the results of tio/olo FDC are discussed in Section 3.3.3). Primary end points were SGRQ total score, FEV_1 area under the curve from 0 to 3 h (AUC_{0-3}) response and trough FEV_1 response. Tiotropium 5 µg significantly improved total SGRQ score compared with placebo (OTMETO1: MD -2.40; 95%CI: -4.42, -0.38); OTEMTO2: -2.85 (-4.80, -0.90)). The results were similar to the meta-analysis by Karner et al 2014 (MD -2.89 (-3.35, -2.44)). Tiotropium 5 µg also significantly improved FEV_1AUC_{0-3} (OTMETO1: 219 mL (181, 258); OTEMTO2: 194 mL (156, 232)) and trough FEV_1 (OTMETO1: 134 mL (96, 172); OTMETO2: 127 mL (90, 165)) compared with placebo. Again, the results for trough FEV_1 were similar to the meta-analysis by Karner et al 2014 (MD 119 (113, 125).

Incidence of AEs was broadly similar across treatment groups, with a higher incidence of AEs leading to discontinuation in the placebo groups compared to the treatment groups in both studies.

3.2.6.2 Beck et al 2015 and Leidy et al 2014

Beck et al 2015 and Leidy et al 2014 examined the efficacy of tiotropium 18 µg compared with placebo in subpopulations of patients with COPD: Beck et al 2015 enrolled patients discharged from hospital following an acute exacerbation; Leidy et al 2015 recruited patients with a respiratory tract infection. Both studies had enrolment difficulties due to the restricted nature of the patient populations targeted. As such, both studies did not enrol the planned number of patients and were underpowered to detect statistical significant differences between tiotropium and placebo. Nevertheless, both studies indicate that patients treated with tiotropium have improved lung function compared with placebo. Patients treated with tiotropium and placebo had similar number of serious AEs. Overall, despite the limitations with the studies, the results are consistent with the meta-analysis by Karner et al 2014.

3.2.6.3 Feldman et al 2016 Tiotropium vs umeclidinium

Feldman et al 2016 was a 12-week double-blind, parallel-group study evaluating the efficacy of umeclidinium 62.5 µg compared with tiotropium 18 µg. The primary endpoint was change in trough FEV_1 after 12 weeks treatment. The authors reported a small but statistically significant improvement in trough FEV_1 for umeclidinium 62.5 µg compared with tiotropium 18 µg FEV_1 (59 mL (95%CI: 29, 88)). Change in TDI and SGRQ score was similar for patients treated with umeclidinium and tiotropium Overall incidence of SAEs was similar for tiotropium (3.2%) and umeclidinium (3.3%). However, the number of patients experiencing a COPD exacerbation was higher for umeclidinium (11.4%) compared with tiotropium (9.4%). Feldman et al 2016 has a high risk of performance bias as it was not properly blinded (the placebo and tiotropium capsules were not identical). As discussed above, blinded comparisons between tiotropium and glycopyrronium showed no difference in lung function (Chapman et al 2014) whereas there were some differences observed for trials in which tiotropium was open-label. The FEV_1 results are also inconsistent with the results presented in recent meta-analyses which show that tiotropium and umeclidinium have similar efficacy in terms of trough FEV_1 (Ismaila et al 2015). In addition, the PBAC has previously noted that there is no significant difference between umeclidinium and tiotropium with respect to airway function, exacerbations and adverse effects (Umeclidinium PSD July 2014). There were fewer patients experiencing an exacerbation treated with tiotropium compared with umeclidinium, However, given the short duration of the trial, it is not possible to assess the relative efficacy of umeclidinium and tiotropium on exacerbations over the longer term. Notably, a 24 week study comparing umeclidinium 125 µg (twice the recommended dose) and tiotropium 18 µg (Decramer et al 2014) also showed that that patients treated with tiotropium had fewer exacerbations (7%) compared with umeclidinium (12%). These exacerbation results are also consistent with the SRs presented above, which demonstrate the treatment benefits of tiotropium in reducing exacerbations, including over the long-term.

3.2.6.4 Summary

The recent RCTs demonstrate that tiotropium improves lung function and QoL compared with placebo. The findings of OTEMTO 1/2 were consistent with the meta-analyses presented in the

Cochrane review by Karner et al 2014. Despite the limitations with Leidy et al 2014 and Beck et al 2015, the results of these studies also show that tiotropium improves lung function compared with placebo. Overall, the results of the recent RCTs demonstrate the treatment benefits of tiotropium and are consistent with recent meta-analyses.

Table 3.17 Study characteristics and results of tiotropium RCTs

Trial	Interventions	Population	Outcomes	Results		Comments
				Primary outcomes	Safety	
Tiotropium vs placebo						
Beck 2015	Tio 18µg (N=79) Pbo (N=79)	COPD plus hospital discharge for acute exacerbation Age, Mean: 59 years % Male: 42 to 49%	Primary Trough FEV_1 Percentage of Patients With Next Adverse Clinical Outcome Event Secondary Trough FVC Adverse clinical events COPD exacerbations All-cause hospitalisations Readmission rates Time to recovery	Trough FEV_1 week 12, mL, MD (SD) Tio: 185 (262) Pbo: 35 (384) Percentage of Patients With Next Adverse Clinical Outcome Event Tio: 53.2% Pbo: 47.4% Exacerbations Tio: 40.5%, Pbo: 44.9%	Serious AEs Tio: 32 Pbo:31	Planned recruitment of 604 patients. Study underpowered Descriptive statistics
Leidy 2015	Tio 18 µg (N=72) Pbo (N=68)	COPD with acute RTI Age, Mean: 58 years % Male: 38%	Primary Trough FEV_1 Secondary Time to recovery Trough FVC Responder status Weekly rescue medication	Trough FEV_1 week 12, mL, MD (95%CI) 57 (-52, 165)	Serious AEs: Tio: 4 Pbo: 4	Planned recruitment of 300 patients. Study underpowered
OTEMTO 1 12 weeks	Tio/olo 2.5/5 µg (N=202) Tio/olo 5/5 (N=203) Tio 5 µg (N=203) Pbo (N=204)	Moderate to severe COPD Age, Mean: 65 years % Male: 57 to 62% FEV_1 % pred, Mean:	Primary SGRQ week 12 FEV_1AUC_{0-3} Trough FEV1 Secondary TDI score	SGRQ week 12, MD (95%CI) -2.40 (-4.42, -0.38) FEV_1AUC_{0-3}week 12, mL, MD (95%CI) 219 (181, 258) Trough FEV_1 week 12, MD	All AEs Tio: 90 (44.3) Pbo: 105 (51.5) Treatment related AEs Tio: 8 (3.9)	

Trial	Interventions	Population	Outcomes	Results		Comments
				Primary outcomes	**Safety**	
		55 to 56%	FVC AUC_{0-3} and Trough FVC SGRQ responder analysis	(95%CI) 134 (96, 172)	Pbo: 12 (5.9) AEs leading to discontinuation Tio: 3 (1.5) Pbo: 11 (5.4) Serious AEs Tio: 6 (3.0) Pbo: 11 (5.4)	
OTEMTO 2 12 weeks	Tio/olo 2.5/5 µg (N=202) Tio/olo 5/5 (N=202) Tio 5 µg (N=203) Pbo (N=202)	Moderate to severe COPD Age, Mean: 64 to 65 years % Male: 58 to 66% FEV_1 % pred, Mean: 54 to 56%	Primary SGRQ week 12 FEV_1AUC_{0-3} Trough FEV_1 Secondary TDI score FVC AUC_{0-3} and Trough FVC SGRQ responder analysis	SGRQ week 12, MD (95%CI) -2.85 (-4.80, -0.90) FEV_1AUC_{0-3}week 12, mL, MD (95%CI) 194 (156, 232) Trough FEV_1 week 12, MD (95%CI) 127 (90, 165)	All AEs Tio: 93 (45.8) Pbo: 93 (46.0) Treatment related AEs Tio: 5 (2.5) Pbo: 10 (5.0) AEs leading to discontinuation Tio: 7 (3.4) Pbo: 10 (5.0) Serious AEs Tio: 12 (5.9) Pbo: 4 (2.0)	
Tiotropium vs umeclidinium						
NCT02207829	Tiotropium 18 µg (N=508) Umeclidinium 62.5 µg (N=509)	Moderate to severe COPD Age, Mean: 64 years % Male: 72%	Primary Trough FEV_1 Secondary TDI score SGRQ	Trough FEV_1 week 12, mL, MD (95%CI) 59 (29, 88) SGRQ week 12, MD (95%CI) -0.46 (-2.04, -1.13)	Serious AEs Tio: 16 (3.2) Ume: 17 (3.3) COPD exacerbation Tio: 48 (9.4)	

Trial	Interventions	Population	Outcomes	Results		Comments
				Primary outcomes	Safety	
		$FEV_1$1 % pred, Mean: NR	COPD Assessment test Inhaler assessments	TDI week 12, MD (95%CI) 0.06 (-0.30, 0.42)	Ume: 58 (11.4)	

Abbreviations: AE, Adverse event; AUCx-x, area under the curve response from x to x hours; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MD, mean difference; pbo, placebo; RCT, randomised controlled trial; RTI, respiratory tract infection; SGRQ, St George Respiratory Questionnaire; tio, tiotropium

Source: Beck et al 2015 abstract, ClinicalTrials.gov NCT01663987/NCT01662986; Leidy et al 2015 abstract, ClinicalTrials.gov NCT01483625; Singh et al 2015 Table 1 pg1316; Table 2 pg 1317, Supplementary Table S2, Supplementary Table S5; ClinicalTrials.gov NCT02207829

3.2.7 Conclusion

Tiotropium has the most substantial body of evidence among the LAMAs, including long-term evidence demonstrating a reduction in exacerbations and hospitalisations, as well as improved lung function, QoL and symptoms. Importantly, patients in many tiotropium RCTs were permitted access to usual-care respiratory medicines (including LABAs) which reflects real-life treatment practice. Therefore, the results of tiotropium RCTs are directly applicable to patients likely to receive tiotropium in clinical practice. Tiotropium is the only LAMA which has shown to reduce exacerbations, associated hospitalisations and mortality over the long-term; events associated with substantial decrease in QoL and increase in healthcare costs.

In terms of FEV_1, SGRQ and TDI, the results presented in this submission are consistent with recent PBAC assessments that tiotropium, aclidinium, glycopyrronium and umeclidinium are non-inferior in terms of efficacy and safety (equi-effective doses: tiotropium HandiHaler 18 µg once daily, tiotropium Respimat 5 µg once daily, glycopyrronium 50 µg once daily, aclidinium 400 µg twice daily, umeclidinium 62.5 µg once daily).

In addition, the results presented in this submission demonstrate that tiotropium has superior efficacy and safety compared with ipratropium and are consistent with the PBAC's original recommendation of tiotropium on a cost-effectiveness basis compared with ipratropium.

Therefore, the results presented in this submission are consistent with the economic evaluations presented in the Section 3.5 which support tiotropium as a cost-effective treatment for COPD.

3.3 Tiotropium/olodaterol (Spiolto®) evidence

3.3.1 Aim

The aim of this section is to assess the efficacy and safety of tio/olo and other PBS-listed LAMA/LABA FDCs for the treatment of COPD. The PBAC has recently considered the clinical evidence supporting the PBS listing of tio/olo and other LAMA/LABA FDCs: glycopyrronium/indacaterol (gly/ind) and umeclidinium/vilanterol (ume/vil) were approved at the July 2014 PBAC meeting, and tio/olo and aclidinium/eformeterol (acl/efor) where approved at the July 2015 meeting. As such, the aim of this submission is to summarise the clinical evidence which the PBAC recently considered in its decision to recommend PBS listing of tio/olo and other LABA/LAMA FDCs. In addition, this submission provides an update of recent tio/olo FDC RCTs published since the PBAC submission.

3.3.2 PSD review

A review of PSDs was conducted to summarise the clinical evidence considered by the PBAC in its recommendation of tio/olo and other LAMA/LABA FDCs. A summary of the clinical evidence presented in the PSDs is provided in Table 3.18.

Tiotropium/olodaterol FDC PSD, July 2015

Tio/olo FDC for the treatment of COPD was considered by the PBAC at the July 2015 meeting. The basis of listing was a cost-minimisation to two LAMA/LABA FDCs which were listed on the PBS at the time of submission; gly/ind and ume/vil FDCs. In addition, the submission compared tio/olo FDC with its components: tiotropium and olodaterol, concurrently and as monotherapy. The primary source of evidence for tio/olo FDC was the TONADO 1/2 trials, which compared tio/olo FDC with its mono-components over 52 weeks. Tio/olo was compared with gly/ind and ume/vil FDC via indirect comparisons with tiotropium (5 or 18 µg) as the common comparator (as previously discussed, the PBAC have assessed that tiotropium 5 µg delivered by Respimat is equivalent to tiotropium 18 µg delivered by HandiHaler (Therapeutic Relativity Sheets April 2016)). The primary outcome for the indirect comparisons was the mean difference (MD) in trough FEV_1 at 24 weeks.

There were no statistically significant differences in trough FEV_1 at 24 weeks between tio/olo FDC and gly/ind FDC, ume/vil FDC or tiotropium plus olodaterol taken concurrently. Furthermore, Tio/olo FDC was superior to tiotropium (60 mL; 95%CI: 40, 80 mL) or olodaterol (80 mL; 95%CI: 70, 100 mL) monotherapy. The PBAC noted that the incremental increase in FEV_1 of tio/olo compared with tiotropium or olodaterol monotherapy was below the minimum clinically important difference (MCID) of 100 to 140 mL. However, the ESC noted discussion in the literature (Jones et al 2014) around the fact that mean incremental improvement with multiple therapies may not reach the MCID. There were no significant differences for COPD exacerbations between tio/olo FDC and gly/ind FDC (COPD exacerbations were not presented for ume/vil) Similar rates of AEs were observed for tio/olo FDC compared with gly/ind FDC, ume/vil FDC and tiotropium or olodaterol monotherapy.

The PBAC recommended the listing of tio/olo FDC on a cost minimisation basis with gly/ind and ume/vil FDCs based on non-inferior comparative effectiveness and safety (equi-effective doses: tio/olo 5/5 µg, gly/ind 50/110 µg, ume/vil 62.5/25 µg). Tio/olo was subsequently listed on the PBS in December 2015.

Aclidinium/eformeterol FDC PSD, July 2015

Acl/efor FDC for the treatment of COPD was also considered by the PBAC at the July 2015 meeting. Similarly to the tio/olo FDC submission, the basis of listing was a cost-minimisation to gly/ind and ume/vil FDCs. Acl/efor was compared with gly/ind and ume/vil FDC via indirect comparisons with placebo as the common comparator. The submission also compared acl/efor FDC with its components: aclidinium and eformeterol. The primary outcome for the indirect comparisons was the MD in trough FEV_1 at 24 weeks.

Treatment with acl/efor FDC resulted in statistically significant lower trough FEV_1 at 24 weeks compared with gly/ind FDC (-54 mL; 95%CI: -101, 0 mL), however this was below the MCID of 100 to 140 mL. No statistically significant difference was observed for the comparison with ume/vil FDC. Acl/efor FDC was superior to aclidinium (28 mL; 95%CI: 4, 52 mL) or eformeterol (68 mL; 95%CI: 44, 92 mL) monotherapy. There were no statistically significant differences between acl/efor FDC and any of the comparators for COPD exacerbations or AEs. The PBAC recommended the listing of acl/efor FDC on a cost minimisation basis with gly/ind and ume/vil FDCs based on non-inferior comparative effectiveness and safety (equi-effective doses: acl/efor 680/24 µg, gly/ind 50/110 µg, ume/vil 62.5/25 µg).

Umeclidinium/vilanterol µg FDC PSD, March 2014 and July 2014

Ume/vil FDC for the treatment of COPD was considered by the PBAC at the March 2014 and July 2015 meetings. The basis of listing was a cost-minimisation to treatment with tiotropium with indacaterol. A secondary comparison vs gly/ind FDC was also presented. Ume/vil was compared with tiotropium with indacaterol and gly/ind FDC via indirect comparisons with tiotropium as the common comparator. The primary outcome for the indirect comparisons was the MD in trough FEV_1 at 24 weeks.

There were no statistically significant differences in trough FEV_1 at 24 weeks between ume/vil FDC and tiotropium 18 µg with indacaterol 150 µg taken concurrently or gly/ind FDC. The PBAC noted a slight increase in AEs for patients treated with ume/vil FDC, however, indirect comparisons indicated that there were no significant difference between ume/vil FDC and tiotropium with indacaterol.

The PBAC initially rejected the March 2014 submission, stating that cost minimisation based on the sum of the prices of tiotropium and indacaterol was not justified. The PBAC subsequently recommended ume/vil FDC at the July 2014 meeting on a cost-minimisation basis compared with tiotropium and indacaterol with a price adjustment to account for FEV_1 efficacy being less than the sum of components (equi-effective doses: ume/vil 62.5/25 µg, tiotropium 18 µg and indacaterol 150 µg).

Glycopyrronium/indacaterol FDC PSD, March 2014 and July 2014

Gly/ind FDC for the treatment of COPD was considered by the PBAC at the March 2014 and July 2015 meetings. The basis of listing was a cost-minimisation to the component products. The submission presented direct comparisons of gly/ind FDC vs glycopyrronium with indacaterol concurrently and as monotherapy. In addition, the submission presented indirect comparisons of gly/ind FDC compared with tiotropium with indacaterol, and tiotropium plus ICS/LABA via tiotropium as the common

comparator. The primary outcome for the indirect comparisons was the MD in trough FEV_1 at 24 weeks.

No statistically significant differences in trough FEV_1 at 24 weeks were observed between gly/ind FDC and glycopyrronium with indacaterol (10 mL, 95%CI: -20, 40) or tiotropium with indacaterol (10 mL, 95%CI: -20, 40). Treatment with gly/ind FDC resulted in statistically significant higher trough FEV_1 at 24 weeks compared with tiotropium plus ICS/LABA (50 mL; 95%CI: 20, 80 mL). In addition, gly/ind FDC was superior to glycopyrronium (90 mL; 95%CI: 60, 100 mL) or indacaterol (70 mL; 95%CI: 50, 100 mL) monotherapy. No statistically significant differences in AEs between gly/ind FDC and the comparators.

Similarly to the initial ume/vil FDC submission, the PBAC rejected the gly/ind FDC March 2014 submission, stating that cost minimisation based on the sum of the prices of glycopyrronium and indacaterol was not justified. The PBAC subsequently recommended gly/ind FDC at the July 2014 meeting on a cost-minimisation basis compared with ume/vil FDC (equi-effective doses: ume/vil 62.5/25 µg, gly/ind 50/110 µg).

Table 3.18 Summary of LAMA/LABA FDC for COPD major submission PSDs

PSD	Comparators	Basis of assessment	Trials presented	Key outcomes	Results	PBAC Decision
Tio/olo 5/5 µg FDC (Spiolto® Respimat®) July 2015	-Gly/ind 50/110 µg FDC -Ume/vil 62.5/25 µg FDC -Tio (5 or 18 µg) and olo 5 µg concurrently and monotherapy	-Indirect comparison via tio monotherapy as common comparator. -Cost minimisation	Tio/olo vs tio Tonado1/2 Gly/ind vs tio SHINE SPARK ARISE Ume/vil vs tio Decramer 1/2 Tio plus olo vs tio ANHELTO 1/2 Study 11/12/13/14	FEV_1 at 24 weeks AEs	Efficacy [a] -No statistically significant differences in trough FEV_1 at 24 weeks between tio/olo FDC and gly/ind FDC, ume/vil FDC or tio plus olo taken concurrently. -Tio/olo FDC superior to tio or olo monotherapy. FEV_1 (mL, MD (95%CI) Vs tio: 60 (40, 80) Vs olo: 80 (70, 100) Safety Similar rates of AEs for tio/olo FDC, gly/ind FDC, ume/vil FDC and tio or olo monotherapy	Recommended Cost minimisation compared with gly/ind and ume/vil FDCs based on non-inferior comparative effectiveness and safety
Acl/efor 680/24 µg FDC (Brimica® Genuair®) July 2015	Gly/ind 50/110 µg FDC -Ume/vil 62.5/25 µg FDC -Acl and efor monotherapy	-Indirect comparison via pbo as common comparator. -Cost minimisation	Acl/efor vs pbo ACLIFORM AUGMENT Gly/ind vs pbo SHINE ENLIGHTEN Ume/vil vs pbo Donohue 2013	FEV_1 at 24 weeks AEs	Efficacy FEV_1 (mL, MD (95%CI) Vs gly/ind: -50 (-101, 0) Vs ume/vil: -31 (-79, 16) Vs acli: 28 (4, 52) Vs efor: 68 (44,92) Safety Similar rates of AEs for acli/efor FDC, gly/ind FDC and ume/vil FDC	Recommended Cost minimisation compared with gly/ind and ume/vil FDCs based on non-inferior comparative effectiveness and safety
Ume/vil 62.5/25 µg FDC (Anoro® Ellipta®)	Same as March 2014 submission	Same as March 2014 submission	Same as March 2014 submission	Same as March 2014 submission	Same as March 2014 submission	Recommended Cost-minimisation basis compared with tio and ind with an

PSD	Comparators	Basis of assessment	Trials presented	Key outcomes	Results	PBAC Decision
July 2014						adjustment to account for efficacy being less than the sum of components
Ume/vil 62.5/25 µg FDC (Anoro® Ellipta®) March 2014	-Tio 18 µg plus ind -Gly/ind 50/110 µg FDC	-Indirect comparison via tio monotherapy as common comparator. -Cost minimisation	Ume/vil vs pbo DB2113360 DB2113374 Tio plus ind vs tio INTRUST 1/2 Gly/ind vs pbo SHINE	FEV_1 at 24 weeks AEs	Efficacy [a] No statistically significant differences in trough FEV_1 at 24 weeks between ume/vil FDC and tio plus ind, and gly/ind FDC. Safety Slight increase in AEs for ume/vil	Rejected Cost minimisation based on sum of prices of tio and ind not justified
Gly/ind 50/110 µg FDC (Ultibro® Breezhaler®) July 2014	Same as March 2014 submission	Same as March 2014 submission	Same as March 2014 submission	Same as March 2014 submission	Same as March 2014 submission	Recommended Cost minimisation compared with ume/vil
Gly/ind 50/110 µg FDC (Ultibro® Breezhaler®) March 2014	-Gly 50 µg and ind 110 µg concurrently and monotherapy -Tio 18 µg plus ind -LABA/ICS plus tio	-Direct comparison of gly/ind FDC vs gly plus ind -Indirect comparison via tio monotherapy as common comparator. -Cost minimisation	Gly/ind vs gly plus ind BEACON Gly/ind vs gly or ind SHINE SPARK Tio plus ind vs tio INTRUST 1/2 LABA/ICS plus tio vs tio Aaron et al. (2007) Cazzola et al. (2007) Hanania et al. (2012)	FEV1 at 4, 12, 26 weeks AEs	Efficacy FEV_1 (mL, MD (95%CI) Vs gly plus ind: -10 (-50, 40) Vs tio plus ind: 10 (-20, 40) Vs LABA/ICS plus tio: 50 (20, 80) Vs ind: 70 (50, 100) Vs gly (SHINE): 90 (60, 110) Vs gly (SPARK): 70 (50, 100) Safety No statistically significant differences in AEs between the fixed combination	Rejected Cost minimisation based on sum of prices of gly and ind not justified

PSD	Comparators	Basis of assessment	Trials presented	Key outcomes	Results	PBAC Decision
			Hoshino et al. (2011) Jung et al. (2012) Welte et al. (2009).		product and the comparators	

Abbreviations: Acl/efor, aclidinium/eformoterol FDC; AE, Adverse event; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FDC, fixed dose combination; FEV_1, forced expiratory volume in 1 second; gly/ind, glycopyrronium/indacaterol FDC; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; PSD, public summary document; tio/olo, tiotropium/olodaterol FDC; Ume/vil, umeclidinium/vilanterol FDC

Source: Tio/olo FDC PSD, July 2015; Acl/efor FDC PSD, July 2015; Gly/ind FDC PSDs, March 2014 and July 2014; Ume/vil µg FDC PSDs, March 2014 and July 2014

Note: all doses shown are recommended daily doses

a Results of indirect comparisons redacted from PSD

3.3.3 Additional evidence published since the tio/olo FDC PBAC submission (March 2015).

A review of the literature was conducted to identify any additional tio/olo FDC SRs or RCTs published since the PBAC recommendation of tio/olo at the July 2015 meeting. The literature search identified RCTs in patients with COPD, with tio/olo 5/5 µg FDC in at least one arm which had not been previously considered by the PBAC. The search strategy and literature search results are presented in Appendix 1. The search identified six RCTs with recently published results (Table 3.19).

Table 3.19 List of studies identified in the literature search

Trial ID	Citation
Systematic reviews	
Schlueter et al 2016	Schlueter M, Gonzalez-Rojas N, Baldwin M, Groenke L, Voss F, Reason T. Comparative efficacy of fixed-dose combinations of long-acting muscarinic antagonists and long-acting β2-agonists: a systematic review and network meta-analysis. Therapeutic Advances in Respiratory Disease. 2016:1753465815624612.
Calzetta et al 2016	Calzetta L, Rogliani P, Matera MG, Cazzola M. A systematic review with meta-analysis of dual bronchodilation with LAMA/LABA for the treatment of stable chronic obstructive pulmonary disease. Chest. 2016 doi: 10.1016/j.chest.2016.02.646.
Oba et al 2016	Oba Y, Sarva ST, Dias S. Efficacy and safety of long-acting β-agonist/long-acting muscarinic antagonist combinations in COPD: a network meta-analysis. Thorax. 2016 Jan 1;71(1):15-25.
Randomised controlled trials	
VIVACITO	NCT01559116 Beeh KM, Westerman J, Kirsten AM, Hébert J, Grönke L, Hamilton A, Tetzlaff K, Derom E. The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease. Pulmonary pharmacology & therapeutics. 2015; 32:53-9;
OTEMTO 1/ OTEMTO 2	NCT01964352 and NCT02006732 Singh D, Ferguson GT, Bolitschek J, Grönke L, Hallmann C, Bennett N, Abrahams R, Schmidt O, Bjermer L. Tiotropium+ olodaterol shows clinically meaningful improvements in quality of life. Respiratory medicine. 2015; 109:1312-9.
MORACTO 1/2	NCT01533922 and NCT01533935 Casaburi R, De Sousa D, Xue W, Frith P, Hamilton A, Kirsten A, Maltais F, O'Donnell D. Effects Of 6 Weeks' Treatment With Once-Daily Tiotropium And Olodaterol Fixed-Dose Combination On Inspiratory Capacity And Exercise Endurance In Patients With COPD: The Moracto™ Studies. Am J Respir Crit Care Med 191;2015:A3972
ENERGITO	NCT01969721 Beeh KM, Derom E, Echave-Sustaeta J, Grönke L, Hamilton A, Zhai D, Bjermer L. The lung function profile of once-daily tiotropium and olodaterol via Respimat® is superior to that of twice-daily salmeterol and fluticasone propionate via Accuhaler®(ENERGITO® study). International journal of chronic obstructive pulmonary disease. 2016;11:193.

3.3.3.1 Systematic reviews

The literature search identified three recently published SRs specifically comparing LAMA/LABA FDCs (Calzetta et al 2016; Oba et al 2016; Schlueter et al 2016). The findings of the three SRs are consistent. Schlueter et al 2016 is discussed further. Schlueter et al 2016 was a SR and network meta-analysis which assessed the comparative efficacy of LAMA/LABA FDCs at approved doses in

patients with COPD (Table 3.20). A total of 27 trials from 26 publications with 30,361 subjects were included in the analysis.

Table 3.20 Characteristics of Schlueter et al 2016

Citation (Date of literature search)	Treatments evaluated (dose/day)	No. of trials/sample size included in the analysis	Summary of main population characteristics	Duration of included trials	Outcomes	AMSTAR quality rating (0 to 11)	Analysis
Schlueter et al 2016	Tio/olo 5/5 µg Gly/ind 110/50 µg Ume/vil 62.5/25 µg Acl/efor 800/24 µg Tiotropium (Respimat 5 µg and 10 µg; HandiHaler 18 µg)	Overall 26/30,361 Tio/olo vs tio 1/2062 Gly/ind vs tio or pbo 3/3,014 Ume/vil vs tio or pbo 5/3,294 Acl/efor vs pbo 2/1,254 Tio vs pbo 12/20,2307	COPD	24 weeks to 4 years	FEV_1 SGRQ TDI Exacerbations Discontinuations	7	Bayesian fixed and random effects meta-analysis to explore the effect of baseline disease severity (FEV_1), concomitant ICS use

Abbreviations: Acl/efor, aclidinium/eformoterol FDC; AE, Adverse event; COPD, chronic pulmonary obstructive disease; FDC, fixed dose combination; FEV_1, forced expiratory volume in 1 second; gly/ind, glycopyrronium/indacaterol FDC; olo, olodaterol; pbo, placebo; SGRQ, St George Respiratory Questionnaire; TDI, transition dyspnoea index; tio, tiotropium; tio/olo, tiotropium/olodaterol FDC; Ume/vil, umeclidinium/vilanterol FDC

Source: Schlueter et al 2016 Text pg 2-5, Table 2 pg 7

Note: tiotropium RCTs were included in the analysis to allow the formation of networks

Daily doses shown

Patient characteristics of the included studies in Schlueter et al 2016 are summarised in Table 3.21. The majority of included trials were assessed as having a low or unclear risk of bias. Some studies that included open-label tiotropium were assessed as high-risk of bias. The duration of studies ranged from 24 weeks to 4 years. The mean age of participants in the included trials was 62 to 68 years and the majority male (range 51% to 98%). Mean baseline severity varied between trials from FEV_1%pred of 37% to (i.e. severe COPD) to 66% (moderate COPD). The different LAMA/LABA FDCs were compared using a Bayesian fixed- and random-effects NMA. Results for the outcomes of interest were compared at 24/26 weeks and 48/52 weeks. In addition, meta-regression was performed for the outcome FEV_1 to assess the impact on treatment effect sizes of use of concomitant ICS and of disease severity (measured as post-bronchodilator %FEV_1 predicted) at baseline.

Table 3.21 Summary of population characteristics from Schlueter et al 2016

Age (years, mean)	Gender (% male, range)	COPD severity (mean FEV_1 %predicted)	Concomitant medications allowed (N trials)
62 to 68	51% to 98%	37% to 66%	NR

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; NR, not reported

Source: Schlueter et al 2016 Table 2 pg 7

Results

The results of the meta-analyses for trough FEV_1 and SGRQ at 24/26 weeks are summarised in Table 3.22. No statistically significant differences were observed for any outcome using random effects models. tio/olo 5/5 µg was associated with a statistically significant 39 mL (95% CrI 2, 75) increase in FEV_1 compared with acl/efor 400/12 µg when using a fixed effects model. Results of the meta-regressions for FEV_1 showed no statistically significant differences between tio/olo and any of the other LAMA/LABA FDCs. No statistically significant differences were observed for SGRQ and TDI. Overall, these results confirm the PBACs assessment that the LAMA/LABA FDCs are of comparable efficacy and safety.

Table 3.22 Summary of results from Schlueter et al 2016

Outcome/comparator	Result MD (95%CrI) [a]	Systematic review interpretation
Trough FEV_1 24/26 weeks, mL		
Tio/olo vs Acl/efor	37 (−11, 82)	NS
Tio/olo vs Gly/ind	−4 (−42, 32)	NS
Tio/olo vs Ume/vil	−24 (−59, 11)	NS
SGRQ 24/26 weeks (% responders)		
Tio/olo vs Acl/efor	1.250 (0.634, 2.509)	NS
Tio/olo vs Gly/ind	1.155 (0.640, 2.145)	NS
Tio/olo vs Ume/vil	1.167 (0.667, 2.102)	NS
TDI 24/26 weeks (% responders)		
Tio/olo vs Acl/efor	0.806 (0.430, 1.572)	NS
Tio/olo vs Gly/ind	0.945 (0.501, 1.877)	NS
Tio/olo vs Ume/vil	1.005 (0.571, 1.808)	NS

Abbreviations: Acl/efor, aclidinium/eformoterol FDC; CrI, credible interval; FDC, fixed dose combination; FEV_1, forced expiratory volume in 1 second; gly/ind, glycopyrronium/indacaterol FDC; MD, mean difference; NS, non-significant; SGRQ, St George Respiratory Questionnaire; TDI, transition dyspnoea index; tio/olo, tiotropium/olodaterol FDC; Ume/vil, umeclidinium/vilanterol FDC

Source: Schlueter et al 2016 Table 3 pg 9; Table 7, Table 8 pg12

a All random effects models shown

3.3.3.2 RCTs

The search did not identify any additional published trials presenting FEV_1 outcomes at 24 or 52 weeks, which was the primary outcome for the tio/olo PBAC submission. However, there were four smaller trials of 6 to 12 weeks duration. The characteristics and results of these trials are

summarised in Table 3.23. Only the results for tio/olo 5/5 µg daily dose are presented here consistent with the recommended dose in Australian clinical practice.

OTEMTO 1/2

OTEMTO 1/2 (Singh et al 2015) are two replicate, double-blind, parallel-group, placebo-controlled trials designed to evaluate the effects of tio/olo FDC on lung-function improvement and QoL after 12 weeks of treatment in patients with moderate to severe COPD. Patients were randomised to receive tio/olo 5/5 µg, 2.5/5 µg, tiotropium 5 µg or placebo for 12 weeks, via the Respimat® inhaler. The results of the tiotropium and placebo arms are discussed here (the results of tiotropium vs placebo are discussed in Section 3.2.6), however, it should be noted that the study was powered for tio/olo vs placebo and not tio/olo vs tiotropium monotherapy. Primary end points were SGRQ total score, FEV_1 area under the curve from 0 to 3 h (FEV_1AUC_{0-3}) response and trough FEV_1 response. Tio/olo 5/5 µg significantly improved total SGRQ score compared with placebo (OTMETO1: MD -4.89 (95%CI: -6.90, -2.88); OTEMTO2: -4.56 (-6.50, -2.63)) and tiotropium 5 µg (OTMETO1: -2.49 (-4.47, -0.51); OTEMTO2: -1.72 (-3.63, 0.19)). Tio/olo 5/5 µg also significantly improved FEV_1AUC_{0-3} compared with placebo and tiotropium 5 µg. Tio/olo 5/5 µg significantly improved trough FEV_1 response compared with placebo (both studies) and tiotropium 5 µg in OTEMTO 2. Incidence of AEs was broadly similar across treatment groups, with a higher incidence of AEs leading to discontinuation in the placebo groups compared with the treatment groups in both studies. These results demonstrate that tio/olo FDC improves QoL and lung function compared with placebo or tiotropium alone over 12 weeks. The findings of OTEMTO 1/2 are consistent with the results of the pivotal 52-week TONADO trials presented in the PBAC submission (Tiotropium/olodaterol PSD July 2015).

VIVACITO

VIVACITO (Beeh et al 2015a) is a randomised, double-blind, placebo-controlled, Phase III trial with an incomplete crossover design. The aim of VIVACITO was to investigate the effect of tio/olo FDC on 24-hour lung function in patients with moderate to severe COPD. Patients were randomised to receive tio/olo 5/5 µg, 2.5/5 µg, component monotherapy or placebo for 6 weeks each. The primary endpoint was FEV_1AUC_{0-24}. The results of trough FEV_1 is also presented in Table 3.23 as this is the primary endpoint used in most LAMA/LABA submissions. Tio/olo 5/5 µg significantly improved FEV_1AUC_{0-24} compared with placebo (MD 280mL (95%CI: 252, 309), tiotropium monotherapy (110 (82, 139)) and olodaterol monotherapy (115 mL (87, 143)). Tio/olo 5/5 µg also significantly improved trough FEV_1 response compared with placebo and tiotropium or olodaterol monotherapies. Overall incidence of adverse events was similar between treatment groups. These results demonstrate that tio/olo FDC improves 24 h lung function compared with placebo or monotherapy alone.

MORACTO 1/2

MORACTO 1/2 (Casaburi et al 2015) are two replicate, double-blind, placebo-controlled, incomplete crossover trials designed to evaluate the effects of tio/olo FDC on inspiratory capacity and exercise endurance in patients with moderate to severe COPD. Patients were randomised to receive tio/olo 5/5 µg, 2.5/5 µg, component monotherapy or placebo for 6 weeks each. The primary endpoints were inspiratory capacity at rest and endurance time during constant work-rate cycle ergometry. Tio/olo 5/5 µg significantly improved inspiratory capacity compared with placebo, tiotropium 5 µg,

and olodaterol. Tio/olo 5/5 µg also significantly improved endurance time versus placebo. No safety concerns were identified during the study.

ENERGITO

ENERGITO (Beeh et al 2016) is a randomised, double-blind, double-dummy, 4-period crossover trial which evaluated the effects of tio/olo FDC and fluticasone/salmeterol (flu/sal) FDC on lung function after 6 weeks in patients with moderate to severe COPD. Patients were randomised to receive tio/olo 5/5 µg, 2.5/5 µg or flu/sal 250/50 or 500/50 µg BID. The primary endpoint was $FEV_1AUC_{0\text{-}12}$. The results of trough FEV_1 is also presented in Table 3.23below as this is the primary endpoint used in most LAMA/LABA submissions. Tio/olo 5/5 µg significantly improved $FEV_1AUC_{0\text{-}12}$ compared with flu/sal 250/50 µg (MD 125 mL; 95%CI: 103, 147) and 500/50 µg (MD 129 (107, 150)). These results demonstrate that Tio/olo FDC provides improved lung function compared with ICS/LABA in patients with moderate to severe COPD.

3.3.4 Discussion

The PSD summary demonstrates that the PBAC has considered tio/olo FDC to be of comparable efficacy and safety to other PBS-listed LAMA/LABA FDCs. The clinical evidence presented in the tio/olo PBAC submission was based on the 52-week TONADO RCTs (Buhl et al 2015) which demonstrate that tio/olo FDC has superior efficacy and comparable safety to tiotropium or olodaterol monotherapy. Results of the indirect comparisons showed that tio/olo FDC had comparable efficacy and safety to gly/ind and ume/vil FDCs. The equi-effective doses are: tio/olo 5/5 µg, gly/ind 50/110 µg, ume/vil 62.5/25 µg.

The NMA by Schuetler et al 2016 showed that tio/olo FDC has similar efficacy and safety to other FDCs. This analysis confirms the PBACs assessment that the LAMA/LABA FDCs are of comparable efficacy and safety.

Since the assessment of tio/olo by the PBAC, there have been several additional tio/olo RCTs published. It should be noted that these RCTs are smaller and shorter duration compared with the pivotal TONADO trials. Nevertheless, all additional trials consistently demonstrate tio/olo FDC provides improved QoL and lung function compared with placebo, tiotropium or olodaterol monotherapy. Therefore, the findings of these recently published RCTs are consistent with the evidence assessed by the PBAC in its recommendation to list tio/olo on the PBS. The evidence considered by the PBAC and the additional published tio/olo FDC RCTs are consistent with Australian and international clinical practice guidelines, which recommend LAMA/LABA combination treatment in patients for which LAMA monotherapy is not adequate (see Section 1).

The literature search also identified one trial (ENERGITO) which shows that patients with moderate to severe COPD treated with tio/olo FDC have improved lung function compared with patients treated with flu/sal FDC. Similar results have been shown in other RCTs comparing LAMA/LABAs to ICS/LABA FDCs. Gly/ind significantly improved lung function, reduced exacerbations and pneumonia compared with fluticasone/salmeterol over 26 weeks (Vogelmeier et al 2013; Zhong et al 2014). These results confirm the recommendation by the TSANZ that LABA/LAMA FDCs are likely to provide an effective, convenient and potentially safer alternative to ICS/LABA (see Section 1).

Table 3.23 Study characteristics and results of tiotropium/olodaterol FDC RCTs published since the PBAC submission (March 2015)

Trial	Interventions	Population	Outcomes	Main results	
				Primary outcomes	**Safety (n, %)**
OTEMTO 1 12 weeks	Tio/olo 2.5/5 µg (N=202) Tio/olo 5/5 (N=203) Tio 5 µg (N=203) Pbo (N=204)	Moderate to severe COPD Age, Mean: 65 years % Male: 57 to 62% FEV_1 % pred, Mean: 55 to 56%	Primary SGRQ week 12 FEV_1AUC_{0-3} Trough FEV_1 Secondary TDI score FVC AUC_{0-3} and Trough FVC SGRQ responder analysis	SGRQ week 12, MD (95%CI) Tio/olo 5/5 vs: Tio 5: -2.49 (-4.47, -0.51) Pbo: -4.89 (-6.90, -2.88) FEV_1AUC_{0-3}week 12, mL, MD (95%CI) Tio/olo 5/5 vs: Tio 5: 111 (75, 148) Pbo: 331 (293, 369) Trough FEV_1 week 12, mL, MD (95%CI) Tio/olo 5/5 vs: Tio 5: 28 (-9, 66) Pbo: 162 (124, 200)	All AEs Tio/olo 5/5: 91 (44.8) Tio: 90 (44.3) Pbo: 105 (51.5) Treatment related AEs Tio/olo 5/5: 8 (3.9) Tio: 8 (3.9) Pbo: 12 (5.9) AEs leading to discontinuation Tio/olo 5/5: 3 (1.5) Tio: 3 (1.5) Pbo: 11 (5.4) Serious AEs Tio/olo 5/5: 10 (4.9) Tio: 6 (3.0) Pbo: 11 (5.4)
OTEMTO 2 12 weeks	Tio/olo 2.5/5 µg (N=202) Tio/olo 5/5 (N=202) Tio 5 µg (N=203) Pbo (N=202)	Moderate to severe COPD Age, Mean: 64 to 65 years % Male: 58 to 66% FEV_1 % pred, Mean: 54 to 56%	Primary SGRQ week 12 FEV_1AUC_{0-3} Change in trough FEV1 Secondary TDI score FVC AUC_{0-3} and Trough FVC SGRQ responder analysis	SGRQ week 12, MD (95%CI) Tio/olo 5/5 vs: Tio 5: -1.72 (-3.63, 0.19) Pbo: -4.56 (-6.50, -2.63) FEV_1AUC_{0-3}week 12, mL, MD (95%CI) Tio/olo 5/5 vs: Tio 5: 105 (69, 141) Pbo: 299 (261, 336) Trough FEV_1 week 12, mL, MD (95%CI) Tio/olo 5/5 vs:	All AEs Tio/olo 5/5: 87 (43.1) Tio: 93 (45.8) Pbo: 93 (46.0) Treatment related AEs Tio/olo 5/5: 10 (5.0) Tio: 5 (2.5) Pbo: 10 (5.0) AEs leading to discontinuation

Trial	Interventions	Population	Outcomes	Main results	
				Tio 5: 39 (2, 76) Pbo: 166 (129, 203)	Tio/olo 5/5: 1 (0.5) Tio: 7 (3.4) Pbo: 10 (5.0) Serious AEs Tio/olo 5/5: 6 (3.0) Tio: 12 (5.9) Pbo: 4 (2.0)
VIVACITO 6 weeks	Tio/olo 2.5/5 µg (N=136) Tio/olo 5/5 (N=139) Tio 2.5 µg (N=137) Tio 5 µg (N=138) Olo 5 µg (N=138) Pbo (N=138)	Moderate to severe COPD Age, Mean: 61 years % Male: 59% FEV_1 % pred, Mean: 54%	Primary FEV_1AUC_{0-24} week 6 Secondary FEV_1AUC_{0-12} FEV_1AUC_{12-24} FEV_1AUC_{0-3} Trough FEV_1 $FVCAUC_{0-24}$ $FVCAUC_{0-12}$ $FVCAUC_{12-24}$	FEV_1AUC_{0-24} week 6, mL, MD (95%CI) Tio/olo 5/5 vs: Tio 5: 110 (82, 139) Olo 5: 115 (87, 143) Pbo: 280 (252, 309) Trough FEV_1 week 6, mL (SE) Tio/olo 5/5: 201 (15)* Tio 5: 122 (15) Olo 5: 109 (15) Pbo: -6 (15) *P<0.0001 vs Pbo and monotherapies	All AEs Tio/olo 5/5: 52 (37.4) Tio 5: 61 (44.2) Olo 5: 52 (37.7) Pbo: 64 (46.4) Treatment related AEs Tio/olo 5/5: 3 (2.2) Tio 5: 8 (5.4) Olo 5: 6 (4.3) Pbo: 9 (6.5) AEs leading to discontinuation Tio/olo 5/5: 1 (0.7) Tio 5: 2 (1.4) Olo 5: 3 (2.2) Pbo: 5 (3.6) Serious AEs Tio/olo 5/5: 1 (0.7) Tio 5: 3 (2.2) Olo 5: 8 (5.8) Pbo: 4 (2.9)
MORACTO 1	Tio/olo 2.5/5 µg	Moderate to severe COPD	Inspiratory capacity	Inspiratory capacity, MD (95%CI)	Serious AEs

Trial	Interventions	Population	Outcomes	Main results	
6 weeks	(N=59) Tio/olo 5/5 (N=59) Tio 5 µg (N=60) Olo 5 µg (N=58) Pbo (N=59)	Age, Mean: 61 years % Male: 70% FEV_1 % pred, Mean: 52%	week 6 Endurance time	Tio/olo 5/5 vs: Tio 5: 114 (61, 167) Olo 5: 119 (65, 172) Pbo: 244 (191, 298) <u>Endurance time, Ratio (95%CI)</u> Tio/olo 5/5 vs: Tio 5: 0.993 (0.930, 1.061) Olo 5: 1.002 (0.937, 1.070) Pbo: 1.209 (1.132, 1.292)	Tio/olo 5/5: 5 (2.3) Tio 5: 8 (3.5) Olo 5: 3 (1.4) Pbo: 4 (1.8)
MORACTO 2 6 weeks	Tio/olo 2.5/5 µg (N=58) Tio/olo 5/5 (N=58) Tio 5 µg (N=58) Olo 5 µg (N=59) Pbo (N=58)	Moderate to severe COPD Age, Mean: 62 years % Male: 72% FEV_1 % pred, Mean: 53%		<u>Inspiratory capacity, MD (95%CI)</u> Tio/olo 5/5 vs: Tio 5: 88 (39, 137) Olo 5: 80 (31, 129) Pbo: 265 (215, 315) <u>Endurance time, Ratio (95%CI)</u> Tio/olo 5/5 vs: Tio 5: 1.043 (0.981, 1.109) Olo 5: 1.111 (1.045, 1.182) Pbo: 1.134 (1.065, 1.206)	<u>Serious AEs</u> Tio/olo 5/5: 4 (1.8) Tio 5: 8 (3.7) Olo 5: 3 (1.4) Pbo: 3 (1.4)
ENERGITO 6 weeks	Tio/olo 2.5/5 QD N=215) Tio /olo 5/5 QD N=221) Flu/sal 250/50 BID (N=212) Flu/sal 500/50 BID (N=219)	Moderate to severe COPD Age, Mean: 64 years % Male: 65% FEV_1 % pred, Mean: 56%	<u>Primary</u> FEV_1AUC_{0-12} week 6 <u>Secondary</u> FEV_1AUC_{0-24} FEV_1AUC_{12-24} Trough FEV_1	<u>FEV_1AUC_{0-12} week 6, mL, MD (95%CIs):</u> Tio/olo 5/5 vs: Flu/sal 250/50: 125 (103, 147) Flu/sal 500/50: 129 (107, 150) <u>Trough FEV_1 week 6, mL, MD (95%CI)</u> Tio/olo 5/5 vs: Flu/sal 250/50: 47 (22, 71) Flu/sal 500/50: 58 (34, 84)	<u>Serious AEs</u> Tio/olo 5/5: 6 (2.7) Flu/sal 250/50: 5 (2.4) Flu/sal 500/50: 11 (5.0)

Abbreviations: AE, Adverse event; AUCx-x, area under the curve response from x to x hours; CI, confidence interval; FDC, fixed dose combination; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; flu/sal, fluticasone/salmeterol FDC; MD, mean difference; olo, olodaterol; pbo, placebo; RCT, randomised controlled trial; SGRQ, St George Respiratory Questionnaire; TDI, transition dyspnoea index; tio/olo, tiotropium/olodaterol FDC; tio, tiotropium

Source: Singh et al 2015 Table 1 pg1316; Table 2 pg 1317, Supplementary Table S2, Supplementary Table S5; Beeh et al 2015 Table 1 pg 56, Table 3 pg 57, Table 4 pg 58, Supplementary Table S5; Casaburi et al 2015 abstract, ClinicalTrials.gov NCT01533922/NCT01533935; Beeh et al 2016 Table 1 pg 198, Table 3 pg 199, Table 5 pg 200; Table 6 pg 201

Note: Only tio/olo 5/5 µg and tio 5 µg dose results presented

3.4 Ipratropium evidence

Ipratropium is a SAMA which improves lung function and provides short-acting relief of symptoms such as breathlessness. The efficacy and safety of ipratropium as a treatment for COPD is well-established. SAMAs are recommended by the GOLD and COPD-X Guidelines to provide short term symptom relief or 'rescue' medication. SAMAs may be used on an as-required basis by patients with all levels of disease severity from mild to severe COPD (refer to Response to ToR 1). The COPD-X recommendation is based primarily on the Cochrane review by Appleton et al 2006 which is summarised below.

3.4.1 Appleton 2006a

The Cochrane review by Appleton et al 2006 compared the relative efficacy and safety of ipratropium and short-acting β2-agonists (salbutamol, metaproterenol or fenoterol) in patients with stable COPD. The SR identified 11 RCTs of at least four weeks duration, which included 3,912 participants with COPD. The SR included studies which compared ipratropium versus short-acting β2-agonists as well as studies comparing combination ipratropium plus short-acting β2-agonists versus short-acting β2-agonists. All included studies were meta-analysed where possible. Subgroup analyses were also planned for risk of bias, type of SABA and formulation (nebuliser or metered dose inhaler. The SR was rated as high quality (AMSTAR rating 11).

Table 3.24 Characteristics of Appleton et al 2006

Citation (Date of literature search)	Treatments evaluated (dose)	No. of trials/sample size included in the analysis	Summary of main population characteristics	Duration of included trials	Outcomes	AMSTAR quality rating (0 to 11)	Analysis
Appleton et al 2006	Ipratropium nebulised solution (0.5 mg) or MDI (18, 21 or 42 µg) SABAs Salbutamol nebulised solution (2.5, 3 or 15 mg) or MDI (240, 100 or 90 µg) Metaproterenol nebulised solution (15 mg) or MDI (1500 µg) Fenoterol MDI (100 µg)	Overall 11/3,912 Ipr vs SABAs 8/2,148 Ipr/SABAs vs SABAs 7/2,252	Stable COPD	4 to 13 weeks	FEV_1 FVC CRQ Symptoms Oral steroid use Drug-related AEs Exacerbations	11	Meta-analysis, fixed-effects. Sensitivity analysis by risk of bias. Subgroup analysis by type of SABA and formulation (nebuliser or MDI)

Abbreviations: AE, Adverse event; COPD, chronic pulmonary obstructive disease; CRQ, Chronic Diseases Respiratory Questionnaire; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; Ipr, ipratropium; MDI, metered dose inhaler; SABA, short-acting β2-agonist

Source: Appleton et al 2006 Text pg 3-5

The mean age of study participants was 64 to 65 years and the mean gender distribution across these studies was 65% male. Study participants had a mean baseline FEV_1 of 1.00 or mean FEV_1%predicted of 37% (i.e. severe COPD).

Table 3.25 Summary of population characteristics from Appleton et al 2006

	Age (years, mean)	Gender (% male, range)	COPD severity	Concomitant medications allowed (N trials)
Ipratropium vs SABAs	64	65	Mean baseline FEV_1: 1.00L	NR
Ipratropium/SABA vs SABA	65	65	Mean baseline FEV_1: 1.00L Mean FEV_1 %predicted: 37%	NR

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; NR, not reported; SABA, short-acting β2-agonist

Source: Appleton et al 2006 Text pg 5-6

The results of the meta-analyses are summarised in Table 3.26.

Ipratropium vs SABAs

Treatment with ipratropium significantly improved lung function (FEV_1: MD 30 mL; 95%CI: 0, 60; FVC: MD 70 mL; 95%CI: 10, 140)) and QoL (Dyspnoea: MD 0.16; 95%CI: 0.09, 0.23; Fatigue: MD 0.13; 95%CI: 0.02, 0.23; Emotion: MD 0.17; 95%CI: 0.04, 0.29; Mastery: MD 18; 95%CI: 0.06, 0.30) compared with SABAs. Treatment with ipratropium also significantly decreased the number of drug-related AEs (OR 0.71; 95%CI: 0.53, 0.97) and the number of patients requiring oral steroids (OR 0.52; 95%CI: 0.37, 0.74) compared with SABAs.

Ipratropium/SABA vs SABA

Patients treated with combination ipratropium/SABA had similar lung function, QoL and Symptoms compared with SABA alone. Importantly, treatment with ipratropium significantly reduced the number of patients experiencing exacerbation (OR 0.42; 95%CI: 0.18, 0.96) and the number of patients requiring oral steroids (OR 0.69; 95%CI: 0.50, 0.94) compared with SABA alone.

Table 3.26 Summary of results from Appleton et al 2006

Outcome	N trials	Result Estimate (95%CI)	Systematic review interpretation
Ipratropium vs SABA			
Mean FEV_1, mL (MD)	8	30 (0.00, 60)	Ipratropium superior
Mean FVC, mL (MD)	8	70 (10, 140)	Ipratropium superior
QoL (CRQ) (MD)			
Dyspnoea	5	0.16 (0.09, 0.23)	Ipratropium superior
Fatigue	5	0.13 (0.02, 0.23)	Ipratropium superior
Emotion	5	0.17 (0.04, 0.29)	Ipratropium superior
Mastery	5	0.18 (0.06, 0.30)	Ipratropium superior
Symptoms (MD)			
Wheezing	5	-0.04 (-0.13, 0.04)	NS
Cough	5	-0.08 (-0.13, -0.03)	Significant for comparator
Shortness of Breath	5	0.00 (-0.09, 0.09)	NS
Tightness of Chest	5	0.01 (-0.06, 0.09)	NS
Drug-related AEs (OR)	6	0.71 (0.53, 0.97)	Ipratropium superior
Increasing/adding oral steroids	4	0.52 (0.37, 0.74)	Ipratropium superior
Ipratropium/SABA vs SABA			
Mean FEV_1, mL (MD)	7	0 (-30, 30)	NS
Mean FVC, mL (MD)	7	50 (-210, 120)	NS
QoL (CRQ) (MD)			
Dyspnoea	5	0.01 (-0.06, 0.08)	NS
Fatigue	5	0.02 (-0.09, 0.13)	NS
Emotion	5	0.02 (-0.12, 0.16)	NS
Mastery	5	0.03 (-0.09, 0.14)	NS
Symptoms (MD)			
Wheezing	7	0.01 (-0.07, 0.08)	NS
Cough	7	0.00 (-0.05, 0.05)	NS
Shortness of Breath	7	0.04 (-0.05, 0.13)	NS
Tightness of Chest	7	-0.02 (-0.09, 0.6)	NS
Drug-related AEs (OR)	5	1.16 (0.86, 1.57)	NS
Increasing/adding oral steroids	5	0.69 (0.50, 0.94)	Ipratropium superior
Exacerbations	1	0.42 (0.18, 0.96)	Ipratropium superior

Abbreviations: AE, Adverse event; CRQ, Chronic Diseases Respiratory Questionnaire; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MD, mean difference; NS, non-significant; OR, odds ratio; QoL, quality of life; SABA, short-acting β2-agonist

Source: Appleton et al 2006 Comparison 1 pg 34, Comparison 2 pg35

3.4.2 Summary

The results reported by Appleton et al 2006 supports the recommendations in the COPD-X Plan, which notes that ipratropium has a significantly greater effect on lung function compared to SABAs, in addition to improving QoL and decreasing need for oral corticosteroid treatment. These benefits occur with a decreased risk of adverse drug effects. In addition, ipratropium combined with SABA treatment reduces the number of patients experiencing exacerbations and the use of oral

corticosteroids, without increasing drug related AEs. The results reported by Appleton et al 2006 and the COPD-X Guidelines support the PBS listing of ipratropium.

3.5 Tiotropium economic evaluations

3.5.1 Aim

Tiotropium was listed on the PBS for treatment of COPD on the basis of acceptable cost-effectiveness compared with ipratropium. A substantial number of economic evaluations involving tiotropium for the treatment of COPD have since been published, and include analyses based on longer-term clinical trials as well as comparisons with other treatment options (e.g. other LAMAs).

The aim of this Submission is therefore to:

- Review and summarise the published literature as well as assessments undertaken by Health Technology Agencies (HTA) on the cost-effectiveness of tiotropium for the treatment of COPD, and;
- Confirm that tiotropium represents a cost-effective therapy for the treatment of COPD when compared to other LAMA's, usual care/placebo, ipratropium and in combination with ICS/LABAs.

3.5.2 Methodology

Literature review

A systematic review of the literature was undertaken in order to identify economic evaluations of tiotropium in COPD. The literature search was conducted using Embase.com, which includes both the Embase and MEDLINE databases. Additionally, a search of health technology agency (HTA) websites was conducted.

Embase and Medline

A literature search was conducted to identify relevant published economic evaluations with a particular emphasis on cost-effectiveness and cost-utility analyses of tiotropium for the treatment of COPD. The search strategy is provided in Appendix 1.

The literature search retrieved a total of 405 citations, which were reviewed by title and abstract. Economic evaluations were considered eligible for initial inclusion in the submission based on the following criteria:

- Population: Patients with COPD
- Intervention: tiotropium
- Comparator: Other LAMAs, placebo/usual care, ipratropium and ICS/LABA
- Study type: Systematic review of economic evaluations, individual economic evaluations, cost-effectiveness analysis or cost-utility analysis.

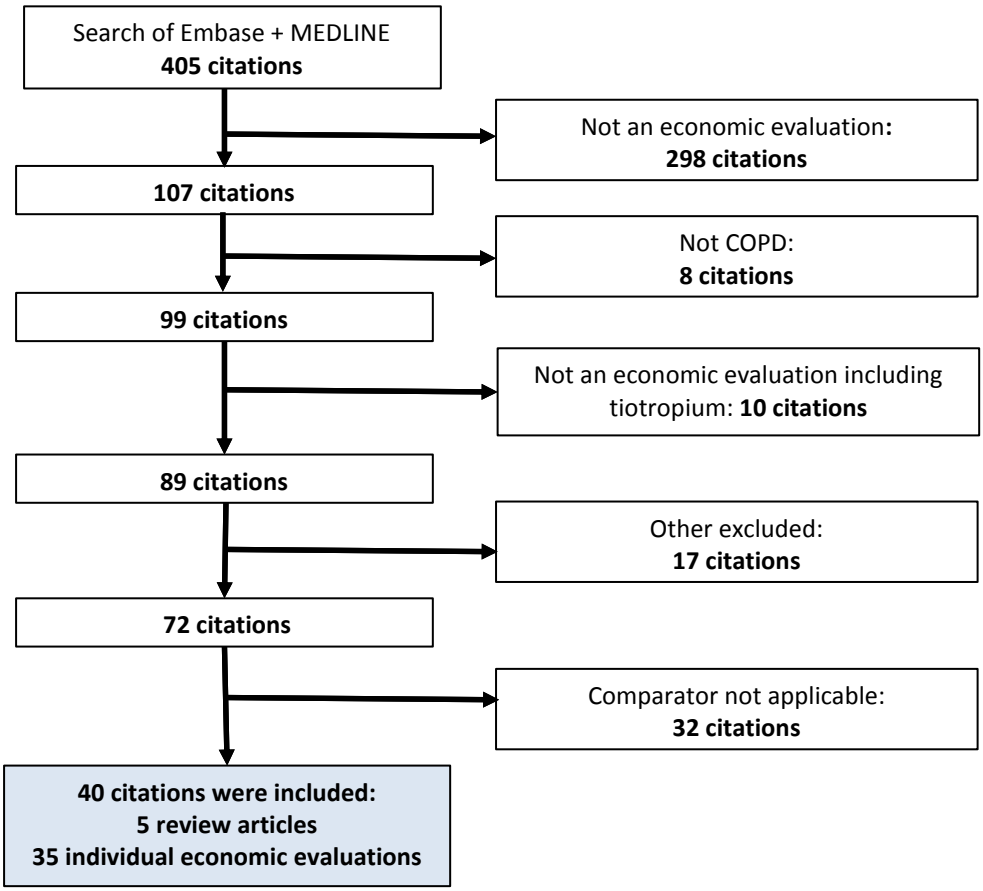
The choice of comparators was based on the PBAC Guidelines and the treatment algorithm for COPD. Section 3.2 summarises relevant comparators for tiotropium in the clinical context. Briefly, consistent with the PBAC Guidelines, other LAMAs are the most relevant comparator in terms of treatments that tiotropium would most likely replace in clinical practice as they are pharmacological analogues and have the same reimbursed indication as tiotropium. In addition, we present an

updated review of the cost-effectiveness of tiotropium versus the original comparator, ipratropium. It is also important for the Review to consider economic evaluations based on long-term evidence for tiotropium as seen in UPLIFT (Tashkin et al 2008); which provided data for long-term outcomes such as exacerbations, hospitalisations and mortality.

It is very important for the Review to note that in the clinical context, ICS/LABA is not considered a comparator to tiotropium. As recommended by clinical practice guidelines and consistent with PBS restrictions, ICS/LABA is intended for a different population of use: ICS/LABA is a treatment option in a subgroup of severe COPD patients with FEV1 <50% predicted and two or more previous exacerbations whereas tiotropium is a long-term maintenance treatment option for patients with moderate to severe COPD, providing symptom relief and exacerbation protection. The PBAC has considered ICS/LABAs are more likely to be added to tiotropium therapy rather than replace tiotropium (Indacaterol PSDs November 2010; July 2011). Therefore, economic evaluations of ICS/LABA as add-on therapy to tiotropium are included in the submission.

Overall, a total of 40 economic evaluations were included in the review of which five were systematic reviews of economic evaluations (D'Souza et al 2006, Mauskopf et al 2010, Rutten-van Mölken and Goossens, 2012, Simoens, 2013, Starkie et al 2008) and the remaining 35 publications were economic evaluations involving tiotropium for the treatment of COPD. A flow diagram of the literature review is presented in Figure 3.3.

Figure 3.3 Flow diagram of Embase + Medline literature review



3.5.2.1 Health technology agency assessments

A review of HTA websites was conducted with the aim of identifying economic evaluations or technology appraisals of tiotropium for COPD that had not already been identified in the systematic review of the literature. The link to the website as well as the search terms used and the number of economic evaluations are presented in Table 3.27.

Table 3.27 List of HTA websites, search strings, and retrieved citations

Organisation	Query	Unique economic evaluations
Canadian Agency for Drugs and Technologies in Health http://www.cadtha.ca	COPD, chronic obstructive pulmonary disease, tiotropium	2
Pharmacology and Therapeutics Advisory Committee http://www.pharmac.govt.nz/ptac	COPD, chronic obstructive pulmonary disease, tiotropium	0
National Institute of Health and Clinical Excellence http://www.nice.org.uk	COPD, chronic obstructive pulmonary disease, tiotropium	3
Scottish Medicines Consortium http://www.scottishmedicines.org.uk	COPD, chronic obstructive pulmonary disease, tiotropium	2

3.5.3 Tiotropium vs other LAMAs

3.5.3.1 Methods Used

A total of 12 economic evaluations were identified that assessed the cost-effectiveness of tiotropium versus other LAMAs (Table 3.28) (Baldwin et al 2012, Chan et al 2014, Costa-Scharplatz et al 2015, Costa-Scharplatz et al 2013, Eklund et al 2015a, Eklund et al 2015b, Eklund et al 2015c, Giraldo et al 2014, Ismaila et al 2014, Karabis et al 2014, Malcolm et al 2013, Torres et al 2013). Ten studies compared tiotropium with glycopyrronium, one with umeclidinium (Ismaila et al 2014) and one with aclidinium (Karabis et al 2014).

The methodologies used included Markov models (Baldwin et al 2012, Costa-Scharplatz et al 2015, Costa-Scharplatz et al 2013, Eklund et al 2015a, Eklund et al 2015b, Eklund et al 2015c, Giraldo et al 2014, Karabis et al 2014, Malcolm et al 2013, Torres et al 2013), a linked equation cohort model (Ismaila et al 2014) and a retrospective cohort model (Chan et al 2014). The Markov models were primarily informed by clinical trial data, including the UPLIFT (Eklund et al 2015a, Eklund et al 2015b, Eklund et al 2015c, Karabis et al 2014), ACCORD I (Karabis et al 2014), SPARK (Eklund et al 2015a, Eklund et al 2015b, Eklund et al 2015c), GLOW 2 (Costa-Scharplatz et al 2015, Costa-Scharplatz et al 2013), a meta-analysis (Giraldo et al 2014) and non-specified clinical trial data (Baldwin et al 2012, Malcolm et al 2013, Torres et al 2013). The retrospective cohort model by Chan et al (2014) was based on observational data obtained from the Taiwanese National Health Insurance Database, whilst the linked equations cohort model by Ismaila et al (2014) was based on a comprehensive systematic review.

The economic evaluations were conducted for a large number of countries including Sweden, Spain, UK, Colombia, US, Taiwan and Canada with time horizons including 24-weeks (1 study), three years

(5 studies), five years (3 studies) and lifetime (3 studies). The most frequently used cycle length in the Markov models was three months.

In the Markov models, patient lung capacity was used to allocate subjects into four mutually exclusive health states. These were based on the GOLD Spirometric classification stages II to IV (GOLD 2016) and were determined based on forced expiratory volume in 1 second (FEV_1). The defined health states were moderate, severe and very severe COPD and the absorbing health state death. Within each cycle and from each health state, subjects could experience a severe or non-severe exacerbation. A severe exacerbation was typically assumed to be associated with a hospitalisation. The analysis by Chan et al (2014) utilised the medical and pharmacy records of one million Taiwanese participants to assess the healthcare resource costs of COPD management. The work by Ismaila et al (2014) was based on a COPD cohort disease progression also based on lung function.

The national health care system and societal perspectives were the most frequently used.

3.5.3.2 Patient Characteristics

Typically, patients with a diagnosis of moderate to very severe COPD were included in the economic evaluations. This was consistent with the population included in clinical trials used to inform the input variables of the models. Patients in all studies were generally at least 40 years of age, with an average age of 65 years (average age range 64-65.1 years). In the retrospective cohort study by Chan et al (2014), 57% of patients were male and 41.6% had hypertension as a comorbidity. The patients included in Karabis et al (2014) model were either current smokers or ex-smokers with consumption of more than ten pack years.

3.5.3.3 Outcomes and costs

Typically, outcomes were measured in quality adjusted life years (QALYs), life years (LYs) and exacerbations avoided.

Eight studies reported outcomes in terms of incremental QALYs (Costa-Scharplatz et al 2015, Costa-Scharplatz et al 2013, Eklund et al 2015a, Ismaila et al 2014, Karabis et al 2014, Torres et al 2013, Eklund et al 2015b, Eklund et al 2015c) and four included LYs (Costa-Scharplatz et al 2015, Ismaila et al 2014, Karabis et al 2014, Torres et al 2013). Four studies reported the impact of treatment on exacerbations (Costa-Scharplatz et al 2015, Eklund et al 2015a, Karabis et al 2014, Malcolm et al 2013).

Five studies reported using utility values from the published literature (Costa-Scharplatz et al 2015, Costa-Scharplatz et al 2013, Karabis et al 2014, Torres et al 2013, Eklund et al 2015a). Eklund et al (2015a) used the baseline utility weights from the work of Ståhl et al (2005) and Karabis et al (2014) used the utility values from the study by Rutten-van Mölken et al (2006). Costa-Scharplatz et al (2015), Costa-Scharplatz et al (2013) and Torres et al (2013) did not specify the source of the published literature used. Eklund et al (2015b), Eklund et al (2015c) and Ismaila et al (2014) did not report if utility values were estimated or obtained from the published literature.

The number of exacerbations avoided was an important outcome in all analyses as a substantial proportion of the total cost of treatment were due to the management of exacerbations (e.g.

hospitalisations). Additional costs that were typically considered in the analyses included disease maintenance costs and intervention costs encompassing, drug acquisition costs, outpatient care, diagnostic tests and oxygen therapy. Indirect costs such as productivity losses were generally not considered since the starting age of patients entering the model of, on average, 65 years often coincided with the onset of retirement from the workforce (Eklund et al 2015a).

3.5.3.4 Results

Karabis et al (2014) evaluated the cost-effectiveness of aclidinium and tiotropium. Over the five-year time horizon, 4.25 life years were gained under both tiotropium and aclidinium. The QALYs for tiotropium and aclidinium were 3.49 and 3.50 respectively. On average, treatment with tiotropium was US$2,317 more costly when compared with aclidinium, which was attributed to marginally more exacerbations experienced by those treated with tiotropium and to the lower unit price of aclidinium (US$11,162 versus US$12,361). Given the similarities in life year and QALY gains, tiotropium could be at least as equally cost effective as aclidinium under an equal price regimen.

At price parity, the study by Ismailia et al (2014) reported that umeclidinium dominated tiotropium. However, there were only marginally more QALYs and LYs associated with umeclidinium (0.0009 and 0.0001 respectively) with an incremental cost reduction of £4.54. Hence, tiotropium may be considered at least as cost effective as umeclidinium in this analysis.

The short term evaluations that compared glycopyrronium with tiotropium reported that glycopyrronium was more cost-effective than tiotropium (Baldwin et al 2012, Chan et al 2014, Costa-Scharplatz et al 2015, Costa-Scharplatz et al 2013, Giraldo et al 2014, Malcolm et al 2013, Torres et al 2013). However, in the long-term evaluations (lifetime horizon), tiotropium was considered cost-effective when compared with glycopyrronium, with superior gains in QALYs and lower risk of exacerbation (Eklund et al 2015a, Eklund et al 2015b, Eklund et al 2015c). These long-term studies were based on the four-year UPLIFT trial (Tashkin et al 2008, see Section 3.2 for further discussion of UPLIFT). In the Swedish context, the QALYs associated with tiotropium and glycopyrronium were 7.25 and 7.02 respectively (Eklund et al 2015a), while the total cost of treatment with glycopyrronium was SEK 180,272 compared with SEK 182,695 for tiotropium. The resultant ICER equalled SEK 10,456 per QALY gained. Tiotropium was therefore considered to be the most cost-effective treatment option, especially because it lowered the risk for severe exacerbations. Similarly, in the Spanish context, treatment with tiotropium resulted in an incremental QALY gain of 0.25 compared with glycopyrronium (Eklund et al 2015c). The corresponding ICER for this analysis was €4,281/QALY. The reduction in exacerbations under tiotropium compensated for the higher cost of tiotropium (incremental cost of €2,014 over a lifetime treatment).

Overall, the cost-effectiveness of tiotropium compared with glycopyrronium is realised in the long term. This is supported by the clinical evidence which shows that tiotropium is the only LAMA which has shown to reduce exacerbations, associated hospitalisations and mortality over the long term (see Section 3.2). Furthermore, the modelled clinical outcomes with tiotropium and either umeclidinium or aclidinium in the cost-effectiveness analyses are similar, demonstrating that the results are predominantly driven by the time horizon and the unit price. It follows that when both these variables are set equal, tiotropium will be similarly cost-effective to other LAMAs.

Table 3.28 Economic evaluations of tiotropium vs other LAMAs

Author	Country	Treatment	Comparator	Method	Data	Time Horizon	Exacerbations	Costs	QALYs/LYs	ICER	Probability of being cost-effective at various thresholds	Author's conclusions
Costa-Scharplatz et al (2013)	Sweden	glycopyrronium	tiotropium	Markov	GLOW2	3 years	N/A	Annual drug costs: €447 (GLY) vs €589 (TIO), Total 3-year cost savings €656/patient under GLY	QALY gain of 0.005 under GLY	N/A	99% of generated samples with GLY to be dominant	GLY cost-effective, lower price than TIO
Torres et al (2013)	Spain	glycopyrronium	tiotropium	Markov	N/A	5 years	N/A	€2,225 (GLY) vs €2375 (TIO)	QALYs: 3388 (GLY) vs 3377 (TIO), LYs:4321 (GLY) vs 4315 (TIO)	N/A	GLY dominant in 100% of PSA simulations	GLY cost-effective, lower TCs than TIO due to marginally higher QALYs/LYs
Malcolm et al (2013)	UK	glycopyrronium	tiotropium	Markov	N/A clinical trials, Optimum Patient Care Research Database	3 years	incremental -0.176 exacerbations under GLY	Incremental cost -£194.80 under GLY at 10% discount to TIO price	N/A	N/A	GLY dominant in 65% of PSA simulations	GLY cost-effective if it assumed that GLY reduces exacerbations risks
Baldwin et al (2014)	Sweden	glycopyrronium	tiotropium	Markov	N/A Phase III trial	3 years	N/A	N/A	N/A	N/A	N/A	GLY cost-effective at $75,188/QALY, up to a public price of $2.78
Giraldoe t al (2014)	Colombia	glycopyrronium	tiotropium	Markov	N/A meta-analysis	5 years	N/A	Savings per patient of $464/year under GLY	N/A	N/A	GLY dominant against TIO in 90% of iterations	GLY cost-effective due to cost savings

Author	Country	Treatment	Comparator	Method	Data	Time Horizon	Exacerbations	Costs	QALYs/LYs	ICER	Probability of being cost-effective at various thresholds	Author's conclusions
Ismaila et al (2014)	UK	umeclidinium	tiotropium	Linked equations cohort model	N/A systematic review	24 weeks	N/A	Drug costs were equal: £33.5/month, incremental cost reduction of £4.54 (UMC)	UMC dominated TIO, incremental QALY 0.0009, LYs 0.0001	N/A	UMC dominant under sensitivity analysis	At price parity, UMC cost-effective due to incremental QALY/LY gains
Karabis et al (2014)	USA	aclidinium	tiotropium	Markov	UPLIFT, ACCORD I	5 years	3.364 exacerbations (ACL) vs 3.390 exacerbations (TIO)	TC: $126,274 (ACL) vs $128,591 (TIO) over 5 years	4.52 LYs gained for both, QALYs: 3.49 (TIO), 3.50 (ACL)	ACL Dominant	Sensitivity driven by costs	ACL cost-effective due to cost savings compared to TIO
Chan et al (2014)	Taiwan	glycopyrronium	tiotropium	Retrospective cohort	Taiwan Health Data	3 years	N/A	N/A	N/A	N/A	GLY dominant under PSA simulations	GLY cost-effective, results determined by time horizon and efficacy of GLY
Eklund et al (2015)	Sweden	tiotropium	glycopyrronium	Markov	UPLIFT & SPARK	Lifetime	Severe exacerbations in very severe COPD disease 0.08 (TIO) vs 0.12 (GLY)	TIO increased total costs by SEK 2423	QALY gain of 0.23 under TIO	SEK 10,456/QALY	At WTP SEK 600,000, TIO is cost effective 90% of iterations	TIO is cost-effective due to exacerbation prevention
Eklund et al (2015)	Canada, Sweden, UK	tiotropium	glycopyrronium	Markov	UPLIFT & SPARK	Lifetime	N/A	Incremental cost under TIO: -$955(Can), SEK3224, -£164 (UK)	Gain in QALYS under TIO: 0.23(Can), 0.24(Swe),0.25(UK)	N/A	N/A	TIO cost-effective in CAN and UK, GLY in Sweden. Results driven by severe exacerbation risks under treatments

Author	Country	Treatment	Comparator	Method	Data	Time Horizon	Exacerbations	Costs	QALYs/LYs	ICER	Probability of being cost-effective at various thresholds	Author's conclusions
Eklund et al (2015)	Spain	tiotropium	glycopyrronium	Markov	UPLIFT & SPARK	Lifetime	N/A	€41,129/patient(TIO) vs €40,063/patient(GLY) over lifetime. i.e. Incremental cost of €2014 under TIO	7.77 QALYs (TIO) vs 7.52 (GLY) i.e. incremental gain of 0.25 QALYs under TIO	€4,281/QALY	N/A	TIO cost-effective, attributed to TIO superiority in preventing exacerbations
Costa-Scharplatz et al (2015)	Sweden	glycopyrronium	tiotropium	Markov	GLOW 2	3 years	Direct exacerbations costs -SEK1228, indirect exacerbations costs -SEK244 under GLY	Incremental cost -SEK 5197 under GLY	0.05 QALYs, 0.001LYs gained under GLY	N/A	GLY dominant in 99% of PSA iterations	GLY cost-effective due to lower unit price

Abbreviations: ACL, aclidinium; Can, Canada; CHF, Swiss Franc; FEV1, forced expiratory volume at 1 second; GLY, glycopyrronium; IC, incremental cost LY(s), life year(s); LYG, life year gained; N/A, not available; NNT, number needed to treat; PBO, Placebo; PSA, probabilistic sensitivity analysis; QALY(s), quality adjusted life year(s); RR, relative risk; SEK, Swedish Krona; SGRQ, St. George's Respiratory Questionnaire; TC, total costs; TIO, tiotropium; UC, usual care; UMC, Umeclidinium; vs, versus; WTP, willingness to pay.

3.5.4 Tiotropium vs usual care/placebo

3.5.4.1 Methods Used

The majority of tiotropium RCTs were designed with tiotropium as add-on to usual-care therapy including the four-year UPLIFT study (see Section 3.2). As such, eight studies were identified that estimated the cost-effectiveness of tiotropium with usual care (Table 3.29) (Atsou et al 2011, Hettle et al 2012, Povero et al 2013, Schramm et al 2005, Zalis' ka et al 2012, Zaniolo et al 2012, Friedman et al 2004, Eklund et al 2015a). A further two studies compared tiotropium with placebo (Lee et al 2006, Oba, 2007).

Of the studies that compared tiotropium with usual care, five adopted a Markov modelling approach (Atsou et al 2011, Eklund et al 2015a, Hettle et al 2012, Schramm et al 2005, Zaniolo et al 2012) while one used a trial based-analysis (Povero et al 2013), one used retrospective analysis (Friedman et al 2004) and one used a combination of trial-based and retrospective analyses (Zalis' ka et al 2012). The trial-based retrospective analyses by Zalis'ka et al (2012) were based on the POET study and Ukrainian outpatient and hospitalisation data. The analyses by Povero et al (2013), Atsou et al (2011) and Schramm et al (2005) were presented as an abstract only and did not specify the data source used to inform the analysis. Three Markov models by Eklund et al (2015a), Hettle et al (2012) and Zaniolo et al 2012 were based on the UPLIFT trial.

The economic evaluations adopted time horizons of one year (5 studies), 24-months (1 study), four years (1 study) and lifetime (3 studies) and were conducted for countries including USA, Sweden, Switzerland, Singapore, France, Ukraine, UK, Belgium and Italy.

Consistent with previously presented Markov models, patient lung capacity measured based on FEV_1 was used to allocate subjects into four mutually exclusive health states of moderate, severe and very severe COPD and the absorbing health state death. Within each cycle and from each health state, subjects could experience a severe or non-severe exacerbation. A severe exacerbation was typically assumed to be associated with a hospitalisation.

The national health care system and societal perspectives were the most frequently used.

3.5.4.2 Patient Characteristics

The economic evaluations typically considered patients with a diagnosis of moderate to very severe COPD, with an average age of 65 years (range: 64.5 - 70.3 years). Baseline patient characteristics in both the tiotropium and placebo arm from the UPLIFT trial were reported as; approximately 75% of subjects were male, 30% were current smokers and 47% were taking some form of respiratory medication (Hettle et al 2012). The patient characteristics in the simulated cohort model by Zaniolo et al (2012) included an average age of 70.3, 27% were female and 18.5% were current smokers, while the patients considered in the Friedman et al (2012) retrospective study had a smoking history of at least ten pack years.

3.5.4.3 Outcomes and costs

The outcomes of the economic evaluations were measured in quality adjusted life years (QALYs), life years (LYs) and exacerbations avoided.

Six studies reported outcomes in terms of QALYs (Atsou et al 2011, Hettle et al 2012, Oba, 2007, Povero et al 2013, Zaniolo et al 2012, Eklund et al 2015a) and three reported LYs (Atsou et al 2011, Zaniolo et al 2012, Eklund et al 2015a). Eight studies also reported the impact of treatment on exacerbations (Friedman et al 2004, Hettle et al 2012, Lee et al 2006, Povero et al 2013, Schramm et al 2005, Zalis' ka et al 2012, Zaniolo et al 2012, Eklund et al 2015a).

For those studies that reported outcomes in terms of QALYs, the utility scores were derived from the clinical trial data or from the literature. Oba (2007) and Povero et al (2013) both used the method by Ståhl et al (2005) to estimate utility values from SGRQ Scores. Hettle et al (2012) and Zaniolo et al (2012) derived utility scores from the UPLIFT trial while Atsou et al (2011) reported estimating values but did not specify the methodology used.

The number of exacerbations avoided was an important outcome in all analyses as a substantial proportion of the total cost of treatment was due to the management of exacerbations (e.g. hospitalisations). Additional costs that were typically considered in the analyses included disease maintenance costs and intervention costs. Similar to the comparison of tiotropium with other LAMAs, indirect costs such as productivity losses were generally not considered as the starting age of patients in the model of, on average, 65 years, coincided with the onset of retirement from the workforce (Oba, 2007, Eklund et al 2015a). However, Zalis' ka et al (2012) did include indirect costs associated with productivity loss and temporary disability related payments.

3.5.4.4 Results

The Markov model by Hettle et al (2012) was based on the UPLIFT study and was applied to the UK and Belgian context. The result of this analysis showed that over the four-year time period, the incremental QALYs associated with the addition of tiotropium to usual care were 0.052 and 0.051 for Belgium and the UK, respectively. The ICERs were €18,617 (Belgium), £15,567 (England) and £15,890 (other UK) per QALY. At a willingness to pay threshold of £30,000 per QALY, the addition of tiotropium to usual care was considered cost-effective in England.

Similarly, the Markov model by Zaniolo et al (2012) was based on the UPLIFT trial and assessed the cost-effectiveness of tiotropium with usual care from the perspective of the Italian national healthcare system. The analysis showed that over a time horizon of a lifetime, patients treated with tiotropium gained an average of 0.50 LYs, 0.42 QALYs and experienced a reduction of 0.79 exacerbation events compared with patients treated with usual care. The associated ICER was €7,916/QALY. Probabilistic sensitivity analysis indicated that tiotropium had a 90% probability of being cost-effective at a willingness to pay threshold of €10,000/QALY and a 100% probability of cost-effectiveness at €16,450/QALY.

The Markov model developed by Eklund et al (2015) was based on the UPLIFT trial and was applied to the Swedish setting. There were 0.007 QALYs and 0.08 LYs gained under tiotropium over a time horizon of a lifetime horizon. The associated ICER was SEK 224,850 per QALY gained, which indicated that tiotropium was considered cost-effective compared with usual care. Sensitivity analysis showed that cost-effectiveness increased with time and this was attributed to a reduction in exacerbations as a result of treatment with tiotropium.

Lee et al (2006) compared tiotropium with placebo using a trial-based method. Tiotropium was considered a cost-effective treatment option in Singapore due to cost-savings achieved from averted hospital admissions caused by exacerbations. It was estimated that up to 79% (at least 32%) of the cost saving associated with tiotropium treatment were due to a reduction in exacerbation related hospitalisations. Oba's (2007) retrospective analysis comparing tiotropium with placebo reported an incremental gain of 0.032 QALYs and an ICER of US$26,094/QALY under tiotropium in the US setting. There was a 93% probability of tiotropium being cost-effective at a willingness to pay of $50,000/QALY. Zalis' ka et al (2012) reported that in the Ukraine, tiotropium was cost-effective compared with usual care, with the decrease in exacerbation costs under tiotropium amounting to €114,380.78 for 1000 patients. Povero et al (2013) found that with tiotropium treatment, in FEV_1≤50% (severe) patient's hospital costs decreased from 74.1% to 67.3% of all COPD costs, while for FEV_1>50% (mild to moderate) patient hospital costs decreased from 64.5% to 31.6% of total costs. The retrospective study by Friedman et al (2004) determined tiotropium to be cost-effective in the United States given that the acquisition costs were less than US$1,043 a year.

Overall, the results of all studies showed that adding tiotropium to usual care is associated with an incremental cost, but this is largely offset by the cost savings achieved from reduced hospitalisations due to exacerbations. All studies conclude that tiotropium is a cost-effective treatment option compared with usual care/placebo for the treatment of COPD, and this is consistent across both short and long term time horizons. The cost-effectiveness of tiotropium is supported by the clinical evidence which shows that tiotropium reduces exacerbations, associated hospitalisations and mortality over the long-term (see Section 3.2).

Table 3.29 Economic evaluations of tiotropium vs Usual care/Placebo

Author	Country	Treatment	Comparator	Method	Data	Time Horizon	Exacerbations	Costs	QALYs/LYs	ICER	Probability of being cost-effective at various thresholds	Author's conclusions
Friedman et al (2004)	USA	tiotropium	usual Care	Retrospective	N/A TIO Studies	1 year	20% decrease in exacerbations under TIO	$US3926 (TIO+UC) vs $4970(UC)	N/A	N/A	TIO cost-effective given acquisition costs are <$US1043/p.a.	Cost of hospital admissions accounted for 48% of total direct costs
Schramm et al (2005)	Switzerland	tiotropium	usual care	Markov	N/A	1 year	NNT TIO is 13 relative to UC	CHF 4788 (TIO) vs CHF 4920 (UC)	N/A	N/A	N/A	Higher acquisition costs of TIO were offset by lower hospitalisation costs due to less exacerbations
Lee et al (2006)	Singapore	tiotropium	placebo	Trial-based	Casaburi et al Brusasco et al Niewoehner et al	1 year	Cost-savings from reduction in exacerbations related hospitalisations ranged from S$57.16 to S$322.49	Cost saving range fromS$145.40 to S$840.37 under TIO	N/A	N/A	The range of cost savings associated with reduced hospitalisations under TIO was between 32% and 79%	TIO cost-effective especially in severe patients
Oba (2007)	USA	tiotropium	placebo	Retrospective	Donohue et al Brusasco et al	1 year	N/A	$835 incremental cost under TIO	Incremental 0.032 QALYs gain (TIO)	$26,094/QALY	93% probability that TIO cost effective at WTP of $50,000/QALY	TIO cost saving compared to UC

Author	Country	Treatment	Comparator	Method	Data	Time Horizon	Exacerbations	Costs	QALYs/LYs	ICER	Probability of being cost-effective at various thresholds	Author's conclusions
Atsou et al (2011)	France	tiotropium	usual care	Markov	N/A	Lifetime	N/A	€5380/patient additional (TIO)	Gain 0.12 LYs, 0.58 QALYs (TIO)	€8,853/QALY	N/A	TIO was cost-effective, however only resulted in modest health gains
Zalis'ka et al (2012)	Ukraine	tiotropium	usual care	Trial-based/retrospective	POET	Year 2012	Decrease in exacerbation costs under TIO was €114,380.78	€508,983,73/1000 employed patients (TIO) vs €498,052.34/1000 employed patients (UC)	N/A	N/A	N/A	TIO more cost-effective due to decrease in exacerbation related costs
Hettle et al (2012)	UK and Belgium	tiotropium+ UC	usual care	Markov	UPLIFT	4 years	Belgium: hospital exacerbations €7590, non-hospital exacerbations €231 UK: hospital exacerbations £3726(England), £3329(rest of UK), non-hospital exacerbations £118 (all UK)	UK: UC/month; £39.50(moderate), £82.88(severe), £40.20(very severe), TIO £32.13/month Belgium: UC/month; €97 (moderate), €173 (severe), €376(very severe), TIO €51/month	Incremental QALYs with addition of TIO: 0.052(Belgium), 0.051 (UK)	(TIO): €18,617/ QALY (Belgium), £15,567/ QALY (England) and £15,890/ QALY (other UK)	England: WTP of £30,000 per QALY, addition of TIO was cost-effective	Addition of TIO to UC is cost-effective, with incremental gain in QALYs
Zaniolo et al (2012)	Italy	tiotropium+ UC	usual care	Markov	UPLIFT	Lifetime	9.33/patient (TIO) vs 10.12/patient(UC)	€33,484/patient (TIO) vs €30,127/patient (UC), Increment of €3,357	Incremental/patient gains with addition of TIO: 0.50LYs, 0.42QALYs	I€6,698/LY, €7,916/QALY, gained, €4,240/exacerbations avoided	PSA TIO 90% probability of being cost-effective at WTP of €10,000/QALY, 100%	Addition of TIO to UC is cost-effective, benefits outweigh incremental costs

Author	Country	Treatment	Comparator	Method	Data	Time Horizon	Exacerbations	Costs	QALYs/LYs	ICER	Probability of being cost-effective at various thresholds	Author's conclusions
											probability of cost-effectiveness at €16,450/QALY	
Povero et al (2013)	Italy	tiotropium	usual care	Trial-based	N/A	24 months	FEV1≤50% hospital costs decrease from 74.1% to 67.3%, FEV1>50% costs decrease from 64.5% to 31.6% of TC	With TIO save €215 for FEV_1≤50%, €900 FEV_1>50%	FEV1≤50% gain 0.07 QALYs, FEV1>50% gain 0.03 QALYS	N/A	TIO dominant in 30% FEV1≤50%, 37% FEV1>50%; 2% FEV1≤50%, 7% FEV1>50% associated with worsening life quality	Additional costs of TIO offset by savings in reduced hospitalisations
Eklund et al (2015)	Sweden	tiotropium	usual Care	Markov	UPLIFT & SPARK	Lifetime	Severe exacerbations in very severe COPD disease 0.08(TIO) vs 0.08(UC)	TIO increased total costs by SEK 15,041	QALY gain of 0.007, 0.08 LYs under TIO	SEK 224,850/QALY	At 5-year time period ICER SEK 592,149	TIO cost-effective than UC, cost-effectiveness increases with time

Abbreviations: Can, Canada; CHF, Swiss Franc; FEV1, forced expiratory volume at 1 second; IC, incremental cost; IPR, ipratropium; JPY, Japanese Yen; LY(s), life year(s); LYG, life year gained; N/A, not available; NNT, number needed to treat; PBO, Placebo; PSA, probabilistic sensitivity analysis; QALY(s), quality adjusted life year(s); RR, relative risk; SEK, Swedish Krona; SGRQ, St. George's Respiratory Questionnaire; TC, total costs; TIO, tiotropium; UC, usual care; vs, versus; WTP, willingness to pay.

3.5.5 Tiotropium vs ipratropium

3.5.5.1 Methods Used

The eleven studies that assessed the cost-effectiveness of tiotropium versus ipratropium are summarised in Table 3.30 (Schramm et al 2005, Ruiz et al 2005, Oostenbrink et al 2005, Oostenbrink and Rutten-van Mölken, 2004, Oostenbrink et al 2004, Onukwugha et al 2008, Igarashi et al 2010, Gani et al 2010, Brosa et al 2009, Rutten-van Mölken et al 2007, Oba, 2007).

The methods used to estimate the cost effectiveness of tiotropium versus ipratropium included Markov models (Gani et al 2010, Igarashi et al 2010, Oostenbrink et al 2005, Rutten-van Mölken et al 2007), trial-based analysis (Oostenbrink et al 2004, Ruiz et al 2005), cox proportional hazards modelling (Oostenbrink and Rutten-van Mölken, 2004), retrospective evaluation (Oba, 2007, Onukwugha et al 2008) and non-specified methods (Schramm et al 2005). Five models were based on the study by Vincken et al (2002) (Gani et al 2010, Oostenbrink et al 2004, Oostenbrink and Rutten-van Mölken, 2004, Oostenbrink et al 2005, Ruiz et al 2005). Onukwugha et al's (2008) retrospective study was based on a comparison of the electronic medical records of ipratropium patients at the Maryland Veteran Affairs Health Care Centre with a hypothetical cohort of patients receiving tiotropium treatment. Rutten-van Mölken et al's (2007) Markov model was based on the study by Oostenbrink et al (2005). The studies by Schramm et al (2005), Brosa et al (2009) and Igarashi et al (2010) did not report the data sources used to inform input variables into the economic evaluation.

The analyses were conducted for a diverse range of countries, including The Netherlands, Belgium, Switzerland, Canada, Spain, USA, Japan, and the UK. The most common time horizon used was one year (seven studies) although two studies employed a time horizon of five years and one study and thirteen years. The most frequently used cycle length was of one-month duration.

Patient lung capacity measured based on FEV_1 was again used to allocate subjects into four mutually exclusive health states of moderate, severe and very severe COPD and the absorbing health state death. Within each cycle and from each health state, subjects could experience a severe or non-severe exacerbation. A severe exacerbation was typically assumed to be associated with a hospitalisation.

All evaluations took the perspective of the national health care system.

3.5.5.2 Patient Characteristics

The population considered in the economic evaluations were consistent with the patients included in the clinical trials that were used to inform the input variables of the model, where this was reported. As such, the analyses considered patients with a diagnosis of moderate to very severe COPD and who were generally at least 40 years of age, with an average age range of 64-69 years. Furthermore, patients were typically also either current or ex-smokers with a history of at least 10 pack-years (Oostenbrink et al 2004, Oostenbrink and Rutten-van Mölken, 2004). Those who required regular supplementary oxygen, had other significant comorbidities or a history of asthma were excluded in the studies based on Vincken et al (2002).

3.5.5.3 Outcomes and costs

The outcomes of the economic evaluations were typically measured in terms of QALYs, LYs and exacerbations avoided.

Four studies reported outcomes in terms of exacerbations, LY and SGRQ score (Brosa et al 2009, Onukwugha et al 2008, Oostenbrink et al 2004, Ruiz et al 2005) while five reported QALYs (Gani et al 2010, Igarashi et al 2010, Oba, 2007, Oostenbrink et al 2005, Rutten-van Mölken et al 2007). For those studies that reported outcomes in terms of QALYs, the utility scores were derived from the clinical trial data or the published literature. Oostenbrink et al (2005) obtained utility values from the observational study by Borg et al (2004) and Oba (2007) used the method by Ståhl et al (2005) to estimate utility values from SGRQ scores. Rutten-van Mölken et al (2007) used utilities from the EuroQol 5-dimension instrument (EQ-5D) scores at baseline in a random subset of patients from the UPLIFT trial. Igarashi et al (2010) reported using utility scores from an assessment of COPD out-patients at the Hokkaido University Hospital. Gani et al (2010) obtained utility scores from the work by Rutten-van Mölken et al (2006).

The number of exacerbations avoided was again a key driver of the economic evaluation. Additional costs that were typically considered in the analyses included disease maintenance costs and intervention costs. Indirect costs such as productivity losses were not considered because less than ten percent of the study population were engaged in paid work at the starting age of the models (on average, 65 years)(Oostenbrink et al 2004).

3.5.5.4 Results

Tiotropium was superior to ipratropium in all studies. Ruiz et al (2005) reported that in the Spanish setting, exacerbations were reduced by 37.6% under tiotropium compared with ipratropium. Moreover, the number of days in hospital were reduced by 33% which was associated with €174,906 in savings per 100,000 people. In the American setting, Onukwugha et al (2008) reported that treatment with tiotropium resulted in cost savings due to the reduction in exacerbations. Cost savings were realised in patients with very severe disease and patients with a previous COPD related hospitalisation, with respective ICERS of -$1,818 and -$4,472 per exacerbation avoided relative to ipratropium. When considering patients in all disease states, the pooled incremental cost-effectiveness ratio was $2,360 per exacerbation avoided. In Spain, Brosa et al (2010) found that tiotropium was cost-effective with an ICER of €4,208 per life year gained.

Many studies reported the probability of being cost-effective at a willingness to pay threshold. This was described in terms of willingness to pay per exacerbation avoided or willingness to pay per QALY. Oostenbrink et al (2004) reported that tiotropium was cost-effective in 80% of simulations at a willingness to pay threshold of €2,000/exacerbation avoided in the Belgian and Dutch context. Oostenbrink et al (2005) evaluated the cost-effectiveness of tiotropium and ipratropium for the treatment of COPD in the Netherlands and Canada but did not find a significant difference in quality adjusted life months between tiotropium and ipratropium (8.42 and 8.11 respectively). Considering all costs, in the Netherlands, tiotropium was the least expensive treatment (€1,760) compared to ipratropium (€1,930). In Canada, ipratropium was €2 less expensive than tiotropium. However, tiotropium had the highest probability of being cost-effective when the ceiling ratio for avoiding an

exacerbation was above €160. In the Dutch context, tiotropium was cost-effective in 60% of iterations at a willingness to pay threshold of €500 to avoid one exacerbation.

Oba (2007) found that there were 0.11 less hospitalisations per year under tiotropium compared with ipratropium. Treatment with tiotropium resulted in a saving of $391 per patient per year. Tiotropium was cost-effective compared with ipratropium in 93% of iterations at a willingness to pay threshold of $50,000/QALY. Rutten-van Mölken et al (2007) found that an outlay of at least €8,157/QALY was required for tiotropium to be cost-effective in Spain. Igarashi et al (2010) found that, if all 220,000 COPD patients in Japan used tiotropium, savings would equate to US$2.34 billion. Gani et al (2010) compared the cost-effectiveness and budget impacts of tiotropium and ipratropium in the UK. In England, the estimated annual cost of tiotropium was £1,350 per patient compared to £1,427 for ipratropium. For the rest of the UK, these costs were £1,439 and £1,631 respectively. At a ceiling ratio of £20,000 per QALY, tiotropium had at least a 97% chance of being cost-effective. In all disease states the incremental QALY was at least 0.02 and in favour of tiotropium therapy.

In summary, the higher unit costs of tiotropium were offset by improved clinical outcomes i.e. fewer severe exacerbations. This lowered overall hospitalisation costs resulting in treatment with tiotropium being highly cost-effective relative to ipratropium. The cost-effectiveness of tiotropium compared with ipratropium is supported by the clinical evidence which shows that tiotropium has superior efficacy and safety including a reduction in exacerbations and hospitalisations compared with ipratropium (see Section 3.2).

Table 3.30 Economic evaluations of tiotropium vs ipratropium

Author	Country	Treatment	Comparator	Method	Data	Time Horizon	Exacerbations	Costs	QALYs/LYs	ICER	Probability of being cost-effective at various thresholds	Author's conclusions
Oostenbrink et al (2004)	Netherlands and Belgium	tiotropium	ipratropium	Trial-based	Vincken et al (2002)	1 year	0.74 (TIO) vs .101(IPR)	€1721(TIO) vs €1541 (IPR)	N/A	€667/exacerbations avoided	80% at WTP €2000/ exacerbations avoided	Higher acquisition costs of TIO were offset by lower hospitalisation costs due to less exacerbations
Oostenbrink et al (2004)	Netherlands and Belgium	tiotropium	ipratropium	Cox PH	Vincken et al (2002)	1 year	RR of hospitalisation was 0.43 (TIO vs IPR)	N/A	N/A	N/A	N/A	90% of exacerbation costs were accounted for by exacerbations resulting in hospitalisation, TIO cost-effective as reduces hospitalisations
Schramm et al (2005)	Switzerland	tiotropium	ipratropium	N/A Cost-effectiveness	N/A	1 year	NNT TIO is 8 relative to IPR	CHF 4788 (TIO) vs CHF 5820 (IPR)	N/A	N/A	N/A	Higher acquisition costs of TIO were offset by lower hospitalisation costs due to less exacerbations
Oostenbrink et al (2005)	Netherlands and Canada	tiotropium	ipratropium	Markov	Vincken et al (2002)	1 year	0.85 (TIO) vs 1.14 (IPR)	Netherlands: €1760 (TIO) vs €1930 (IPR), Canada €1309 (TIO) vs €1307 (IPR)	QAL months 8.42 (TIO) vs 8.11 (IPR)	N/A	Netherlands 60% when WTP was €500/exacerbations avoided, Canada TIO dominant when WTP to gain one QAL month was at least €120 and WTP to avoid one exacerbation was at least €160	Outcome most sensitive to changes in exacerbation rates
Ruiz et al (2005)	Spain	tiotropium	ipratropium	Trial-based	Vincken et al (2002)	1 year	5.5/100 patients (TIO) vs 11.7/100 patients (IPR), reduction of 37.6%	€689.28 (TIO) vs €135.78 (IPR), save €174,906/100 ,000 patients	N/A	€182.67/SGRQ unit	N/A	Under TIO exacerbations were fewer and there were less hospital days

Author	Country	Treatment	Comparator	Method	Data	Time Horizon	Exacerbations	Costs	QALYs/LYs	ICER	Probability of being cost-effective at various thresholds	Author's conclusions
							exacerbations under TIO, 33.3% less hospital days					
Oba (2007)	USA	tiotropium	ipratropium	Retrospective	van Noord et al (2005)	1 year	0.13 hospitalisations TIO vs. 0.24 under IPR	$391/year. cost savings under TIO	Incremental 0.036 QALYs gained under (TIO)	N/A	93% probability that TIO cost effective at WTP of $50,000/QALY	TIO cost saving compared to IPR
Rutten-van Molken et al (2007)	Spain	tiotropium	ipratropium	Markov	Oostenbrink et al (2005)	5 years	3.50 exacerbations (TIO) vs 4.71 exacerbations (IPR) for 5 years	€6,424 (TIO) vs €5,181 (IPR)	3.15 QALYs (TIO) vs 3.00 QALYs(IPR) for 5 years	N/A	TIO dominant at WTP of €8,157/QALY, TIO dominant at WTP €639/exacerbations free month	TIO cost-effective due to reduced exacerbations and incremental QALY gains compared to IPR
Onukwugha et al (2008)	USA	tiotropium	ipratropium	Retrospective evaluation	Veterans Affairs Health Care System	1 year	N/A	Save $1818 in very severe patients, $4472 in patients with a previous COPD related hospitalisation	N/A	US$2,360 /exacerbations avoided	Sensitive to TIO price	Less exacerbations under TIO corresponds to cost savings
Brosa et al (2009)	Spain	tiotropium	ipratropium	Trial-based	N/A	13 years	N/A	N/A	N/A	€4208/LYG	Sensitive to future costs of surviving patients	Results most sensitive to COPD severity and future costs of surviving patients
Igarashi et al (2010)	Japan	tiotropium	ipratropium	Markov	N/A	5 years	0.46 (TIO) vs 0.99 (IPR)	Cost savings of US$10,500	3.30 QALYs (TIO) vs 3.042 (IPR)	N/A	If all 220,000 COPD patients used TIO, savings would be JPY215 bil (USD2.34bil)	TIO cost-effective due to lower exacerbation rates and incremental QALY gain

Author	Country	Treatment	Comparator	Method	Data	Time Horizon	Exacerbations	Costs	QALYs/LYs	ICER	Probability of being cost-effective at various thresholds	Author's conclusions
Gani et al (2010)	UK	tiotropium	ipratropium	Markov	Vincken et al (2002)	1 year	Cost £307 (TIO) vs £661 (IPR) for severe	England £1350 p.a./patient (TIO) vs £1427p.a./patient (IPR), Rest of UK £1439 (TIO) vs £1631 (IPR)	0.744 QALYs (TIO) vs 0.723 (IPR)	TIO dominant except for severe patients	At a ceiling ratio of £20,000 per QALY TIO had at least 97% chance of being cost-effective	TIO cost-effective due to lower price and higher QALYs compared to IPR

Abbreviations: Can, Canada; CHF, Swiss Franc; Cox PH, Cox proportional hazards; FEV1, forced expiratory volume at 1 second; IC, incremental cost; IPR, ipratropium; JPY, Japanese Yen; LY(s), life year(s); LYG, life year gained; N/A, not available; NNT, number needed to treat; PBO, Placebo; PSA, probabilistic sensitivity analysis; QALY(s), quality adjusted life year(s); RR, relative risk; SEK, Swedish Krona; SGRQ, St. George's Respiratory Questionnaire; TC, total costs; TIO, tiotropium; UC, usual care; vs, versus; WTP, willingness to pay.

3.5.6 Tiotropium vs ICS/LABA

3.5.6.1 Methods Used

The four studies that compared tiotropium with ICS/LABA treatment are presented in Table 3.31 (Bueno and Godoy, 2009, Mittmann et al 2011, Najafzadeh et al 2008, Nielsen et al 2013). Three studies examined ICS/LABA as add-on therapy to tiotropium whereas only one study compared tiotropium with ICS/LABA therapy. Bueno and Godey (2009) compared tiotropium monotherapy against fluticasone/salmeterol, Najafzadeh et al (2008) compared tiotropium monotherapy against tiotropium in combination with fluticasone/salmeterol, while the remaining two studies compared tiotropium monotherapy against tiotropium in combination with budesonide/formoterol (Mittmann et al 2011, Nielsen et al 2013).

The methods used for the evaluations included trial-based analysis, retrospective cohort analysis and Markov models. The time horizons used in the analyses varied from three months (2 studies), one year (1 study) and five years (1 study) and were conducted for Canada, Brazil, Australia, Sweden, Finland, Norway and Denmark.

In Bueno and Godoy's (2009) Markov model, patient lung capacity (FEV_1) was used to allocate subjects into four mutually exclusive health states including moderate, severe and very severe COPD and the absorbing health state of death. Within each cycle and from each health state, subjects could experience a severe or non-severe exacerbation. The studies by both Mittmann et al (2011) and Nielsen et al (2013) were based on the data from the CLIMB study. Najafzadeh et al's (2008) study was based on the OPTIMAL trial.

3.5.6.2 Patient Characteristics

The patients considered in the analyses were those enrolled in the clinical trials and were generally at least 40 years of age. The study by Najafzadeh et al (2008) required patients to have a smoking history of at least 10 pack-years. In three of the four studies (Mittmann et al 2011, Najafzadeh et al 2008, Nielsen et al 2013), the inclusion criteria required COPD patients to have had a history of exacerbation. These studies assessed ICS/LABA therapy in combination with tiotropium monotherapy. Hence, ICS/LABA was not considered an alternative to tiotropium but a complementary therapy for patients whose disease was more difficult to control.

3.5.6.3 Outcomes and costs

Outcomes were measured in the analyses in terms of QALYs, LYs and exacerbations avoided. The studies presented the results of the economic evaluation in terms of incremental cost per QALY gained (Najafzadeh et al 2008) or exacerbations avoided (Mittmann et al 2011, Nielsen et al 2013, Bueno and Godoy, 2009). When applicable, utility scores were derived from the clinical trial data or the published literature.

For reasons described previously, the cost of exacerbations was a key driver of the economic evaluation in all analyses. Additional costs that were typically considered in the models included disease maintenance costs and intervention costs. The study by Nielsen et al (2013) separately considered direct costs (healthcare system perspective) and both direct and indirect costs combined (societal perspective).

3.5.6.4 Results

Najafzadeh et al (2008) demonstrated that tiotropium plus fluticasone/salmeterol versus tiotropium monotherapy resulted in an ICER of CAN $243,180/QALY gained in the Canadian context. Triple therapy resulted in a reduction in exacerbations of 0.21 per year. At a willingness to pay threshold of $6,000/exacerbation avoided, tiotropium monotherapy was cost-effective compared with triple therapy. Bueno and Godoy (2009) concluded that fluticasone/salmeterol therapy was cost-effective compared with tiotropium in the Brazilian setting. The higher price of tiotropium was not fully offset by the reduction in exacerbations under tiotropium.

In the studies by Mittmann et al (2011) and Nielsen et al (2013) treatment with formoterol/budesonide in combination with tiotropium was considered cost-effective compared with tiotropium monotherapy. Mittmann et al (2011) reported that the cost per exacerbation avoided under triple therapy in Sweden was €244.4. Furthermore, at a willingness to pay threshold of €1,000 to avoid a severe exacerbation, the probability of tiotropium being cost-effective was 99%, 93% and 89% for Australia, Canada and Sweden respectively. Nielsen et al (2013) reported that from the healthcare perspective, costs per severe exacerbation avoided were €212, €307 and €165 for Denmark, Finland and Sweden respectively. From the societal perspective, the cost per severe exacerbation avoided in Finland was €174.

The cost-effectiveness evaluations demonstrate that ICS/LABA is considered an add-on to tiotropium for treatment of more severe disease. Combination therapy of tiotropium with formoterol/ budesonide was more cost-effective than tiotropium monotherapy whilst tiotropium alone was more cost-effective than fluticasone/salmeterol.

Table 3.31 Economic evaluations of tiotropium vs ICS/LABA

Author	Country	Treatment	Comparator	Method	Data	Time Horizon	Exacerbations	Costs	QALYs/LYs	ICER	Probability of being cost-effective at various thresholds	Author's conclusions
Najafzadeh et al (2008)	Canada	fluticasone/ salmeterol+ tiotropium	tiotropium+ placebo	Trial-based	OPTIMAL	1 year	1.35 exac/year (FLU/SAL+TIO) vs 1.56 (TIO+PBO)	CAN$4042 (FLU/SAL+TIO) vs CAN$2678 (TIO+PBO)	0.7217QALYs (FLU/SAL+TIO) vs 0.7092 (TIO+PBO), Incremental 0.0056(FLU/SAL +TIO)	CAN $243,180/ QALY gain (FLU/SAL+TIO)	Using WTP of $50,000/QALY, TIO monotherapy was cost-effective 80% of iterations, Using WTP of $6000/exacerbations avoided TIO monotherapy was dominant	TIO monotherapy cost-effective due to reduced costs compared to comparator
Bueno et al (2009)	Brazil	fluticasone/ salmeterol	tiotropium+ placebo	Markov	American Thoracic Society Guidelines	5 years	6.75(TIO)vs 6.82(Flu+Sal)	TC US$4840 (TIO) vs US$3025(Flu+ Sal)	N/A	CE: US$1,904/ exacerbations avoided (Flu+Sal) vs US$1,649 (TIO)	N/A	Cost-effectiveness of FLU/SAL is sensitive to the price of TIO
Mittman et al (2011)	Australia, Canada, Sweden	budesonide /formoterol +tiotropium	tiotropium+ placebo	Retrospective	CLIMB	3 months	0.11/patient(BUD/FOR+TIO) vs 0.29 (TIO+PBO)	Incremental costs -€58 (Aus), -€3 (Can), €43 (Sweden)	N/A	IC/ avoided exacerbations was €244.4 (Sweden)	Using WTP of €600 to avoid severe exacerbations cost-effective 96%(Aus), 83% (Canada), 74% (Sweden)/WTP €1000, 99% (Aus), 93% Canada), 89% Sweden	BUD/FOR+TIO most cost-effective, savings associated with fewer exacerbations offset higher treatment costs
Nielsen et al (2013)	Finland, Norway, Sweden, Denmark	budesonide /formoterol +tiotropium	tiotropium+ placebo	Trial-based	CLIMB	3 months	0.11/patient(BUD/FOR+TIO) vs 0.29 (TIO+PBO)	Over 3 months incremental costs (BUD/FOR+TIO) -€42 (Denmark), €31 (Finland), -€514	N/A	Per severe exacerbations avoided: €212 (Denmark), €307 (Finland), €165 (Sweden) and dominant in	Using WTP of €600, cost-effective 73% (Denmark), 74% (Finland), 86% (Norway) and 77% (Sweden)	BUD/FOR+TIO cost effective for severe patients who experience severe exacerbations

Author	Country	Treatment	Comparator	Method	Data	Time Horizon	Exacerbations	Costs	QALYs/LYs	ICER	Probability of being cost-effective at various thresholds	Author's conclusions
								(Norway), -€82 (Sweden)		Norway		

Abbreviations: ACL, aclidinium; BUD/FOR, budesonide/formoterol; Can, Canada; CHF, Swiss Franc; Cox PH, Cox proportional hazards; FEV1, forced expiratory volume at 1 second; FLU/SAL, fluticasone/salmeterol; GLY, glycopyrronium; IC, incremental cost; IPR, ipratropium; JPY, Japanese Yen; LY(s), life year(s); LYG, life year gained; N/A, not available; NNT, number needed to treat; PBO, Placebo; PSA, probabilistic sensitivity analysis; QALY(s), quality adjusted life year(s); RR, relative risk; SEK, Swedish Krona; SGRQ, St. George's Respiratory Questionnaire; TC, total costs; TIO, tiotropium; UC, Usual care; UMC, umeclidinium; vs, versus; WTP, willingness to pay.

3.5.7 Review articles

A total of five systematic reviews of economic evaluations involving tiotropium were identified in the literature search, with the corresponding citations presented in Table 3.32.

Table 3.32 Systematic reviews included in the literature search

Study	Citation
Simoens 2013	Simoens, S. (2013). "Cost-effectiveness of pharmacotherapy for COPD in ambulatory care: a review." Journal of Evaluation in Clinical Practice **19**(6): 1004-1011.
Rutten-Van Mölken et al 2012	Rutten-van Mölken, M. P. M. H. and L. M. A. Goossens (2012). "Cost Effectiveness of Pharmacological Maintenance Treatment for Chronic Obstructive Pulmonary Disease: A Review of the Evidence and Methodological Issues." PharmacoEconomics **30**(4): 271-302.
Mauskopf et al 2010	Mauskopf, J. A., C. L. Baker, B. U. Monz and M. D. Juniper (2010). "Cost effectiveness of tiotropium for chronic obstructive pulmonary disease: a systematic review of the evidence." Journal of Medical Economics **13**(3): 403-417.
Starkie et al 2008	Starkie, H. J., A. H. Briggs and M. G. Chambers (2008). "Pharmacoeconomics in COPD: lessons for the future." International journal of chronic obstructive pulmonary disease **3**(1): 71-88.
D'Souza et al 2006	D'Souza, A. O., M. J. Smith, L. A. Miller and J. Kavookjian (2006). "An Appraisal of Pharmacoeconomic Evidence of Maintenance Therapy for COPD." Chest **129**(6): 1693-1708.

3.5.7.1 Methods used

Five systematic reviews that evaluated the cost-effectiveness of COPD medications were retrieved, and only the findings relevant to tiotropium are considered. The most commonly cited databases used to inform the systematic reviews included MEDLINE (D'Souza et al 2006, Rutten-van Mölken and Goossens, 2012, Simoens, 2013, Starkie et al 2008), Embase (Mauskopf et al 2010, Starkie et al 2008) and the National Health Service economic evaluation database (Rutten-van Mölken and Goossens, 2012, Simoens, 2013). Between all five reviews, the time range of included studies ranged between the years 1980 and 2012. The most recent study by Simoens (2013) appraised previous literature reviews on economic evaluations of tiotropium in addition to individual studies, while the remaining reviews focused exclusively on individual economic evaluations.

3.5.7.2 Results

The review by D'Souza et al (2006) examined seven studies to assess the cost-effectiveness of maintenance therapies for COPD. The review identified the study by Oostenbrink et al (2004) which is relevant to this submission. Oostenbrink et al (2004) is described above, and concluded that tiotropium was cost-effective when compared with ipratropium.

Starkie et al (2008) reviewed fifteen economic evaluations to aid decision makers in allocating funding for COPD. The two studies that were relevant for this submission were also identified in the literature search and discussed previously (Oostenbrink et al 2005, Oostenbrink et al 2004). Both

these studies demonstrated that tiotropium is cost-effective when compared with ipratropium due to savings achieved from reduced exacerbations.

Mauskopf et al (2010) presented a systematic review on the cost-effectiveness of different therapies in the treatment of COPD, and included five studies that were identified in the literature search (Onukwugha et al 2008, Oostenbrink et al 2004, Oostenbrink et al 2005, Schramm et al 2005, Rutten-van Mölken et al 2007) and two that had not been previously identified for this review (de Lucas Ramos et al 2004, Sanz-Martinez and Perez-Maroto, 2004). Both studies were in Spanish and could not be retrieved, however, results can be reported from the Mauskopf et al (2010) study. de Lucas Ramos et al (2004) compared tiotropium with ipratropium and reported that notwithstanding the higher price of tiotropium, there were less hospital costs (-€276) and patients experienced 0.27 less exacerbations with tiotropium. The cost per exacerbation avoided under tiotropium was €1,189 with sensitivity analysis indicating that the cost per successfully treated patient ranged between €1,508 and €2,266. The study by Sanz-Martinez and Perez-Maroto (2004) also compared tiotropium with ipratropium and concluded that while tiotropium was more expensive than ipratropium, it was associated with less hospital costs (-€201) and 0.11 less exacerbations. The cost per exacerbation avoided under tiotropium was €3,523**.** Overall conclusions were that tiotropium monotherapy was cost-effective or cost-saving compared with other monotherapy interventions. This was attributed to lower average hospital costs, non-medication costs and improved health outcomes.

Rutten-van Mölken and Goossens (2012) examined 40 studies to assess maintenance treatments for COPD. Ten of the 15 evaluations that included tiotropium were relevant and had already been retrieved for this review (Friedman et al 2004, Gani et al 2010, Lee et al 2006, Mittmann et al 2011, Najafzadeh et al 2008, Oba, 2007, Onukwugha et al 2008, Oostenbrink et al 2004, Oostenbrink et al 2005, Schramm et al 2005). Overall it was concluded that tiotropium was cost-effective compared with placebo and ipratropium, however, results were sensitive to the assumed mortality rates and the time horizons that were considered.

The most recent review paper was conducted by Simoens (2013) and evaluated cost-effectiveness of COPD therapy in the outpatient setting. Thirty-four economic evaluations and 10 literature reviews were assessed. The two reviews that examined tiotropium had been retrieved for this review (D'Souza et al 2006, Mauskopf et al 2010), as had four of the economic evaluations (Gani et al 2010, Lee et al 2006, Rice et al 2007, Zaniolo et al 2012). The majority of studies demonstrated favourable cost-effectiveness for tiotropium monotherapy.

3.5.8 Health technology assessments

3.5.8.1 Methods used

Seven relevant economic evaluations were identified in the search of the HTA websites (Scottish Medicines Consortium, 2012a, CADTH, 2013, Gaebel et al 2010, NICE, 2013a, NICE, 2013b, NICE, 2015, Scottish Medicines Consortium, 2012b). A summary of each study is presented in Table 3.33. Two were Canadian based and compared tiotropium with tiotropium in combination with LABA/ICS therapy (CADTH, 2013, Gaebel et al 2010). Three were from the UK and assessed tiotropium against other LAMAs (aclidinium, glycopyrronium and umeclidinium) (NICE, 2013b, NICE, 2013a, NICE, 2015). The remaining two economic evaluations were from the Scottish Medicines Consortium (SMC) and

compared tiotropium against the LAMAs aclidinium and glycopyrronium (Scottish Medicines Consortium, 2012a, Scottish Medicines Consortium, 2012b).

The methods used included Markov models (Gaebel et al 2010), meta-analysis (CADTH, 2013), unit price comparison (NICE, 2013b, NICE, 2013a, NICE, 2015) and cost-minimisation (Scottish Medicines Consortium, 2012a, Scottish Medicines Consortium, 2012b).

Gaebel et al (2010) developed a Markov model for the Canadian setting. The study estimated the cost-effectiveness of tiotropium with a triple therapy regimen of either tiotropium plus fluticasone/salmeterol or tiotropium plus budesonide/formoterol compared with tiotropium monotherapy. Model parameters including demographics, lung function, transition and exacerbation probabilities were derived from two large studies that examined triple therapy interventions for COPD (Aaron et al 2007, Welte et al 2009). A baseline time horizon of five years with three-month cycle lengths was used. Patient lung capacity (measured as forced expiratory volume in 1 second (FEV1%)) was used to allocate subjects into two mutually exclusive health states based on the GOLD Spirometric classification stages (Global Initiative for Chronic Obstructive Pulmonary Disease, 2015). Twenty-five percent of patients were assumed to have moderate COPD, while seventy-five percent of patients entered the model with severe COPD.

The second Canadian based study compared tiotropium with a triple therapy of tiotropium plus budesonide/formoterol. The CLIMB trial informed the data for the economic analysis (CADTH, 2013).

The three identified studies from the National Institute for Health Care and Excellence (NICE) website used a unit price comparison to compare tiotropium with other LAMA treatments. Two of the reports used a twelve week time horizon (NICE, 2013b, NICE, 2015) whilst the other used one year (NICE, 2013a).

Both Scottish studies took a cost-minimisation approach, however the only costs considered were the unit prices of each respective treatment (Scottish Medicines Consortium, 2012a, Scottish Medicines Consortium, 2012b). A one-year time period was considered in both evaluations.

3.5.8.2 Patient characteristics

Gaebel et al's (2010) Markov model included patients with an average age of 65 years, who had a diagnosis of moderate to severe COPD. Sixty-six percent of patients were male. The CADTH (2013) study that was based on meta-analysis included patients with COPD of any age and with any level of disease severity. The remaining UK and Scottish studies simply compared the unit price of tiotropium with its respective comparator with no breakdown of specific patient characteristics.

3.5.8.3 Outcomes and costs

The utility values used in the Markov model were obtained from a previous evaluation that used the EuroQol 5-dimension instrument (EQ-5D) scores from a subset of patients in the UPLIFT trial (Rutten-van Mölken et al 2007, Tashkin et al 2008). Medication, exacerbation (hospitalisation and emergency department) and maintenance costs were considered in the analyses.

3.5.8.4 Results

Gaebel et al's (2010) Canadian based Markov model found that the weighted cost of the two triple therapy tiotropium + LABA/ICS regimens had an incremental cost of $5,095 relative to tiotropium monotherapy. However, there were 0.70 less exacerbations under triple therapy corresponding to a cost of $7,253/exacerbation avoided. The incremental QALYs were 0.046 under triple therapy with a 5 year ICER of $111,458/QALY. This was derived from the weighted average of an ICER of $133,982/QALY under tiotropium plus fluticasone/salmeterol and $63,593/QALY under tiotropium plus budesonide/formoterol treatment. Sensitivity analysis indicated that for a twenty-year time horizon, the weighted average ICER for tiotropium triple therapy was $61,571, indicating long term cost-effectiveness.

The Canadian analysis that compared tiotropium with a triple therapy of tiotropium plus budesonide/formoterol demonstrated that over the three-month time period, triple therapy was associated with 0.18 less exacerbations and was $4.51 less expensive than tiotropium monotherapy (CADTH, 2013). The savings derived from reduced exacerbations offset the additional costs of adding ICS/LABA to tiotropium. Thus, triple therapy was deemed cost-effective compared with tiotropium monotherapy.

The three identified UK based studies used unit price comparisons to assess the cost-effectiveness of tiotropium against other LAMA treatments. In each case, a simple price comparison was appropriate due to the similarities in efficacy between tiotropium and other LAMAs. All three treatments; aclidinium, glycopyrronium and umeclidinium were found to be less expensive than tiotropium based on unit price (NICE, 2013b, NICE, 2013a, NICE, 2015).

Both Scottish studies used a cost-minimisation approach to compare tiotropium to an equivalent LAMA therapy, however the only costs considered were the unit prices of each respective treatment. As was the case in the UK studies, this was because tiotropium and other LAMAs were considered alike in terms of efficacy and clinical outcomes. The Scottish Medicines Consortium (2012a) found that over the one-year time period aclidinium and tiotropium cost £343 and £403 respectively. Similarly, over a one-year period, the cost of glycopyrronium was less than tiotropium, costing £334.59 and £408.95 respectively (Scottish Medicines Consortium, 2012b).

Table 3.33 Health Technology Agency assessments of tiotropium

Author	Country	Treatment	Comparator	Comparator Drug Class	Model design	Costs	Incremental exacerbations	Incremental QALYs	ICER
Gaebel et al (2010)	Canada	tiotropium	TIO+ fluticasone/salmeterol OR TIO+ budesonide/formoterol	LAMA+ LABA/ICS	Markov	$17,662 (TIO) vs weighted triple therapy costs $22,757	-0.70 (Triple therapy), $7,253/exacerbations avoided (Triple therapy)	0.046 (Triple therapy)	5 years: $111,458/QALY (Triple therapy), 20 years: $61,571/QALY
CADTH (2012)	Canada	tiotropium	TIO+budesonide/formoterol	LAMA+ LABA/ICS	Meta-analysis	$566.7 (TIO) vs $562.19 (Triple therapy)	-0.18(Triple therapy)	N/A	Triple therapy more cost-effective
SMC (2015)	Scotland	tiotropium	glycopyrronium	LAMA	Cost-minimisation	£335 (GLY) vs £409 (TIO) 18 µg)	N/A	N/A	N/A
NICE (2012)	UK	tiotropium	aclidinium	LAMA	Unit price comparison	30 day: £28.60 (ACL) vs £34.87 (TIO 18 µg daily)	N/A	N/A	N/A
NICE (2013)	UK	tiotropium	glycopyrronium	LAMA	Unit price comparison	30 day: £27.50 (GLY) vs £34.87 (TIO 18 µg daily)	N/A	N/A	N/A
NICE (2013)	UK	tiotropium	umeclidinium	LAMA	Unit price comparison	30 day: £27.50 (UMC) vs £34.87 (TIO 18 µg daily)	N/A	N/A	N/A
SMC (2013)	Scotland	tiotropium	aclidinium	LAMA	Cost-minimisation	£343 (ACL) vs £403 (TIO 18 µg)	N/A	N/A	N/A

Abbreviations: ACL, aclidinium; GLY, glycopyrronium; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; N/A, not available; QALY, quality adjusted life year; TIO, tiotropium; UMC, umeclidinium; µg, micrograms.

3.5.9 Conclusion

The economic evaluations presented in the submission confirm that tiotropium is a cost-effective treatment for COPD. Tiotropium is similarly cost-effective to other LAMA therapies and cost-effective compared with usual care and ipratropium. The cost-effectiveness of tiotropium was consistent across different countries, despite differences in healthcare systems and costs. The cost effectiveness of tiotropium was driven primarily by its effectiveness in preventing exacerbations and associated hospitalisations compared with other treatments. The cost-effectiveness of tiotropium is supported by the clinical evidence. Notably, tiotropium is the only LAMA which has shown to reduce exacerbations, associated hospitalisations and mortality compared with usual care over the long term. As discussed in ToR 2, exacerbations are associated with reductions in QoL and lung function as well as increased risk of mortality and considerable healthcare costs due to hospitalisation.

Overall, the economic evaluations indicate that tiotropium is similarly cost-effective to comparator LAMA therapies. The modelled clinical outcomes with tiotropium and either umeclidinium or aclidinium in the cost-effectiveness analyses are similar, demonstrating that the results are predominantly driven by the cost of therapy. In the short term, some authors reported that glycopyrronium studies was cost-effective compared with tiotropium. However, this was due to the lower unit price of glycopyrronium and time horizon. In contrast, the long term analyses showed that tiotropium was the more cost-effective therapy, which was driven primarily by the effectiveness of tiotropium in preventing exacerbations. As discussed above, this is supported by the clinical evidence which shows that tiotropium is the only LAMA which has demonstrated to reduce exacerbations, associated hospitalisations and mortality over the long term (see Section 3.2). Given that COPD is a progressive, chronic disease, long term cost-effectiveness is more useful for informing policy decisions. The findings of this submission to the Review are supported by the UK and Scottish HTA evaluations which considered tiotropium to have similar clinical efficacy to the other LAMAs resulting in the cost of therapy driving the results of the cost-effectiveness analyses.

In addition, tiotropium was cost-effective compared with usual care and this was consistent across both short and long term time horizons. The additional costs of adding tiotropium to usual care were offset by the costs saved from reduced hospitalisations due to exacerbations.

Tiotropium was cost-effective compared with ipratropium (the original comparator considered by the PBAC in the listing of tiotropium) in all economic evaluations. This was due to reduced exacerbations and incremental QALY gains under tiotropium treatment. Tiotropium was listed on the PBS for the treatment of COPD based on superior efficacy and safety compared with ipratropium. The recent evidence included in this submission confirms tiotropium to still be a cost-effective intervention compared with ipratropium.

The majority of economic evaluations considered ICS/LABA treatments as *add-on* to tiotropium for treatment of more severe disease rather than a comparator replacement therapy for tiotropium. Combination therapy of tiotropium with formoterol/budesonide was considered cost-effective compared with tiotropium monotherapy whilst tiotropium alone was more cost-effective than fluticasone/salmeterol. Therefore, the addition of ICS/LABA add-on to tiotropium therapy may be a

cost-effective option in a subgroup of patients with severe COPD and a history of exacerbations, which is consistent with its PBS restriction.

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

The recent literature regarding the safety of ICS (as monotherapy or in combination with other COPD medicines) has been reviewed by the COPD-X 2015/2016 and GOLD 2016 Guidelines. The GOLD 2016 Guidelines state that ICS use is associated with higher prevalence of oral candidiasis, hoarse voice, skin bruising, increased risk of pneumonia and possible increased risk of fractures. Due to the potential of severe AEs, ICS/LABA combinations are recommended as one of the last options in the treatment algorithm for patients with severe COPD and previous history of exacerbations (COPD-X 2015/2016, GOLD 2016; See Response to ToR 1 for further details).

As discussed in response to ToR 1, the PBS prescribing criteria place the ICS/LABA FDCs much later in the treatment algorithm compared with all other COPD treatment options. Not only do the prescribing criteria require patients to have COPD, but the ICS/LABA must be for symptomatic treatment and patients must meet spirometry requirements (FEV1 <50%), and also have a history of repeated exacerbations with significant symptoms despite regular LABA use. PSDs for recent LAMA/LABA and ICS/LABA submissions to the PBAC (March 2014: glycopyrronium/indacaterol FDC; umeclidinium/vilanterol FDC; fluticasone/vilanterol FDC) contained statements from the TSANZ in relation to the COPD treatment algorithm. The TSANZ recommended that given the current practice to prescribe ICS/LABA FDC when stepping up therapy in persistently symptomatic patients, the LABA/LAMA FDC products are likely to provide an effective, convenient and potentially safer alternative to ICS/LABA FDCs. Based on the comments from TSANZ, the PBAC noted that the treatment algorithm for COPD is changing and considered it appropriate to delay the introduction of ICS/LABA FDCs in favour of LAMA/LABA combinations in less severe disease. The PBAC acknowledged the potential safety risks associated with ICS use and considered that combination of LAMA and LABA (given concurrently or as a FDC treatment) was preferred to earlier introduction of an ICS/LABA FDC. The PBAC also noted that delaying ICS use would be consistent with the Australian COPD-X Guidelines, where introduction of an ICS is recommended for patients with more severe disease. The view of the PBAC with respect to delaying the use of ICS in favour of bronchodilators is consistent with the treatment algorithm.

Recent studies have helped to narrow the COPD population to which ICS therapy is likely to be beneficial. In the WISDOM study (Magnussen et al 2014) patients with a history of COPD exacerbations previously receiving ICS/LAMA/LABA triple therapy (tiotropium/salmeterol/fluticasone) were randomised to continue triple therapy or withdrawal of fluticasone. The study found that the risk of moderate or severe exacerbations was similar among those who discontinued inhaled glucocorticoids (e.g. received tiotropium/LABA therapy) and those who continued glucocorticoid therapy. Post-hoc analysis showed that withdrawal of ICS significantly increased the risk of exacerbations in patients with a blood eosinophil count of 4% or greater (Watz et al 2016). Patients with a blood eosinophil count of 4% or greater accounted for approximately 20% of patients in the WISDOM study. The exacerbation benefit was not observed in the majority of patients in WISDOM, who had eosinophil counts below this threshold. These results suggest that

patients with severe COPD and a history of COPD exacerbations and a blood eosinophil count of 4% or greater may benefit from the addition of ICS therapy.

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

5.1 Introduction

The response to ToR 1 summarises PBS restrictions and clinical guidelines for COPD medicines. Briefly, tiotropium is listed on the PBS with the following restrictions:

- COPD (Spiriva® HandiHaler®); or
- Bronchospasm and dyspnoea associated with COPD for long term maintenance treatment (Spiriva® Respimat®).

The COPD-X Plan recommends a stepwise approach for the management of COPD. The first step in the treatment algorithm includes the use of short-acting reliever medications, as required, from mild to severe disease. Initiation of long-acting bronchodilator therapy can occur from mild stage disease with a LAMA, such as tiotropium, or a LABA. If adequate control has still not been achieved with one long acting bronchodilator, the guidelines recommend long-acting bronchodilators be combined in the next step, as a LAMA and a LABA used concurrently, or as a combination product, such as tio/olo FDC. For patients with FEV_1 <50% predicted and $\geq$2 exacerbations in 12 months, the COPD-X Plan recommends initiation of an ICS/LABA FDC (and discontinuation of any concurrent LABA therapy). 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 FDC.

The aim of this section was to analyse current utilisation data to determine whether tiotropium is being prescribed appropriately in accordance with clinical practice guidelines and PBS restrictions.

5.2 Methods

Two independent data sources were obtained to examine prescribing patterns of tiotropium. A Medicare data sample, obtained via an independent third party (Hi Connections), included a random 10% PBS patient sample scaled up to national estimates. Longitudinal tracking was applied over the period January 2011 to May 2013, which linked patients using Medicare numbers (the Medicare data sample was commissioned for the recent tio/olo PBAC submission). All patients that had been prescribed tiotropium over the observation period were included, along with details of their concurrent medication use including LABA, ICS and ICS/LABA FDC. Given their recent listings, no data was available for LAMA/LABA FDCs at the time as they were not PBS listed.

In addition, Australian Medical Index (AMI, IMS Health 2016) data examined prescribing patterns of tiotropium over the period January to December 2015. All patients that had been prescribed tiotropium over the observation period were included, along with details of their concurrent medication use including LABA, ICS and ICS/LABA FDC.

5.2.1 Results and discussion

The Medicare sample indicates appropriate prescribing of tiotropium as monotherapy and in combination with other long-acting COPD medications (Table 5.1). Tiotropium is most frequently

prescribed as monotherapy (50.2%) or in combination with ICS/LABA (46.9%) or LABA (2.0%), which is consistent with the COPD-X Plan (2015/2016), GOLD Guidelines (2016) and PBS prescribing criteria.

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The IMS Health sample also indicates appropriate prescribing of tiotropium as monotherapy or in combination with other long-acting COPD medications. Tiotropium is most frequently prescribed as monotherapy (31.3%) or in combination with ICS/LABA (34.4%) or LABA (21.1%). Again, this is consistent with the COPD-X Plan (2015/2016), GOLD Guidelines (2016) and PBS prescribing criteria. The Medicare and IMS Health data indicate that prescribing patterns of tiotropium monotherapy and in combination with other therapies is appropriate and consistent for each year.

The findings from the Medicare 10% sample and the IMS Health data are consistent with a recent report from the AIHW on the use of respiratory medicine for COPD and asthma in Australia (AIHW 2015c, Respiratory medication use in Australia 2003–2013: treatment of asthma and COPD. Cat. no. ACM 31). The AIHW analysed all PBS data between 2003 and 2013 to assess respiratory medicine prescriptions for COPD and asthma. The AIHW noted that LAMA inhalers have been shown to improve lung function and reduce exacerbations in COPD and may avert the need for adding high dose ICS. In addition, the authors concluded that it is likely that a substantial number of prescriptions for ICS/LABA and for the most potent formulations of ICS are dispensed to people for whom treatment with less potent formulations of ICS alone would be effective (AIHW 2015c).

In summary, the Medicare and IMS Health data indicate appropriate prescribing of tiotropium as monotherapy and in combination with other long-acting COPD medications. Therefore, the current use of tiotropium is consistent with PBS restrictions and clinical practice guidelines.

6 Term of Reference 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

6.1 Utilisation

In response to ToR 5, this submission presented an analysis of prescribing patterns of tiotropium in Australia. A recent Medicare sample, obtained via an independent third party, included a random 10% PBS patient sample scaled up to national estimates. Patients were tracked longitudinally using their Medicare number. All patients that had been prescribed tiotropium over the observation period were included, along with details of their concurrent medication use including LABA, ICS and ICS/LABA FDC. The Medicare data shows that there is appropriate prescribing of tiotropium as monotherapy and in combination with other long-acting COPD medications. In addition, recent AMI data from IMS Health further support that tiotropium is used appropriately in accordance with clinical practice guidelines and PBS restrictions. Therefore, the current use of tiotropium is consistent with PBS restrictions and clinical practice guidelines. Boehringer Ingelheim supports the QUM with initiatives aimed at prescriber education to ensure appropriate use.

6.2 Efficacy and Safety

In response to ToR 3, this submission summarised the recent evidence on the efficacy and safety of tiotropium, ipratropium and tio/olo for the treatment of COPD.

Tiotropium evidence

The submission presented an overview of systematic reviews on the efficacy and safety of tiotropium compared with other LAMAs, usual care and ipratropium (ToR 3).

- Tiotropium has the most substantial body of evidence among the LAMAs, demonstrating a reduction in exacerbations and hospitalisations, as well as improved lung function, QoL and symptoms compared with usual care therapy. Tiotropium is the only LAMA which has shown to reduce exacerbations, associated hospitalisations and mortality over the long-term compared with usual care (e.g. UPLIFT 4-years duration). Furthermore, tiotropium was the only LAMA to show a statistically significant reduction in severe exacerbations compared with usual care.
- In terms of FEV_1, SGRQ and TDI, the results of the systematic reviews are consistent with recent PBAC assessments that tiotropium, aclidinium, glycopyrronium and umeclidinium are non-inferior in terms of efficacy and safety (equi-effective doses: tiotropium HandiHaler 18 µg once daily, tiotropium Respimat 5 µg once daily, glycopyrronium 50 µg once daily, aclidinium 400 µg twice daily, umeclidinium 62.5 µg once daily).
- Patients in many tiotropium RCTs were permitted access to usual-care respiratory medicines (including LABAs) which reflects real-life treatment practice whereas trials of other LAMAs were often more restricted in the background respiratory medicines permitted. Therefore, the results of tiotropium RCTs are directly applicable to patients likely to receive tiotropium in clinical practice.

- The effect of tiotropium and other LAMAs on all-cause and cardiovascular mortality was similar with no significant differences observed between the treatments. There was no difference in mortality between the different formulations of tiotropium (HandiHaler and Respimat). This is consistent with the PBAC's previous evaluation that tiotropium HandiHaler 18 µg and Respimat 5 µg are equivalent.
- Tiotropium has superior efficacy and safety compared with ipratropium, which is consistent with the PBAC's original recommendation of tiotropium on a cost-effectiveness basis compared with ipratropium.

Tiotropium/olodaterol evidence

A review of PSDs was conducted to summarise the clinical evidence considered by the PBAC in its recommendation of tio/olo and other LAMA/LABA FDCs.

- Tio/olo FDC has superior efficacy and comparable safety to tiotropium or olodaterol monotherapy.
- The RCT evidence presented in the PSDs demonstrates that tio/olo FDC is of comparable efficacy and safety to other PBS-listed LAMA/LABA FDCs, which is consistent with the PBAC's recent recommendations.

Ipratropium evidence

A summary of evidence supporting ipratropium's use by the COPD-X Plan was presented.

- Ipratropium has a significantly greater effect on lung function compared to SABAs, in addition to improving QoL and decreasing need for oral corticosteroid treatment.

Ipratropium combined with SABA treatment reduces the number of patients experiencing exacerbations and the use of oral corticosteroids, without increasing drug related AEs.

6.3 Cost-effectiveness

The submission presented a systematic review to summarise the published literature on the cost-effectiveness of tiotropium for the treatment of COPD compared with other LAMA's, usual care/placebo, ipratropium and in combination with ICS/LABAs.

- The economic evaluations indicate that tiotropium is similarly cost-effective to other LAMA therapies. Tiotropium is cost-effective compared with usual care and ipratropium.
- The cost effectiveness of tiotropium was driven primarily by its effectiveness in preventing exacerbations and hospitalisations; events associated with substantial decrease in QoL and increase in healthcare costs and mortality.
- The cost-effectiveness of tiotropium was consistent across different comparators and across different countries, despite differences in healthcare systems and costs.
- The cost-effectiveness of tiotropium is supported by the clinical evidence which shows that tiotropium is the only LAMA which has demonstrated to reduce exacerbations, associated hospitalisations and mortality over the long term.

- The majority of economic evaluations considered ICS/LABA treatments as *add-on* to tiotropium for treatment of more severe disease rather than a comparator replacement therapy for tiotropium. ICS/LABAs are pharmacologically different from LAMAs with different clinical and adverse event profiles, in particular pneumonia, in addition to being used in a more severe patient population. Therefore, ICS/LABA FDCs should not be considered interchangeable or a relevant comparator to other pharmacological classes such as LAMAs in the COPD treatment algorithm. The COPD Review should recognise this and there should not be any therapeutic relativity link between drugs of different classes, especially if further cost-effective analyses are recommended by the Review.

Based on the utilisation data, recent clinical evidence and economic evaluations presented in this submission, the clinical and cost-effectiveness of tiotropium in COPD remains unchanged to that originally recommended by the PBAC. Since the original PBAC recommendation there has been additional RCT evidence including long-term studies to support the use of tiotropium as a cost-effective treatment option as monotherapy and more recently, as a FDC with olodaterol.

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Watz H, Tetzlaff K, Wouters EFM, Kirsten A, Magnussen H, Rodriguez-Roisin R, Volgelmeier C, Fabbri LM, Chanez P, Dahl R, Disse B, Finnigan H, Calverley PMA. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. Lancet Respir Med 2016: http://dx.doi.org/10.1016/S2213-2600(16)00100-4

Welsh EJ, Cates CJ, Poole P. Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2013;5:CD007891

Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine 2009; 180(8): 741-50.

WHO 2015. Chronic obstructive pulmonary disease (COPD): Fact sheet N°315. 2015.

Wise R, Anzueto A, Cotton D, Dahl R, Devins T, Disse B et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med 2013;369:1491–1501

Wise R, Fowler A, Metzdorf N, Dewberry H, Mueller A, Kowey P. Safety of tiotropium in patients with cardiac events in the TIOSPIR™ trial. European Respiratory Journal. 2015;46:PA985.

Zalis' ka O, Tolubaiev V, Bocharova V. PRS19 Cost-Benefit Analysis of Tiotropium and Salmeterol Treatment Compare to Usual Practice on Sample of Employed Economicaly Active COPD Patients in Ukraine. Value in Health 2012; 15(7): A562.

Zaniolo O, Iannazzo S, Pradelli L, Miravitlles M. Pharmacoeconomic evaluation of tiotropium bromide in the long-term treatment of chronic obstructive pulmonary disease (COPD) in Italy. The European Journal of Health Economics 2012; 13(1): 71-80.

Zhong N, Wang C, Zhou X, Zhang F, Patalano F, Humphries M, Wang L, Banerji D. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol/fluticasone combination (SFC) in patients with COPD: the LANTERN study. Eur Respir J. 2014 Sep 8;44(Suppl 58):P2815.

Appendices

Appendix 1 literature searches

Table A0.1 Tiotropium systematic review search

Database (dates covered and search date)	Search string		Citations retrieved
Embase (1988 to present) *(Searched 7 March 2016)*	#1	(COPD or 'chronic obstructive pulmonary disease').ti,ab,kw. or exp 'Pulmonary Disease, Chronic Obstructive'/	99236
	#2	(tiotropium or Spiriva or HandiHaler or Respimat).ti,ab,kw. or exp 'tiotropium bromide'/	4703
	#3	exp meta analysis/ or 'meta analysis'.tw,ot,hw. or 'systematic review'.tw,ot,hw. or (pooled adj4 analys?s).tw,ot,hw. or ((exp review/ or review.tw,ot,hw. or overview.tw,ot,hw.) and (systemat$ or pool$ or quantitative or methodologic$)).tw,ot,hw. or cochrane$.jn.	355531
	#4	#1 AND #2 AND #3	390
	#5	#1 AND #2 AND #3 (limited to Year 2011 to present)	**269**
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations Ovid OLDMEDLINE(R) (1946 to Present) *(Searched 7 March 2016)*	#1	(COPD or 'chronic obstructive pulmonary disease').ti,ab,kw. or exp Pulmonary Disease, Chronic Obstructive/	61549
	#2	(tiotropium or Spiriva or HandiHaler or Respimat).ti,ab,kw. or exp tiotropium bromide/	1372
	#3	exp meta analysis/ or 'meta analysis'.tw,ot,hw. or 'systematic review'.tw,ot,hw. or (pooled adj4 analys?s).tw,ot,hw. or ((exp review/ or review.tw,ot,hw. or overview.tw,ot,hw.) and (systemat$ or pool$ or quantitative or methodologic$)).tw,ot,hw. or cochrane$.jn.	130
	#4	#1 AND #2 AND #3	132671
	#5	#1 AND #2 AND #3 (limited to Year 2011 to present)	**120**
Cochrane library (Cochrane Reviews, Other Reviews, Technology assessments *(Searched 7 March 2016)*	#1	COPD or "chronic obstructive pulmonary disease":ti,ab,kw or MeSH descriptor: [Pulmonary Disease, Chronic Obstructive]	10777
	#2	tiotropium or Spiriva or HandiHaler or Respimat:ti,ab,kw or MeSH descriptor: [Tiotropium Bromide]	1244
	#3	#1 AND #2	**1023**
	#4	#1 and #2 (limited to Year 2011 to present; Cochrane Reviews, Other Reviews, Technology assessments)	**66**
Manual searching	NA		**0**
Total			**455**

Table A0.2 Tiotropium and tiotropium/olodaterol RCT update search

Database (dates covered and search date)		Search string	Citations retrieved
Embase (1988 to present) *(Searched 21 March 2016)*	#1	(COPD or 'chronic obstructive pulmonary disease').ti,ab,kw. or exp 'Pulmonary Disease, Chronic Obstructive'/	99483
	#2	(tiotropium or Spiriva or HandiHaler or Respimat).ti,ab,kw. or exp 'tiotropium bromide'/	4713
	#3	(spiolto or olodaterol).ti,ab,kw.	184
	#4	#2 or #3	4750
	#5	(clinical trial, all or clinical trial or comparative study or controlled clinical trial or randomized controlled trial).pt. or (exp comparative study/ or exp Prospective Studies/ or exp clinical trial/ or exp Randomized Controlled Trial/ or exp Single-Blind Method/ or exp Double-Blind Method/ or exp Cross-Over Studies/ or exp Placebos/ or exp Random Allocation/) or (((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$ or dummy)) or ((clinical or controlled or compar$ or prospective) adj5 (trial$ or study or studies)) or placebo$ or random$ or RCT).tw,ot,hw. or ('cross over' or crossover or 'open label' or 'open trial' or 'parallel design' or 'comparison group' or 'comparison groups' or quasiexperimental or 'quasi experimental' or pseudoexperimental or 'pseudo experimental').tw,ot,hw.	7811054
	#6	#1 or #4 or #5	2612
	#7	#1 or #4 or #5 limit to yr="2014 -Current"	**640**
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations Ovid OLDMEDLINE(R) (1946 to Present) *(Searched 21 March 2016)*	#1	(COPD or 'chronic obstructive pulmonary disease').ti,ab,kw. or exp 'Pulmonary Disease, Chronic Obstructive'/	61848
	#2	(tiotropium or Spiriva or HandiHaler or Respimat).ti,ab,kw. or exp 'tiotropium bromide'/	1383
	#3	(spiolto or olodaterol).ti,ab,kw.	71
	#4	#2 or #3	1404
	#5	(clinical trial, all or clinical trial or comparative study or controlled clinical trial or randomized controlled trial).pt. or (exp comparative study/ or exp Prospective Studies/ or exp clinical trial/ or exp Randomized Controlled Trial/ or exp Single-Blind Method/ or exp Double-Blind Method/ or exp Cross-Over Studies/ or exp Placebos/ or exp Random Allocation/) or (((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$ or dummy)) or ((clinical or controlled or compar$ or prospective) adj5 (trial$ or study or studies)) or placebo$ or random$ or RCT).tw,ot,hw. or ('cross over' or crossover or 'open label' or 'open trial' or 'parallel design' or 'comparison group' or 'comparison groups' or quasiexperimental or 'quasi experimental' or pseudoexperimental or 'pseudo experimental').tw,ot,hw.	3692839
	#6	#1 or #4 or #5	714

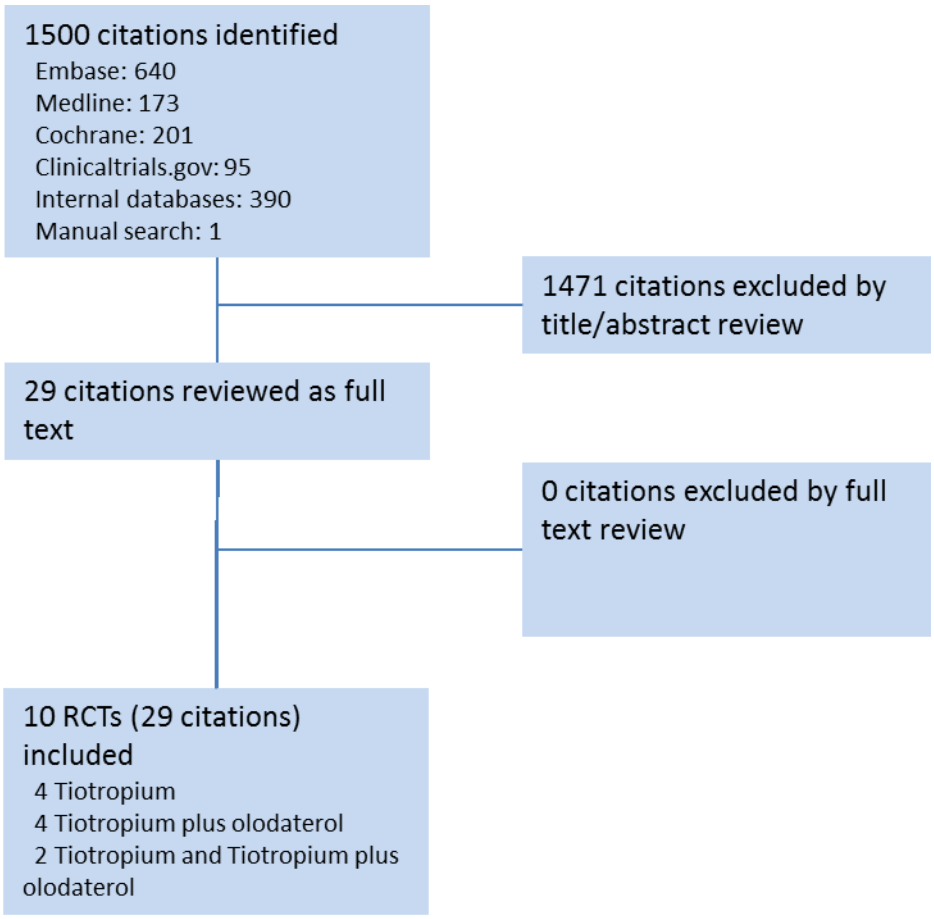
Database (dates covered and search date)	Search string		Citations retrieved
	#7	#1 or #4 or #5 limit to yr="2014 -Current"	**173**
Cochrane library[a] *(Searched 21 March 2016)*	#1	COPD or "chronic obstructive pulmonary disease":ti,ab,kw or MeSH descriptor: [Pulmonary Disease, Chronic Obstructive]	10777
	#2	tiotropium or Spiriva or HandiHaler or Respimat:ti,ab,kw or MeSH descriptor: [Tiotropium Bromide]	1244
	#3	spiolto or olodaterol:ti,ab,kw	80
	#3	#1 or #2	1032
	#4	#1 and #2 (limited to Year 2014 to present; Trials)	**201**
Clinicaltrials.gov *(Searched 21 March 2016)*	#1	tiotropium OR olodaterol (Completed , Studies With Results, Interventional Studies, COPD, Phase 2, 3, 4)	**95**
Internal company trial databases *(Searched 20 November 2015)*	#1	Substance name [tiotropium or (tiotropium plus olodaterol)]	**390**
Manual searching	NA		**1**
Total			**1500**

Table A0.3 Embase and Medline economic evaluation literature search

No.	Query	Citations
#21	#5 AND #9 AND #20	405
#20	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	805902
#19	(decision* NEAR/2 (tree* OR analy* OR model*)):ab,ti	20133
#18	((economic OR econometric OR cost OR costs OR costing OR pharmacoeconomic OR 'pharmaco economic' OR 'decision analytic' OR 'decision analysis' OR markov OR 'monte carlo') NEXT/1 model*):ab,ti	17845
#17	'economic model':de OR 'cost model':de OR 'decision analysis':de OR 'decision model':de OR markov:de	2776
#16	'statistical model'/de OR 'hidden markov model'/de OR 'monte carlo method'/de OR 'decision theory'/de OR 'decision tree'/de	147516
#15	'cost effectiveness analysis':de,ab,ti OR 'cost utility analysis':de,ab,ti	115882
#14	'economics'/de	215123
#13	'health economics'/de	35563
#12	'economic aspect'/de	106448
#11	'economic evaluation'/exp	235050
#10	'pharmacoeconomics'/de OR 'pharmacoeconomics'/exp	174431
#9	#6 OR #7 OR #8	4398
#8	'136310 93 5':rn	3322
#7	tiotropium:tn,ab,ti OR spiriva:tn,ab,ti OR 'tiova rotacaps':tn,ab,ti OR 'ba 679 br':tn,ab,ti OR 'ba679 br':tn,ab,ti	2491
#6	'tiotropium bromide'/de	4286
#5	#1 OR #2 OR #3 OR #4	105347
#4	copd:ab,ti OR coad:ab,ti	54125
#3	(chronic NEXT/1 ('airflow obstruction' OR 'airway obstruction')):ab,ti	999
#2	('chronic obstructive' NEXT/1 (airway OR bronchitis OR bronchopulmonary OR lung OR pulmonary OR respiratory)):ab,ti	50960
#1	'chronic obstructive lung disease'/de	86071

Searched 23 December 2015

Figure A0.1 Figure results of the Tiotropium and tiotropium/olodaterol RCT update search



Appendix 2 Quality appraisal of systematic reviews

Table A0.4 Quality review of included systematic reviews (AMSTAR rating)

	1. Was an 'a priori' design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Was the conflict of interest included?	Rating
Tiotropium vs placebo (usual care)												
Karner et al 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Tiotropium vs ipratropium												
Cheyne et al 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Tiotropium vs other LAMAs												
Oba and Lone 2015	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	8
Ismaila et al 2015	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes	7
Karabis	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	8

	1. Was an 'a priori' design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Was the conflict of interest included?	Rating
et al 2013												
Ni et al 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Tricco et al 2015	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	10
Tiotropium/olodaterol FDC vs other LAMA/LABA FDCs												
Schlueter et al 2016	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	7
Ipratropium vs SABAs; Ipratropium/SABA vs SABAs												
Appleton et al 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β2-agonist

Appendix 3 Tiotropium RCTs included in the systematic reviews

Table A0.5 Tiotropium RCTs reported in SRs

Citation/*Trial ID*	Comparison	Systematic reviews[2]					
		Karner et al 2014	**Ismaila et al 2015**	**Oba and Lone 2015**	**Karabis et al 2013**	**Ni et al 2014**	**Cheyne et al 2015**
		TIO vs. PBO	**LAMA vs. LAMA**	**LAMA vs. LAMA**	**ACL vs. LAMA**	**ACL vs. LAMA**	**TIO vs. IPR**
		Cochrane	NMA	NMA	NMA	Cochrane	Cochrane
Ambrosino 2008	TIO vs. PBO			✓			
Bateman 2010a	TIO vs. PBO	✓		✓	✓		
Bateman 2010b	TIO vs. PBO	✓		✓	✓		
Bateman 2013/*SHINE*	TIO vs. PBO vs. GLY		✓	✓			
Beeh 2006	TIO vs. PBO	✓		✓			
Beier 2013	TIO vs. ACL vs. PBO					✓	
Brusasco 2003	TIO vs. PBO	✓	✓	✓	✓		
Casaburi 2002	TIO vs. PBO	✓	✓	✓	✓		
Chan 2007/*SAFE*	TIO vs. PBO	✓	✓[3]	✓	✓		
Chanez 2010	TIO vs. ACL vs. PBO					✓	
Chapman 2014/*GLOW 5*	TIO vs. GLY		✓	✓			
Cooper 2010/*EXACTT* Cooper 2013	TIO vs. PBO	✓		✓			
Covelli 2005	TIO vs. PBO	✓	✓		✓		
Donoghue 2002	TIO vs. PBO vs. SAL		✓		✓		
Donoghue 2010	TIO vs. PBO vs. IND		✓	✓	✓		
Dusser 2006	TIO vs. PBO	✓		✓			
Freeman 2007/*SPRUCE*	TIO vs. PBO	✓		✓			
Garcia 2007/*NCT00144326*	TIO vs. PBO	✓	✓				
Johansson 2008	TIO vs. PBO	✓					
Kerwin 2012/*GLOW2*	TIO vs. GLY vs. PBO		✓	✓	✓		
Magnussen 2008	TIO vs. PBO	✓					
Moita 2008/*SAFE-Portugal*	TIO vs. PBO	✓	[4]		✓		
Niewoehner 2005	TIO vs. PBO	✓	✓	✓	✓		
Novartis 2012/*GLOW4*	TIO vs. GLY			✓			
Powrie 2007	TIO vs. PBO	✓		✓			
Sun 2007	TIO vs. PBO	✓					
Tashkin 2008/*UPLIFT*	TIO vs. PBO	✓	✓	✓	✓		
Tonnel 2008/*TIPHON*	TIO vs. PBO	✓	✓	✓	✓		
Troosters 2011	TIO vs. PBO	✓					
Verkindre 2006	TIO vs. PBO	✓	✓		✓		
Vincken 2002	TIO vs. IPR						✓
Vogelmeier 2008	TIO vs. PBO		✓	✓	✓		
Voshaar 2008	TIO vs. PBO vs. IPR	✓			✓		✓
Wedzicha 2013/*SPARK*	TIO vs. GLY		✓	✓			
Wise 2013/*TIOSPIR*	TIO vs. TIO			✓			

Note: Shaded ticks represent the systematic review that provides the primary source; bolded ticks represent systematic reviews that provide an additional data source.

Abbreviations: ACL, aclidinium; GLY, glycopyrronium; IND, indacaterol; IPR, ipratropium; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; NMA, network meta-analysis; PBO, placebo; SAL, salbutamol; TIO, tiotropium.

[2] In order of selected hierarchy. The SR by Tricco et al 2015 did not report individual RCT study results

[3] Includes SAFE-Portugal study (Moita 2008).

[4] Included under SAFE study (Chan 2007).

Table A0.6 Citations for included RCTs

Citation/*Trial ID*	Citation details[5]
Ambrosino 2008	Ambrosino N, Foglio K, Balzano G, Paggiaro P, Lessi P and Kesten S. Tiotropium and exercise training in COPD patients: effects on dyspnea and exercise tolerance. Int J Chron Obstruct Pulmon Dis 2008;3:771–780.
Bateman 2010a	Bateman ED, Tashkin D, Siafakas N, Dahl R, Towse L, Massey D, et al. A one-year trial of tiotropium Respimat plus usual therapy in COPD patients. Respiratory Medicine 2010;104(10):1460–72.
Bateman 2010b	Bateman E, Singh D, Smith D, Disse B, Towse L, Massey D, et al. Efficacy and safety of tiotropium Respimat SMI in COPD in two 1-year randomized studies. International Journal of Chronic Obstructive Pulmonary Disease 2010;5:197–208.
Bateman 2013/*SHINE*	Bateman ED, Ferguson GT, Barnes N, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur Respir J. 2013;42:1484–1494.
Beeh 2006	Beeh KM, Beier J, Buhl R, Stark-Lorenzen P, Gerken F, Metzdorf N, et al. Efficacy of tiotropium bromide (Spiriva) in patients with chronic-obstructive pulmonary disease (COPD) of different severities [Wirksamkeit von Tiotropiumbromid (Spiriva)bei verschiedenen Schweregraden derchronisch−obstruktiven Lungenerkrankung (COPD)]. Pneumologie 2006;60(6):341–6.
Beier 2013	Beier J, Kirsten AM, Mruz R, Segarra R, Chuecos F, Caracta C, et al. Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a six-week, randomised, controlled phase IIIb study. COPD 2013;10(4):511–22.
Brusasco 2003	Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax 2003;58 (5):399–404.
Casaburi 2002	Casaburi R, Mahler DA, Jones PW, Wanner A, San Pedro G, Zuwallack RL, et al. A long-term evaluation of once daily inhaled tiotropium in chronic obstructive pulmonary disease. European Respiratory Journal 2002;19(2):217–24.
Chan 2007/*SAFE*	Chan CK, Maltais F, Sigouin C, Haddon JM, Ford GT, Group SS. A randomized controlled trial to assess the efficacy of tiotropium in Canadian patients with chronic obstructive pulmonary disease. Canadian Respiratory Journal 2007;14(8):465–72.
Chanez 2010	Chanez P, Burge PS, Dahl R, Creemers J, Chuchalin A, Lamarca R, et al. Aclidinium bromide provides long-acting bronchodilation in patients with COPD. Pulmonary Pharmacology and Therapeutics 2010;23(1):15–21.
Chapman 2014/*GLOW 5*	Chapman KR, Beeh KM, Beier J, et al. A blinded evaluation of the efficacy and safety of glycopyrronium, a once-daily long-acting muscarinic antagonist, versus tiotropium, in patients with COPD: the GLOW5 study. BMC Pulm Med.2014;14:4.
Cooper 2010/*EXACTT*	Cooper CB, Abrazado M, Legg D, Kesten S. Development and implementation of treadmill exercise testing protocols in COPD. International Journal of COPD 2010;5:375–85. Cooper C, Celli B, Jardim J, Wise R, Legg D, Guo J et al. Treadmill endurance during 2-year treatment with tiotropium in patients with COPD: a randomized trial. Chest 2013;144:490–497.
Covelli 2005	Covelli H, Bhattacharya S, Cassino C, Conoscenti C, Kesten S. Absence of electrocardiographic findings and improved function with once-daily tiotropium in patients with chronic obstructive pulmonary disease. Pharmacotherapy 2005;25(12):1708–18.
Donoghue 2002	Donohue JF, van Noord JA, Bateman ED, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest 2002;122(1):47–55.
Donoghue 2010	Donohue J, Fogarty C, Lotvall J, Mahler D, Worth H, Yorgancioglu A et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med 2010;182:55–162.
Dusser 2006	Dusser D, Bravo ML, Lacono P. The effect of tiotropium on exacerbations and airflow in patients with COPD. European Respiratory Journal 2006;27(3):547–55.
Freeman 2007/ *SPRUCE*	Freeman D, Lee A, Price D. Efficacy and safety of tiotropium in COPD patients in primary care-the SPiRiva Usual CarE (SPRUCE) study. Respiratory Research 2007;8:45.
Garcia 2007/ *NCT00144326*	Garcia RF. A randomised, double-blind, placebo-controlled, 12 weeks trial to evaluate the effect of Tiotropium Inhalation Capsules on the magnitude of exercise, measured using an accelerometer, in patients with Chronic Obstructive Pulmonary Disease (COPD). Boehringer Ingelheim Trial Results. NLM Identifier: NCT00144326. 2007. Available from: http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/results/205/205.269.pdf. Accessed October 19, 2015.
Johansson 2008	Johansson G, Lindberg A, Romberg K, Nordstrom L, Gerken F, Roquet A. Bronchodilator efficacy of tiotropium in patients with mild to moderate COPD. Primary Care Respiratory Journal 2008; Vol. 17, issue 3:169–75.

[5] Based on the primary publication included in the primary source systematic review.

Citation/*Trial ID*	Citation details[5]
Kerwin 2012/*GLOW2*	Kerwin E, Hebert J, Gallagher N, et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. Eur Respir J. 2012;40:1106–1114.
Magnussen 2008	Magnussen H, Bugnas B, Van Noord J, Schmidt P, Gerken F, Kesten S. Improvements with tiotropium in COPD patients with concomitant asthma. Respiratory Medicine 2008;102(1):50–6. [
Moita 2008/ *SAFE-Portugal*	Moita J, Barbara C, Cardoso J, Costa R, Sousa M, Ruiz J, et al. Tiotropium improves FEV1 in patients with COPD irrespective of smoking status. Pulmonary Pharmacology and Therapeutics 2008;21(1):146–51.
Niewoehner 2005	Niewoehner DE, Rice K, Cote C, Paulson D, Cooper Jr JAD, Korducki L, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: A randomized trial. Annals of Internal Medicine 2005;143(5): 317–326.
Novartis 2012/*GLOW4*	Novartis (2012) Long Term Safety and Tolerability of NVA237 Versus Tiotropium in Japanese Patients (GLOW4). ClinicalTrials.gov identifier: NCT01119937. Available at: http://clinicaltrials.gov/ct2/show/results/NCT01119937 (accessed 29 October 2014).
Powrie 2007	Powrie DJ, Wilkinson TMA, Donaldson GC, Jones P, Scrine K, Viel K, et al. Effect of tiotropium on sputum and serum inflammatory markers and exacerbations in COPD. European Respiratory Journal 2007;30(3):472–8.
Sun 2007	Sun LH, Tan Y, Qiao Y, Fang SR, Xie H. Evaluation of clinical effect and safety of tiotropium bromide in treating stable chronic obstructive pulmonary disease. Zhongguo Xinyao yu Linchuang Zazhi 2007;26(5):328–31.
Tashkin 2008/*UPLIFT*	Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. New England Journal of Medicine 2008;359(15):1543–54.
Tonnel 2008/*TIPHON*	Tonnel AB, Perez T, Grosbois JM, Verkindre C, Bravo ML, Brun M. Effect of tiotropium on health-related quality of life as a primary efficacy endpoint in COPD. International Journal of COPD 2008;3(2):301–10.
Troosters 2011	Troosters T, Weisman I, Dobbels F, Giardino N, Valluri SR. Assessing the impact of tiotropium on lung function and physical activity in GOLD Stage II COPD patients who are naive to maintenance respiratory therapy: a study protocol. The Open Respiratory Medicine Journal 2011;5: 1–9.
Verkindre 2006	Verkindre C, Bart F, Aguilaniu B, Fortin F, Guerin JC, Le Merre C, et al. The effect of tiotropium on hyperinflation and exercise capacity in chronic obstructive pulmonary disease. Respiration 2006;73(4):420–7.
Vincken 2002	Vincken W, van Noord JA, Greefhorst A, Bantje TA, Kesten S, Korducki L, et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. European Respiratory Journal 2002;19(2):209–16.
Vogelmeier 2008	Vogelmeier C, Kardos P, Harari S, Gans SJM, Stenglein S, Thirlwell J. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. Respir Med. 2008;102:1511–1520.
Voshaar 2008	Voshaar T, Lapidus R, Maleki-Yazdi R, Timmer W, Rubin E, Lowe L, et al. A randomized study of tiotropium Respimat Soft Mist inhaler vs. ipratropium pMDI in COPD. Respiratory Medicine 2008;102(1):32–41.
Wedzicha 2013/*SPARK*	Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. Lancet Respir Med. 2013;1:199–209.
Wise 2013/*TIOSPIR*	Wise R, Anzueto A, Cotton D, Dahl R, Devins T, Disse B et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med 2013;369:1491–1501.

Table A 0.7 Study and patient characteristics of tiotropium RCTs included in SRs

Citation *Trial ID*	Duration	Interventions	Population – COPD severity	Baseline age	Male	Baseline FEV_1% pred	Concomitant respiratory medications allowed	Concomitant respiratory medications not allowed	Outcomes	
		Daily dose (formulation)	FEV_1 inclusion criteria	Mean	%	Mean			Primary	Secondary
Ambrosino 2008	25 w	TIO 18 µg (DPI) PBO	NR	67 y	84%	41%	NR	NR	NR	NR
Bateman 2010a	48 w	TIO 5µg (SMI) PBO	Pre-BD FEV_1 ≤ 60% pred FEV_1/FVC ≤ 70%	65 y	78%	40%	Salbutamol pMDI provided Others allowed	Inhaled anticholinergics	• Trough FEV_1 response[6] • Time to first COPD exacerbation	• Mean COPD exacerbations/ patient year • Total exacerbations requiring urgent medical care • COPD hospitalisations • All-cause hospitalisations • Change in HRQoL • Dyspnoea • Lung function
Bateman 2010b	48 w	TIO 5 µg (SMI) PBO	Pre-BD FEV_1 ≤ 60% pred FEV_1/FVC ≤ 70%	65 y	74%	38%	Salbutamol pMDI as rescue medication OCS/ICS, theophylline preparations, mucolytic agents and antileukotrienes if stabilised for at least 6 weeks prior to and during study	-	• Trough FEV_1 response[6] • SGRQ total score at week 48 • Mahler TDI focal score at week 48 • COPD exacerbations per patient year	• FVC • PEFR • Mean weekly rescue medication use • COPD symptom scores • PGE • PGR • Clinical efficacy measures • HRQoL

[6] Defined as the difference between pre-dose FEV_1 on day 1 of the treatment period and the corresponding value after full treatment duration

Citation *Trial ID*	Duration	Interventions	Population – COPD severity	Baseline age	Male	Baseline FEV_1% pred	Concomitant respiratory medications allowed	Concomitant respiratory medications not allowed	Outcomes	
		Daily dose (formulation)	FEV_1 inclusion criteria	Mean	%	Mean			Primary	Secondary
Bateman 2013 *SHINE*	26 w	TIO (DPI) 18 µg PBO GLY 50 µg[7]	Post-BD FEV_1 ≥ 30% and < 80% pred Post-BD FEV_1/FVC < 0.7	64 y	73% to 77%	55%	Salbutamol/ albuterol as rescue medication ICS or INCS in constant doses	LABA, LAMA, LABA/ICS	NR	NR
Beeh 2006	12 w	TIO (DPI) 18 µg PBO	FEV_1 ≤ 70% pred FEV_1/FVC < 70%	62 y	76%	45%	Short-acting relief medications substituted for fenoterol as needed	LABAs	No primary outcome/s reported	• Spirometry • FVC • IVC • Tolerability
Beier 2013	6 w	TIO (DPI) 18 µg ACL 800 µg PBO	Post-BD FEV_1 ≥ 30% and < 80% Post-BD FEV_1/FVC < 70%	62 to 63 y	56% to 73%	NR	Stable oral sustained-release theophylline, ICS or OCS (≤10 mg/day prednisone equivalent)	NR	• Change from baseline in normalised FEV_1 AUC over the 24-h period post morning dose at week 6	• Change from baseline in normalised FEV_1 AUC over the night-time or morning period post morning dose at week 6
Brusasco 2003	24 w	TIO (DPI) 18 µg PBO	FEV_1 < 65% pred FEV_1/FVC < 70%	64 y	77%	39%	Previously prescribed regular ICS or OCS not exceeding 10 mg prednisone daily	-	No primary outcome/s reported	• FEV_1 • FVC • Dyspnoea • HRQoL • Exacerbations • Hospital admissions • Concomitant medications • Health care contacts • Disability days

[7] Results only available for the TIO vs. PBO comparison and exacerbation results comparing TIO vs. GLY.

Citation ***Trial ID***	**Duration**	**Interventions**	**Population – COPD severity**	**Baseline age**	**Male**	**Baseline FEV_1% pred**	**Concomitant respiratory medications allowed**	**Concomitant respiratory medications not allowed**	**Outcomes**	
		Daily dose (formulation)	**FEV_1 inclusion criteria**	**Mean**	**%**	**Mean**			**Primary**	**Secondary**
Casaburi 2002	49 w	TIO (DPI) 18 µg PBO	FEV_1 < 65% pred FEV_1/FVC < 70%	65 y	64%	39%	Albuterol MDI as needed Stable doses of theophylline ICS or OCS (≤ 10 mg oral prednisone) Any other treatment for acute COPD exacerbation (except anticholinergics or LABAs)	Anticholinergics or LABAs	No primary outcome/s reported	• FEV_1 and FVC • PEFR • Exacerbations • BDI, TDI • SF-36/SGRQ • COPD symptom scores
Chan 2007 *SAFE*	48 w	TIO (DPI) 18 µg PBO	FEV_1 ≤ 65% pred FEV_1/FVC ≤ 70%	67 y	60%	39%	Stable doses ICS, OCS (≤ 10 µg prednisone daily or equivalent), theophylline preparations, mucolytic preparations, LABAs, as needed salbutamol MDI	Inhaled anticholinergics Oral β2 agonists	• Trough FEV_1 response[6]	• FVC • FEV_6 • SGRQ • Exacerbations and associated hospitalisations • Treatment for exacerbations
Chanez 2010	4 w	TIO (DPI) 18 µg ACL 25 µg, 50 µg, 100 µg, 200 µg or 400 µg PBO	FEV_1 30-65% pred FEV_1/FVC ≤70%	60 to 62 y	72% to 90%	NR	Salbutamol allowed as rescue medication ICS, oral sustained-release theophyllines, antihistamines, nedocromil and ketotifen allowed as long as dose stabilised prior to randomisation	Other medications for COPD Medications with pro-arrhythmic effects of that affect heart rate or QTc	•Trough FEV1 on day 29 for aclidinium vs placebo	• FEV1, FVC • SGRQ • TDI • Days with • COPD symptoms • PEFR • Rescue medication use

Citation *Trial ID*	Duration	Interventions	Population – COPD severity	Baseline age	Male	Baseline FEV_1% pred	Concomitant respiratory medications allowed	Concomitant respiratory medications not allowed	Outcomes	
		Daily dose (formulation)	FEV_1 inclusion criteria	Mean	%	Mean			Primary	Secondary
Chapman 2014 *GLOW5*	12 w	TIO (DPI) 18 µg GLY 50 µg	Post-BD FEV_1 ≥ 30% and < 80% pred Post-BD FEV_1/FVC < 70%	63 to 64 y	44% to 45%	53% to 54%	ICS and SABA for rescue medication	LABA	NR	NR
Cooper 2010 *EXACTT*	96 w	TIO (DPI) 18 µg PBO	Pre-BD FEV_1 ≤ 60% pred Post-BD FEV_1 ≤ 65% pred FEV_1/FVC ≤ 70%	65 y	77%	38%	Theophylline preparations, mucolytics, ICS, LABAs and OCS	Antileukotrienes, cromolyns, antibiotics, long-acting anticholinergics, other investigational drugs	• Endurance time at 4 and 9 w	• Endurance time at 100 w • Pulmonary function tests • Lung function tests • SGRQ • Modified Borg scale • Exacerbations • Physician's and Patient's Global Evaluation
Covelli 2005	12 w	TIO (DPI) 18 µg PBO	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 70%	65 y	47% to 66%	39%	ICS, SABAs and LAMAs and theophyllines	Cromones, leukotriene antagonists and inhaled anticholinergics	• Trough FEV_1 response[6]	• Pre-dose FEV_1 on day 56 and FVC days 56 and 84 • Post-dose FEV_1 and FVC on all days • Patient and physician global COPD rating • EQ-5D • Use of rescue medication
Donoghue 2002	24 w	TIO (DPI) 18 µg PBO SAL[8]	FEV_1 ≤ 60% FEV_1/FVC ≤70%	65 to 66 y	74% to 75%	41%	Usual ICS and OCS	Inhaled anticholinergics, LABAs	NR	NR

[8] Results only available for the TIO vs. PBO comparison; no results comparing TIO vs. SAL.

Citation *Trial ID*	Duration	Interventions	Population – COPD severity	Baseline age	Male	Baseline FEV_1% pred	Concomitant respiratory medications allowed	Concomitant respiratory medications not allowed	Outcomes	
		Daily dose (formulation)	FEV_1 inclusion criteria	Mean	%	Mean			Primary	Secondary
Donoghue 2010	26 w	TIO (DPI) 18 µg PBO IND[9]	Post-BD FEV_1 ≥ 30% and < 80% pred FEV_1/FVC < 70%	64 y	65%	54% to 56%	Albuterol as needed ICS if stable for 1 month prior	Anticholinergic bronchodilators Fixed combination BD/ICS	NR	NR
Dusser 2006	48 w	TIO (DPI) 18 µg PBO	Pre-BD FEV_1 ≤ 30% to 65% pred FEV_1/SVC ≤ 70%	65 y	88%	48%	ICS and OCS (≤ 10 mg prednisone) if stable for at least 6 weeks; any other medications deemed necessary excluding anticholinergics and LABAs	Oral or inhaled LABAs Inhaled anticholinergics or theophylline	No primary outcome/s reported	• Exacerbations and hospital admissions for exacerbation • Concomitant/ rescue medications and non-scheduled physicians contacts • PEF • Respiratory condition scale • FEV_1, FVC, SVC, IC
Freeman 2007 *SPRUCE*	12 w	TIO (DPI) 18 µg PBO	Pre-BD FEV_1 ≤ 30% to 65% pred FEV_1/FVC ≤ 70%	65 y	50% to 59%	49%	Usual treatment	-	• Trough FEV_1 response[6]	• Trough FEV_1 at 2 and 6 w • Trough FVC at 2, 6 and 12 w • Mean daily SABA use • COPD exacerbations • Dyspnoea measured by the Oxygen Cost Diagram

[9] Results only available for the TIO vs. PBO comparison; no results comparing TIO vs. IND.

Citation ***Trial ID***	**Duration**	**Interventions**	**Population – COPD severity**	**Baseline age**	**Male**	**Baseline FEV_1% pred**	**Concomitant respiratory medications allowed**	**Concomitant respiratory medications not allowed**	**Outcomes**	
		Daily dose (formulation)	**FEV_1 inclusion criteria**	**Mean**	**%**	**Mean**			**Primary**	**Secondary**
Garcia 2007 *NCT00144326*	12 w	TIO (DPI) 18 µg PBO	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 70%	63 y	78%	46%	SABAs as needed Theophyllines, mucolytics, ICS, OCS, antibiotics, antihistamines	β-blockers, cromolyns, antileukotrienes, inhaled LABAs, long-acting anticholinergics or other investigational drugs	• Difference in daily physical activity at 12 w	• Difference in daily physical activity at 4 and 8 w • pre-dose trough/post-dose peak FEV1 on study days • Trough and peak SVC, IC, FIV • Trough and peak IC • 6MWD • Modified Borg Dyspnoea Scale • CRQ • Rescue medication use • Physician's Global Assessment
Johansson 2008	12 w	TIO (DPI) 18 µg PBO	Post-BD FEV_1 > 60% pred Post-BD FEV_1/FVC ≤ 70%	62 y	43% to 53%	73%	Salbutamol MDI as rescue medication For exacerbations only: antibiotics and OCS (< 2 w) or theophylline (≤ 7 days)	Short-acting anticholinergics, β2-agonsts (other than rescue medication), ICS or OCS, theophylline	• Change in FEV_1 AUC from pre-dose to 2 h post-dose from baseline to 12 w	• FEV_1 and FVC trough responses • Rescue medication use • Adverse events • Dyspnoea BDI • MRC dyspnoea scale • EQ-5D and VAS • COPD exacerbations
Kerwin 2012 *GLOW2*	52 w	TIO (DPI) 18 µg PBO GLY 50 µg[10]	Post-BD FEV_1 ≥ 30% and < 80% pred Post-BD FEV_1/FVC < 70%	64 y	63% to 65%	56%	ICS or INCS and H1 antagonists Salbutamol/albuterol as rescue medication	LAMAs; LABAs or LABA/ICS combinations	NR	NR

[10] Results only available for the TIO vs. PBO comparison and exacerbation results comparing TIO vs. GLY.

Citation ***Trial ID***	**Duration**	**Interventions**	**Population – COPD severity**	**Baseline age**	**Male**	**Baseline FEV_1% pred**	**Concomitant respiratory medications allowed**	**Concomitant respiratory medications not allowed**	**Outcomes**	
		Daily dose (formulation)	**FEV_1 inclusion criteria**	**Mean**	**%**	**Mean**			**Primary**	**Secondary**
Magnussen 2008	12 w	TIO (DPI) 18 µg PBO	Post-BD FEV_1 < 80% pred Post-BD FEV_1/FVC ≤ 70%	60 y	61%	53%	Continued inhaled LABAs, ICS, OCS (≤ 10 mg/day prednisone), theophyllines, leukotriene antagonists, cromones Salbutamol for as needed relief	Anticholinergic therapy	No primary outcome/s reported	• FEV_1 and FVC AUC 0-6h • PEFR • Symptom relief • Rescue medication use
Moita 2008 *SAFE-Portugal*	12 w	TIO (DPI) 18 µg PBO	FEV_1 ≤ 70% pred FEV_1/FVC ≤ 70%	64 y	95%	38% to 44%	Salbutamol MDI as needed LABAs and continued use of theophylline Mucolytics, ICS, OCS (≤ 10mg) if stabilised for ≥ 6 w prior to study Temporary increases in dose of theophylline and OCS for exacerbation	Short-acting anticholinergics, oral β_2-agonists, antileukotrienes, other investigational drugs	• Trough FEV_1 response[6]	• Trough FEV_1 after 6 w • Trough FVC after 6 and 12 w • Physician's Global Evaluation • EQ-5D • Rescue medication use • Adverse events

Citation *Trial ID*	Duration	Interventions	Population – COPD severity	Baseline age	Male	Baseline FEV_1% pred	Concomitant respiratory medications allowed	Concomitant respiratory medications not allowed	Outcomes	
		Daily dose (formulation)	FEV_1 inclusion criteria	Mean	%	Mean			Primary	Secondary
Niewoehner 2005	26 w	TIO (DPI) 18 µg PBO	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 70%	68 y	98%	36%	Continued usual medical care including ICS and LABAs	Anticholinergic bronchodilator	• Percentage of patients experiencing at least 1 exacerbation and the percentage of patients experiencing at least 1 hospitalisation for an exacerbation	• Time to exacerbation /hospitalisation • Exacerbation frequency • Exacerbation-related healthcare utilisation • All-cause hospitalisation and hospitalisation days • Spirometry
Novartis 2012 *GLOW4*	52w	TIO (DPI) 18 µg GLY 50 µg	NR	63 y	74%	37%	NR	NR	NR	NR
Powrie 2007	52 w	TIO (DPI) 18 µg PBO	FEV_1 80% pred FEV_1/FVC 70%	66 y	41% to 48%	50%	NR	Anticholinergics	• Sputum IL-6 concentration	• Sputum IL-8 and MPO level • Serum IL-6 and CRP levels • Sputum bacterial colonisation • FEV_1 and exacerbation frequency
Sun 2007	12 w	TIO (DPI) 18 µg PBO	NR	62 y	66% to 77%	47%	Salbutamol as needed	NR	• Magnitude of symptom improvement	• COPD worsening • Clinical symptoms • Lung function • Safety
Tashkin 2008 *UPLIFT*	208 w	TIO (DPI) 18 µg PBO	Post-BD FEV_1 ≤ 70% pred Post-BD FEV_1/FVC 70%	65 y	75%	39%	All except other inhaled anticholinergics	Inhaled anticholinergics	• Yearly rate of decline in pre- and post-BD FEV_1	• Rate of decline of FVC and SVC • SGRQ • Exacerbations/ hospitalisations • All-cause mortality • Lower respiratory case mortality

Citation ***Trial ID***	**Duration**	**Interventions**	**Population – COPD severity**	**Baseline age**	**Male**	**Baseline FEV_1% pred**	**Concomitant respiratory medications allowed**	**Concomitant respiratory medications not allowed**	**Outcomes**	
		Daily dose (formulation)	**FEV_1 inclusion criteria**	**Mean**	**%**	**Mean**			**Primary**	**Secondary**
Tonnel 2008 *TIPHON*	39 w	TIO (DPI) 18 µg PBO	Pre- and post-BD FEV1 ≤ 20%-70% pred Pre- and post-BD FEV_1/SVC 70%	64 y	86%	44%	Salbutamol MDI as needed Theophylline, ICS, OCS if < 10 mg prednisone equivalent) if dosage stabilised for ≥ 6 weeks OCS and antibiotics for exacerbations	β-blockers, antileukotrienes, oral or inhaled LABAs, short-acting anticholinergics or other investigational drug	• Proportion of patients with ≥ 4 point reduction in SGRQ	• VSRQ total score • FEV_1, FVC, SVC and FIV_1 • Exacerbations
Troosters 2011	24 w	TIO (DPI) 18 µg PBO	Post-BD FEV_1 ≥ 50% and < 80% pred Post-BD FEV1/FVC < 70%	62 y	69%	66%	Salbutamol provided for rescue therapy	NR	No primary outcome/s reported	• Pre- and post-dose FEV_1 and FVC • Activity Monitor • Physician's and Patient's Global Assessment • WPAI questionnaire • Rescue medication use
Verkindre 2006	12 w	TIO (DPI) 18 µg PBO	FEV_1 ≤50% pred FEV_1/SVC ≤ 70%	60 y	94%	35%	Salbutamol MDI, as needed OCS (≤ 10 mg prednisone equivalents), ICS, theophylline, mucolytic agents	Short-acting anticholinergics, oral β_2-agonists, LABAs	• Change from baseline in trough FVC	• FVC, IC and SVC • Daily PEFR • SWT • Modified Borg scale for dyspnoea • BDI/TDI • SGRQ

Citation ***Trial ID***	**Duration**	**Interventions**	**Population – COPD severity**	**Baseline age**	**Male**	**Baseline FEV_1% pred**	**Concomitant respiratory medications allowed**	**Concomitant respiratory medications not allowed**	**Outcomes**	
		Daily dose (formulation)	**FEV_1 inclusion criteria**	**Mean**	**%**	**Mean**			**Primary**	**Secondary**
Vincken 2002	52 w	TIO (DPI) 18µg IPR 160 µg	FEV1 ≤65% pred FEV_1/FVC ≤70%	64 to 65 y	84% to 86%	39% to 42%	Salbutamol MDI as needed	Other inhaled anticholinergics and other inhaled SABAs/LABAs	No primary outcome/s reported	• Trough FEV_1 and FVC at 1 year • FEV_1, FVC, PEFR • BDI, TDI SGFR and SF-36 • Exacerbations and adverse events • Concomitant medications
Vogelmeier 2008	24 w	TIO (DPI) 18 µg PBO	FEV_1 < 70% pred FEV_1/FVC < 70%	63 y	78% to 79%	51% to 52%	Salbutamol ICS monotherapy	NR	NR	NR
Voshaar 2008	12 w	TIO (soft mist inhaler) 5µg TIO (soft mist inhaler) 10 µg PBO IPR 36 µg (pMDI)	Pre-BD FEV_1 ≤ 60% FEV_1/FVC ≤ 70%	64 y	70%	52%	Salbutamol pMDI as needed Theophylline, mucolytics, ICS, OCS if < 10 mg prednisone equivalent) if dosage stabilised for ≥ 6 weeks	Oral β-adrenergics and investigational drugs not allowed for 1 month prior Cromolyn sodium and nedocromil sodium not allowed for 3 months prior Anticholinergics, inhaled β-adrenergics other than salbutamol or fixed combination inhalers not allowed during treatment period	• Trough FEV_1 response[6]	• FVC, PEFR and FEV_1 responders • Rescue medication use • COPD symptom severity • Physician's Global Evaluation
Wedzicha 2013	24 w	TIO (DPI) 18 µg GLY 50 µg	Post-BD FEV_1< 50% pred FEV1/FVC < 70%	63 to 64 y	73% to 75%	37%	ICS	LABAs	NR	NR
Wise 2013 *TIOSPIR*	120 w	TIO (SMI) 5 µg TIO (SMI) 2.5 µg TIO (DPI) 18 µg	NR	65 y	72%	48%	NR	NR	NR	NR

Abbreviations: 6MWD, six-minute walk distance; AUC, area under the curve; BD, bronchodilator; BDI, Baseline Dyspnoea Index; COPD, chronic obstructive pulmonary disorder; CRP, C-reactive protein; CRQ, Chronic Respiratory Questionnaire; DPI, dry powder inhaler/HandiHaler; EQ-5D, EuroQoL-5D; FEV, forced expiratory volume; FIV, forced inspiratory volume; FVC, forced vital capacity; h, hours; HRQoL, health-related quality of life; IC, inspiratory capacity; ICS, inhaled corticosteroids; IL, interleukin; INCS, intranasal corticosteroids; IPR, ipratropium; IVC, inspiratory vital capacity; LABA, long-acting β-agonist; MPO, myeloperoxidase; MRC, Medical Research Council; NR, not reported; OCS, oral corticosteroids; PEF/PEFL/PEFR, peak expiratory flow rate; PGE, Physician's Global Evaluation; PGR, Patient's Global Rating; PBO, placebo; pMDI, pressurised metered dose inhaler; pred, predicted; SABA, short-acting β-agonist; SMI, soft mist inhaler/Respimat; SVC, slow vital capacity; SWT, Shuttle Walking Test; TDI, Transition Dyspnoea Index; TIO, tiotropium; VAS, Visual Analogue Scale; VSRQ, Visual Simplified Respiratory Questionnaire; w, weeks; WPAI, Work Productivity and Activity Impairment; y, years.

Table A0.8 Quality appraisal of tiotropium RCTs included in SRs

Citation/*Trial ID*	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Overall risk[11]
Ambrosino 2008	-	Unclear risk	Low risk	-	-	-	-
Bateman 2010a	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	-
Bateman 2010b	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	
Bateman 2013/*SHINE*	Low risk	High risk	High risk	-	-	-	High
Beeh 2006	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	-
Beier 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	-
Brusasco 2003	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low
Casaburi 2002	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low
Chan 2007/*SAFE*	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low
Chanez 2010	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	High risk	-
Chapman 2014/*GLOW5*	Unclear risk	Low risk	Low risk	-	-	-	Low
Cooper 2010/*EXACTT*	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	-
Covelli 2005	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low
Donoghue 2002	Unclear risk	Low risk	Low risk	-	-	-	Low
Donoghue 2010	Unclear risk	High risk	High risk	-	-	-	High
Dusser 2006	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	-
Freeman 2007/*SPRUCE*	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	-
Garcia 2007/*NCT00144326*	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low
Johansson 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	-
Kerwin 2012/*GLOW2*	Unclear risk	Unclear risk	Low risk	-	-	-	Low
Magnussen 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	-
Moita 2008/*SAFE-Portugal*	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low
Niewoehner 2005	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low
Novartis 2012/*GLOW4*	-	Unclear risk	Low risk	-	-	-	-
Powrie 2007	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	-
Sun 2007	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	-
Tashkin 2008/*UPLIFT*	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low
Tonnel 2008/*TIPHON*	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low
Troosters 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	-

[11] Reported by Ismaila et al (2015) only.

Citation/*Trial ID*	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Overall risk[11]
Verkindre 2006	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low
Vincken 2002	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	-
Vogelmeier 2008	Unclear risk	High risk	High risk	-	-	-	High
Voshaar 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	-
Wedzicha 2013/*SPARK*	Low risk	High risk	High risk	-	-	-	High risk
Wise 2013/*TIOSPIR*	-	Low risk	Low risk	-	-	-	-

Table A0.9 Results of tiotropium RCTs included in SRs[12]

Citation *Trial ID*	N	QoL			Exacerbations						Safety	
		Mean QoL (MD, 95%CI)	N clinically significant improvement	N clinically significant deterioration	Overall	Hospitalisation due to exacerbation	Trough FEV_1, mL	TDI	All-cause hospitalisation	All-cause mortality	SAEs	Withdrawals
		MD (95% CI)[13] or MD ± SE[14]	OR (95%CI)[15]	OR (95%CI)[16]	OR (95%CI)[17] or % vs. %[18]	OR (95%CI)[19]	MD (95%CI)[20] or MD ± SE[21]	MD (95%CI)[22] or MD ± SE[21]	OR (95%CI)[20]	OR (95%CI)[20]	OR (95%CI)[20]	OR (95%CI)[20]
Tiotropium vs placebo												
Ambrosino 2008	234	-	-	-	18% vs. 27%	-	-	-	-	-	-	-
Bateman 2010a	3991	**-2.90 (-3.86, -1.94)**	**1.39 (1.21, 1.59)**	**0.69 (0.60, 0.81)**	**0.72 (0.64, 0.82)**	0.80 (0.65, 1.00)	**101 (81.4, 127)**	-	0.96 (0.81, 1.13)	1.38 (0.91, 2.10)	1.03 (0.87, 1.21)	**0.83 (0.71, 0.98)**
Bateman 2010b	1990	**-3.65 (-4.81, -2.49)**	**1.52 (1.24, 1.86)**	**0.61 (0.48, 0.76)**	**0.75 (0.62, 0.90)**	0.86 (0.59, 1.26)	**141 (129, 153)**	-	0.97 (0.75, 1.26)	1.60 (0.84, 3.02)	1.04 (0.81, 1.34)	**0.51 (0.41, 0.63)**
Bateman 2013 *SHINE*	712	-0.88 ± SE 1.04	-	-	23% vs. 38%	1% vs. 3%	130 ± SE 17.9	0.58 ± SE 0.24	-	-	--	-
Beeh 2006	1639	-	-	-	**0.69 (0.51, 0.92)**	1.36 (0.59, 3.13)	**79.0 (45.7, 112)**	-	1.06 (0.61, 1.84)	0.25 (0.03, 2.47)	0.93 (0.56, 1.53)	**0.74 (0.56, 0.98)**
Brusasco 2003	802	**-2.70 (-4.64, -0.76)**	**1.48 (1.09, 2.00)**	**0.64 (0.46, 0.91)**	**0.74 (0.55, 0.99)**	**0.47 (0.32, 0.68)**	**120 (106, 134)**	1.10 ± SE 0.30	**0.47 (0.32, 0.68)**	0.26 (0.05, 1.30)	0.68 (0.43, 1.06)	**0.53 (0.37, 0.75)**
Casaburi 2002	921	**-3.44 (-5.24, -1.64)**	**2.25 (1.68, 3.02)**	**0.55 (0.41, 0.75)**	0.78 (0.59, 1.02)	**0.55 (0.33, 0.92)**	**150 (123, 177)**	0.80 ± SE 0.19	0.94 (0.66, 1.33)	0.66 (0.23, 1.95)	0.82 (0.59, 1.15)	**0.60 (0.44, 0.82)**

[12] All results are taken from the primary systematic review, or the additional systematic review data source, except where indicated. All results are presented as mean differences or odds ratios (as indicated in the table header), unless otherwise specified.
[13] SGRQ total score (Karner et al, 2014; Cheyne et al, 2015)
[14] SGRQ change from baseline (Ismaila et al, 2015).
[15] Defined as patients with a ≥ 4 unit improvement in SGRQ (Karner et al, 2014).
[16] Defined as patients with a ≥ 4 unit worsening in SGRQ (Karner et al, 2014).
[17] Defined as patients with ≥ 1 exacerbation (Karner et al, 2014; Cheyne et al, 2015).
[18] Defined as number of exacerbations/patients (Oba and Lone, 2015).
[19] Defined as patients with ≥ 1 exacerbation requiring hospitalisation (Karner et al, 2014; Cheyne et al, 2015).
[20] Karner et al (2014); Cheyne et al (2015).
[21] Ismaila et al (2015).
[22] Cheyne et al (2015).

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		MD (95% CI) [13] or MD ± SE [14]	OR (95%CI) [15]	OR (95%CI) [16]	OR (95%CI) [17] or % vs. % [18]	OR (95%CI) [19]	MD (95%CI) [20] or MD ± SE [21]	MD (95%CI) [22] or MD ± SE [21]	OR (95%CI) [20]	OR (95%CI) [20]	OR (95%CI) [20]	OR (95%CI) [20]
Chan 2007 *SAFE*	913	**-2.79** **(-4.69, -0.89)**	**1.43** **(1.05, 1.95)**	0.79 (0.55, 1.14)	1.14 (0.86, 1.50)	1.38 (0.80, 2.38)	**100** **(60.8, 139)**	-	1.42 (0.96, 2.12)	2.50 (0.85, 7.37)	1.35 (0.92, 1.99)	0.75 (0.55, 1.03)
Cooper 2010 *EXACTT*	519	**-4.03** **(-6.97, -1.09)**	1.48 (0.94, 2.32)	0.67 (0.43, 1.06)	1.16 (0.82, 1.65)	1.33 (0.68, 2.62)	**75.0** **(22.1, 128)**	-	1.12 (0.73, 1.71)	1.00 (0.32, 3.13)	1.08 (0.72, 1.63)	**0.58** **(0.40, 0.84)**
Covelli 2005	196	-	-	-	0.69 (0.28, 1.73)	1.94 (0.17, 21.7)	**184** **(111, 257)**	-	0.96 (0.27, 3.42)	NE	0.96 (0.27, 3.42)	0.52 (0.22, 1.19)
Donoghue 2002	410	-2.71 ±SE 1.31	-	-	-	-	137 ± SE 20.0	1.00 ±SE 0.33	-	-	-	-
Donoghue 2010	845	-1.00 ±SE 0.92	-	-	-	-	140 ± SE 20.4	0.90 ±SE 0.23	-	-	-	-
Dusser 2006	1010	-	-	-	**0.65** **(0.51, 0.83)**	0.86 (0.51, 1.44)	**120** **(80.8, 159)**	-	0.96 (0.69, 1.32)	0.89 (0.32, 2.47)	0.90 (0.65, 1.24)	0.75 (0.57, 1.00)
Freeman 2007 *SPRUCE*	395	-	-	-	**0.48** **(0.26, 0.87)**	1.96 (0.18, 21.8)	**60.0** **(14.9, 105)**	-	0.67 (0.25, 1.80)	0.29 (0.05, 1.69)	0.57 (0.20, 1.61)	**0.49** **(0.26, 0.90)**
Garcia 2007 *NCT00144326*	250	-	-	-	0.94 (0.40, 2.22)	5.25 (0.25, 110)	70.0 (-39.8, 180)	-	1.58 (0.43, 5.73)	NE	1.58 (0.43, 5.73)	0.66 (0.28, 1.53)
Johansson 2008	224	-	-	-	0.54 (0.10, 3.00)	NE	**119** **(56.3, 182)**	-	3.35 (0.34, 32.7)	0.15 (0.00, 7.46)	3.35 (0.34, 32.7)	0.54 (0.10, 3.00)
Kerwin 2012 *GLOW2*	128	-2.52 ± SE 1.11	-	-	62% vs. 80%	4.9% vs 6.0%	84 ± SE 21.6	0.94 ± SE 0.30	-	-	-	-
Magnussen 2008	472	-	-	-	0.51 (0.25, 1.01)	9.80 (0.52, 183)	**98.0** **(52.9, 143)**	-	3.30 (0.88, 12.4)	0.14 (0.01, 2.31)	2.19 (0.74, 6.52)	0.47 (0.16, 1.39)
Moita 2008 *SAFE-Portugal*	311	-	-	-	1.12 (0.35, 3.55)	1.12 (0.07, 18.0)	**102** **(41.2, 163)**	-	1.89 (0.44, 8.05)	8.35 (0.52, 135)	1.50 (0.33, 6.82)	1.13 (0.47, 2.68)
Niewoehner 2005	1829	-	-	-	**0.81** **(0.66, 0.99)**	0.72 (0.51, 1.00)	**100** **(74.5, 125)**	-	-	1.16 (0.63, 2.16)	1.03 (0.80, 1.33)	**0.53** **(0.42, 0.67)**
Powrie 2007	142	-	-	-	**0.43** **(0.22, 0.84)**	0.70 (0.11, 4.30)	**190** **(17.5, 362)**	-	1.28 (0.56, 2.94)	0.54 (0.06, 5.26)	1.57 (0.66, 3.70)	1.08 (0.53, 2.23)

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Sun 2007	60	-	-	-	0.19 (0.01, 4.06)	0.19 (0.01, 4.06)	**209** **(103, 315)**	-	-	NE	NE	0.13 (0.01, 2.61)
Tashkin 2008 *UPLIFT*	5993	**-2.28** **(-3.02, -1.54)**	**1.45** **(1.27, 1.67)**	**0.71** **(0.62, 0.82)**	0.95 (0.85, 1.06) **RR 0.86** **(0.81, 0.91)** [23] **HR 0.86** **(0.81, 0.91)** [24]	0.92 (0.82, 1.03) RR 0.94 (0.82, 1.07) [25] **HR 0.86** **(0.78, 0.95)** [26]	**107** **(93.3, 121)**	-	1.03 (0.93, 1.14)	0.92 (0.79, 1.07) HR 0.89 (0.79, 1.02) [27] **HR 0.87** **(0.76, 0.99)** [28]	1.06 (0.96, 1.17)	**0.71** **(0.64, 0.78)**
Tonnel 2008 *TIPHON*	554	**-4.18** **(-6.67, -1.69)**	**1.56** **(1.09, 2.22)**	**0.40** **(0.25, 0.63)**	0.74 (0.53, 1.04)	1.51 (0.60, 3.81)	**104** **(37.4, 171)**	-	1.32 (0.81, 2.16)	0.55 (0.15, 2.06)	1.23 (0.77, 1.98)	**0.50** **(0.32, 0.76)**
Troosters 2011	457	-	-	-	**0.39** **(0.19, 0.82)**	-	**166** **(109, 223)**	-	-	NE	0.83 (0.35, 1.99)	1.21 (0.66, 2.20)
Verkindre 2006	100	**-6.50** **(-12.2, -0.82)**	**2.71** **(1.15, 6.36)**	**0.44** **(0.17, 1.13)**	1.60 (0.57, 4.46)	0.16 (0.01, 3.15)	**110** **(27.7, 192)**	-	0.36 (0.07, 1.90)	NE	0.36 (0.07, 1.90)	**0.11** **(0.01, 0.91)**
Vogelmeier 2008	430	-2.05 ± SE 1.27	-	-	13% vs. 16%	-	-	-	-	-	-	-
Voshaar 2008	541	-	-	-	1.03 (0.59, 1.80)	2.53 (0.12, 53.0)	**134** **(96.8, 171)**	-	1.11 (0.38, 3.24)	4.51 (0.24, 85.3)	1.21 (0.42, 3.50)	0.75 (0.43, 1.33)
Tiotropium Respimat vs HandiHaler												
Wise 2013 *TIOSPIR*	17,116	-	-	-	162% vs. 159% HR 0.98 (0.93, 1.03) [29]	-	-10 (-38, 18) [30]	-	-	HR 0.96 (0.84, 1.09) [29]	32.4% vs. 32.4% [29]	-

[23] Exacerbations per patient year (from the RCT publication; Tashkin et al, 2008).
[24] Time to exacerbation (from the RCT publication; Tashkin et al, 2008).
[25] Exacerbations leading to hospitalisation per patient year (from the RCT publication; Tashkin et al, 2008).
[26] Time to exacerbation leading to hospitalisation (from the RCT publication; Tashkin et al, 2008).
[27] Mortality – ITT population (from the RCT publication; Tashkin et al, 2008).
[28] Mortality – population with vital status available (from the RCT publication; Tashkin et al, 2008).
[29] From the RCT publication (Wise et al, 2013).

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Tiotropium vs glycopyrronium												
Bateman 2013 *SHINE*	953	-	-	-	23% vs. 26%	1.0% vs 1.9%	-	-	-	-	-	-
Kerwin 2012 *GLOW2*	450	-	-	-	62% vs. 54%	4.9% vs 3.6%	-	-	-	-	-	-
Novartis 2012 *GLOW4*	164	-	-	-	43% vs. 30%	0.0% vs 1.6%	-	-	-	-	-	-
Chapman 2014 *GLOW5*	657	-	-	-	8.2% vs. 8.9%	0.9% vs 0.6%	4 ± SE 15.1	-	-	-	-	-
Wedzicha 2013 *SPARK*	1476	0.10 ± SE 0.88	-	-	115% vs. 117%	**9.9% vs 14.7%**	-10 ± SE 13.1	-	-	-	-	-
Tiotropium vs aclidinium												
Beier 2013	414	-	-	-	4.68 (0.22, 98.1) [31]	0.31 (0.01, 7.57)	0.04 (-0.01, 0.09)	-	-	NE	0.69 (0.15, 3.12) [32]	-
Chanez 2010	464	-	-	-	1.38 (0.07, 27.0) [31]	0.98 (0.05, 20.7)	-	-	-	-	0.59 (0.02, 14.6) [32]	-
Tiotropium vs ipratropium												
Vincken 2002	535	**-3.30 (-5.63, -0.97)**	-	-	**0.64 (0.44, 0.92)**	0.59 (0.32, 1.09)	**150 (110, 190)**	**0.90 (0.39, 1.41)**	-	1.52 (0.41, 5.69)	**0.55 (0.36, 0.85)**	0.66 (0.42, 1.05)

[30] In 1370 patients included in the spirometry sub-study (from the RCT publication; Wise et al, 2013).
[31] Patients with exacerbation requiring steroids, antibiotics or both.
[32] Non-fatal SAEs.

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Voshaar 2008	538	-	-	-	5 µg: 0.67 (0.30, 1.47) 10 µg: 1.08 (0.52, 2.26)	5 µg: 0.49 (0.03, 7.95) 10 µg: 0.24 (0.02, 2.72)	**5 µg: 64.0** **(8.63, 119)** **10 µg: 95.0** **(39.6, 150)**	-	-	5 +10 µg: 0.99 (0.09, 11.0)	5 µg: **0.23** **(0.07, 0.79)** 10 µg: 0.52 (0.20, 1.34)	5 µg: 0.48 (0.23, 1.03) 10 µg: 0.51 (0.24, 1.05)

Notes: Risk estimates and 95% CIs shown in bold are statistically significant in favour of tiotropium. The statistical significance of MD ± SE results and % comparisons have not been assessed.

Abbreviations: CI, confidence interval; FEV, forced expiratory volume; HR, hazard ratio; MD, mean difference; NE, not estimable (0 events in both treatment groups); OR, odds ratio; QoL, quality of life; RR, relative risk; SAE, serious adverse event; SE, standard error; SGRQ, St. George's Respiratory Questionnaire; TDI, Transition Dyspnoea index.