

6.07 TIOTROPIUM BROMIDE
solution for inhalation, 2.5 µg per actuation
Spiriva® Respimat®
Boehringer Ingelheim Pty Limited

1 Purpose of Application

1.1 The submission proposed the inclusion of tiotropium 2.5 µg on the Pharmaceutical Benefits Scheme (PBS) as a restricted benefit item for adult patients with asthma who are currently treated with the optimised combination of inhaled corticosteroids (ICS) and long-acting β₂ agonist (LABA), unless LABA was contraindicated or not tolerated, and who experienced one or more severe exacerbations in the previous year. Tiotropium 2.5 µg is a once daily (2 puffs of 2.5 µg) maintenance bronchodilator treatment.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TIOTROPIUM tiotropium 2.5 microgram inhalation: solution for, 60 actuations	1	5	\$ [REDACTED]	Spiriva® Respimat® Boehringer Ingelheim

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Severe
Condition:	Asthma
PBS Indication:	Severe asthma
Restriction Level / Method:	<input checked="" type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

Public Summary Document – July 2015 PBAC Meeting

Clinical criteria:	<p>Patient must have experienced at least one severe exacerbation in the previous year 12 months while receiving optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, <i>which has been documented.</i></p> <p>AND</p> <p><i>The treatment must be used in combination with a maintenance combination of an inhaled corticosteroid and a long acting beta-2 agonist.</i></p> <p>Optimised asthma therapy must include at least, adherence to recommended doses of inhaled corticosteroids and long acting beta-2 agonist therapy, unless contraindicated or not tolerated.</p>
Population criteria:	<p>Patient must be aged 18 years or older.</p>
Prescriber Instructions	<p><i>Optimised asthma therapy includes adherence to maximal inhaled therapy, including high dose inhaled corticosteroid (at least budesonide 1600 micrograms per day or fluticasone propionate 1000 micrograms per day or equivalent), plus long-acting beta-2 agonist therapy (at least salmeterol 50 micrograms bd or eformoterol 12 micrograms bd) for at least 12 months, unless contraindicated or not tolerated.</i></p>
Administrative Advice	<p>Tiotropium bromide is not PBS subsidised for use in patients who are receiving maintenance treatment with inhaled corticosteroid monotherapy without a long-acting beta-2 agonist, unless combination therapy with a long-acting beta-2 agonist is contraindicated or not tolerated.</p> <p><i>Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.humanservices.gov.au or www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).</i></p>

2.2 The submission presented a cost-effectiveness analysis of tiotropium plus ICS and LABA compared to placebo plus ICS and LABA. The proposed listing could be broader than the TGA indication, which aims to restrict tiotropium listing to patients who have experienced at least one severe exacerbation in the previous year while receiving optimised asthma therapy (ICS and LABA). The proposed PBS listing would allow tiotropium to be added to ICS when patients cannot tolerate or are contraindicated to a LABA. The clinical, economic and financial evidence provided in the submission was not in line with the proposed PBS restriction (ICS and LABA, unless contraindicated or not tolerated); rather it was in line with the proposed TGA indication (ICS and LABA). Further, the listing is for patients who have experienced exacerbations (no severity specified) while on existing medication, while the clinical trial described this as unplanned need for medical care at any GP, pulmonologist, emergency department or hospital due to aggravation of asthma symptoms that required an addition or increased dose of systemic corticosteroids. The TGA indication is also for patients who have experienced one or more severe exacerbations in the previous year.

- 2.3 The Pre-Sub-Committee Response (PSCR) proposed the following updated wording for the prescriber instructions to ensure consistency with the indication agreed by ACPM:
- Optimised asthma therapy includes adherence to the maintenance combination of inhaled corticosteroids ($\geq 800 \mu\text{g}$ budesonide/day or equivalent) and long-acting $\beta 2$ agonists.
- DUSC commented that the definition of high dose ICS in the prescriber instructions of $1600 \mu\text{g}$ budesonide/day is twice as high as the definition of high dose ICS in adults, and twice the maximum dose recommended for children, in the Australian Asthma Handbook.¹
- 2.4 The ESC considered that ‘unless contraindicated or not tolerated’ should not be included in the restriction, as this is beyond the clinical trial evidence presented by the submission.
- 2.5 DUSC noted the administrative advice proposed in the Secretariat suggested wording for the restriction, which suggested inclusion of a reference to the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique.² While this paper contains general information on inhaler technique that might be relevant in formally assessing inhaler technique, DUSC noted that it does not include specific advice on the correct inhaler technique for the Respimat® inhaler.
- 2.6 The sponsor accepted the updates to the restriction wording as suggested by the Secretariat, the ESC and the DUSC, subject to approval by the PBAC (Pre-PBAC response).
- 2.7 The ESC and DUSC expressed concern regarding potential use of tiotropium for less severe asthma in practice. Current asthma guidelines outline that most patients can be managed on a regular low dose ICS alone.¹ However, in practice, most patients are supplied their ICS in the form of a combination ICS/LABA inhaler³. Given that the intended population are essentially treatment resistant severe asthmatics which, according to current asthma guidelines¹ should be referred to a respiratory specialist, the ESC and DUSC considered that it may be appropriate to limit prescribing to be by, or in consultation with, specialist physicians to minimise inappropriate use.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

3 Background

- 3.1 TGA status at time of PBAC consideration: The submission was made under the TGA/PBAC Parallel Process. Effective from 1 June 2015, the TGA approved

¹ National Asthma Council Australia. Australian Asthma Handbook – Quick Reference Guide, Version 1.1. National Asthma Council Australia, Melbourne, 2015. Available from: <http://www.astmahandbook.org.au>

² National Asthma Council Australia. *Inhaler technique in adults with asthma or COPD*. Melbourne: National Asthma Council Australia, 2008. Available from:

<http://www.nationalasthma.org.au/publication/inhaler-technique-in-adults-with-asthma-or-copd>

³ AIHW: Correll PK, Poulos LM, Ampon R, Reddel HK & Marks GB 2015. Respiratory medication use in Australia 2003–2013: treatment of asthma and COPD. Cat. no. ACM 31. Canberra: AIHW.

tiotropium as add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥ 800 microgram budesonide/day or equivalent) and long-acting beta-2 agonists and who experienced one or more severe exacerbations in the previous year.

- 3.2 Tiotropium is currently listed on the PBS for use in patients with chronic obstructive pulmonary disease (COPD).

For more detail on PBAC's view, see section 7 "PBAC outcome"

4 Clinical place for the proposed therapy

- 4.1 The proposed clinical treatment algorithm places tiotropium as an add-on therapy to an ICS and a LABA for adult patients with severe persistent asthma who have experienced at least one (severe) exacerbation in the previous year. The proposed management algorithm was consistent with the approved TGA indication.

- 4.2 The ESC considered that the clinical evidence may not have been applicable to the way tiotropium would be used to treat asthma in practice. This was further supported by the treatment by subgroup interactions, which indicated that patients who were more severe at baseline appeared to achieve a better response to tiotropium treatment.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 Placebo plus ICS and LABA. This was the appropriate comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from organisations (2) via the Consumer Comments facility on the PBS website. The Lung Foundation commented that in two randomised controlled clinical trials in adults with asthma receiving inhaled corticosteroid and long-acting beta2 agonist treatment, the addition of regular tiotropium increased the time to the first severe flare-up and improved lung function, compared with placebo and the Lung Foundation was therefore supportive of the addition of tiotropium as an additional treatment option for severe asthma. The PBAC noted that this advice was supportive of the evidence provided in the submission;

however, the increased time to first severe exacerbation may not translate into clinically meaningful differences.

- 6.3 The PBAC noted The Centre of Research Excellence in Severe Asthma supported the clinical need for additional treatment options for severe asthma.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Clinical trials

- 6.4 The submission was based on two randomised, placebo-controlled twin trials, conducted concurrently, that compared tiotropium plus ICS and LABA to placebo plus ICS and LABA. A combined analysis of Trials 205.416/205.417 (n=912) was specified a priori.

- 6.5 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
205.416	A Phase III randomised, double-blind, placebo-controlled, parallel group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (5µg/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma.	Date: 25 April 2013 (revision) NCT00772538
205.417	A Phase III randomised, double-blind, placebo-controlled, parallel group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (5µg/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma.	Date: 25 April 2013 (revision) NCT00776984
205.416/205.417	A Phase III randomised, double-blind, placebo-controlled, parallel group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (5 ig/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma	Date: 31 August 2012
Kerstjens, H.A	Kerstjens, H.A., Engel, M., Dahl, R., <i>et al.</i> Tiotropium in asthma poorly controlled with standard combination therapy.	N Eng J Med 2012; 367 (13): 1198-1207
Supplementary randomised trial		
205.341	A Randomised, Double-Blind, Placebo-Controlled, Crossover Efficacy and Safety Evaluation of 8-Week Treatment Periods of Two Doses [5 µg (2 actuations of 2.5 µg) and 10 µg (2 actuations of 5 µg)] of Tiotropium Inhalation Solution Delivered by the Respimat® Inhaler as Add-on Therapy in Patients with severe persistent Asthma.	Date: 22 October 2008 NCT00365560
Kerstjens, H.A	Kerstjens, H.A., Disse, B., Schroder-Babo, W., <i>et al.</i> Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial.	J Allergy Clin Immunol 2011; 128 (2): 308-314

Source: Table B.3, pp47-49 of the submission

- 6.6 The submission considered Trial 205.341 as supplementary evidence, as the trial was a three-arm crossover trial of eight weeks, without washout between treatments.

6.7 The key features of the direct randomised trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Tiotropium vs. placebo						
205.416	459	R, DB, MC 52 weeks	Low	Severe asthma	FEV ₁ peak (0-3h) at 24 weeks Trough FEV ₁ at 24 weeks Time to 1st severe exacerbation to 48 weeks ACQ-7	Not used
205.417	453	R, DB, MC 52 weeks	Low	Severe asthma	FEV ₁ peak (0-3h) at 24 weeks Trough FEV ₁ at 24 weeks Time to 1st severe exacerbation to 48 weeks	Not used
Pooled data	912	Included 205.416/205.417			Time to 1st severe exacerbation to 48 weeks Time to 1 st exacerbation to 48 weeks	Asthma control states from ACQ-7. Exacerbation health states

Source: compiled during the evaluation

DB = double blind; MC = multi-centre; CO = crossover; R = randomised; MC = multi-centre; FEV₁ = forced expiratory volume in one second; ACQ-7 = asthma control questionnaire (7-item version)

6.8 The definitions of the exacerbation and Asthma Control Questionnaire, 7-item version (ACQ-7) are presented in the Table below.

Table 3: Definition of asthma exacerbation and asthma control questionnaire in the submission

Type of exacerbation	Definition
Asthma exacerbation	An episode of progressive increase in one or more asthma symptoms outside the patient's usual range of day-to-day asthma symptoms for at least two consecutive days. With or without a decrease of patient's best morning PEF of $\geq 30\%$ from the patient's mean morning PEF for at least two consecutive days
Severe asthma exacerbation	All asthma exacerbations that required treatment with systemic corticosteroids for at least three days or if already receiving systemic corticosteroids, a doubling of the previous daily dose for at least three days.
Non-severe exacerbation	All asthma exacerbations that were not considered a severe asthma exacerbation (see definitions above).
Asthma control questionnaire -7 (ACQ-7)	A self-reported measure with 7 items based on 5 symptom questions (night-time waking, symptoms on waking, activity limitation, shortness of breath, and wheeze), one score for reliever use, and a score for pre-bronchodilator FEV ₁ . The score ranges from 0-6, where a higher score represents poorer asthma control and successful treatment will reduce the ACQ-7 score.

Source: compiled during the evaluation

PEF = peak expiratory flow; FEV₁ = forced expiratory volume in one second; ACQ-7 = asthma control questionnaire (7-item version)

Comparative effectiveness

6.9 Table 4 presents the key results from Trials 205.416 and 205.417.

Table 4: Results of patient-relevant outcomes across the direct randomised trials

Trial ID	Tiotropium 5 µg		Placebo		Adjusted mean difference ^a (95% CI)	
	N	mean ^a (SE)	N	mean ^a (SE)		
Trough FEV₁ response (litres) at 24 weeks						
205.416	217	0.144 (0.024)	211	0.056 (0.025)	0.088 (0.03, 0.15)	
205.417	204	0.155 (0.023)	218	0.044 (0.022)	0.111 (0.05, 0.17)	
Meta-analysis result (I ² statistic = 0%) Chi-square for heterogeneity: P=0.59					0.10 (0.06, 0.14)	
ACQ-7 score to 48 weeks						
205.416	215					
205.417	200					
Meta-analysis result (I ² statistic = %) Chi-square for heterogeneity: P=						
	N	n with event (%)	N	n with event (%)	NNT (95% CI)	HR (95% CI)
Exacerbation (any severity) – HR for time to first event – secondary pre-specified outcome						
Pre specified analysis	453	226 (49.9%)	454	287 (63.2%)	8 (5, 14)	0.69 (0.58, 0.82)
Severe exacerbation – HR for time to first event – primary pre-specified outcome						
Pre specified analysis	453	122 (26.9%)	454	149 (32.8%)	NE	0.79 (0.62, 1.00)
Hospitalisation for asthma exacerbation – HR for time to first event – secondary pre-specified outcome						
205.416	237		222		NE	
205.417	216		232		NE	
Meta-analysis result (I ² = %) ^a Chi-square for heterogeneity: P=					NE	
ACQ-7 responders to 48 weeks						RR (95% CI)
205.416	215				NE	
205.417	200					
^b Meta-analysis (I ² statistic = %) Chi-square for heterogeneity: P=						

Source: Table B.24, p89; Table B.25, p92; Table B.26, p93; Table B.28-29, pp97-98 of the submission and compiled during the evaluation

HR = hazard ratio; CI = confidence interval; RR = relative risk; NNT = number needed to treat; SE = standard error; FEV₁ = forced expiratory volume in one second; ACQ = asthma control questionnaire; NE = not estimated; **Bold** = statistically significant

^a Tests for heterogeneity for relative risk presented, tests for heterogeneity for HR not provided in the submission

^b Meta-analysis for relative risk

- 6.10 The ESC noted that while the time to first severe exacerbation was a co-primary outcome, emphasis seemed to be on the time to first exacerbation (any), which was more convincing statistically but may not be clinically or resource meaningful.
- 6.11 The ESC noted the third co-primary endpoint, time to first severe exacerbation, was not significant in the unadjusted analysis (p=0.0535) but significant after adjusting for the interim analysis (HR 0.79, 95% CI 0.62 to 1.00 p=0.0343). Based on this, the difference in time until at least 25% of patients had a severe exacerbation was approximately 56 days. The ESC also noted that the upper limit of the CI still overlaps 1 (no difference). The sensitivity of the adjusted results was not tested against alternative procedures.

- 6.12 The ESC considered that the main body of the submission did not present all patient relevant outcomes, e.g. the number of exacerbations per patient (Tables 5 and 6).

Table 5: Number of patients categorised by the frequency of experienced asthma exacerbations (any severity)

Frequency of any asthma exacerbation	0	1	2	3	4	5	6	7-10	11-20	21+
Placebo	█	█	█	█	█	█	█	█	█	█
Tiotropium	█	█	█	█	█	█	█	█	█	█

Source: Table 15.2.1.1.2: 8, p 114 of Appendix 4 of the submission (Pooled Trial 205.416/205.417)

Table 6: Number of patients categorised by the frequency of experienced severe asthma exacerbations

Frequency of severe asthma exacerbation	0	1	2	3	4	5	6	7-10	11-20
Placebo	█	█	█	█	█	█	█	█	█
Tio R5	█	█	█	█	█	█	█	█	█

Source: Table 15.2.1.1.2: 7, p 113 of Appendix 4 of the submission (Pooled Trial 205.416/205.417)

- 6.13 The clinical trial report presented a Poisson regression model to analyse the differences in rates of severe exacerbations per patient. In this model log exposure was used as offset and adjusted for overdispersion; the treatment ratio tiotropium to placebo was █ (█% CI: █ to █). The majority of patients in both treatment groups did not have any severe exacerbation. Further, the distribution for both treatment groups was reasonably similar, which did not suggest large differences in the number of severe exacerbations per patient, as also indicated with a confidence interval reaching █.

Comparative harms

- 6.14 Tiotropium provided a reduction in relative risk (RR) for any adverse events (RR: 0.92, 95% confidence interval (CI): 0.86 to 0.99) and respiratory, thoracic and mediastinal disorders (RR: 0.84, 95% CI: 0.74 to 0.96) over placebo controlled usual care. Other common adverse events (≥2%) included: infections and infestations, investigations, diarrhoea, musculoskeletal and connective tissue disorders, headache, chest pain, insomnia, and hypertension. Tiotropium did not result in any difference in relative risk for adverse events leading to discontinuation, severe adverse events or serious adverse events over placebo controlled usual care.

Benefits/harms

- 6.15 A summary of the comparative benefits and harms for tiotropium versus placebo is presented in the following table.

Table 7: Summary of comparative benefits and harms for tiotropium and placebo

Benefits							
Trough FEV ₁ response (litres) at 24 weeks ^a							
	Tiotropium			Placebo			MD (95% CI)
	n	MD baseline	SD	n	MD baseline	SD	
205.416/205.417	421	0.149	0.342	429	0.050	0.345	0.10 (0.06, 0.14)
		Tiotropium	Placebo	Absolute Difference		HR (95% CI)	
Time for first exacerbation (any severity) ^b							
Event*	226/453		287/454		13%		
Median (days)	315 (268, nc)		181 (148, 218)		134		0.69 (0.58, 0.82)
Time to first exacerbation (severe) ^b							
Event*	122/453		149/454		6%		
Median (days)	nc (282, nc)		nc (226, nc)		nc		0.79 (0.62, 1.00)
Harms ^c							
	Tiotropium n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)	
				Tiotropium	Placebo		
Any adverse event							
205.416/205.417	335/456	366/456	0.92 (0.86, 0.99)	73	80	-0.07 (-0.12, -0.01)	
Any serious adverse events							
205.416/205.417	37/456	40/456	0.93 (0.61, 1.43)	8	9	-0.01 (-0.04, 0.03)	
Respiratory, thoracic and mediastinal disorders							
205.416/205.417			()			(- , -)	
Adverse events leading to discontinuation							
205.416/205.417	8/456	14/456	0.56 (0.17, 1.90)	2	3	-0.01 (-0.03, 0.01)	

Source: Table B.24, p89; Table B.28, p97; Table B.32, p104; Tables B.33-B.34, pp108-110 and Figure B.4, p90 of the submission and compiled during the evaluation

RD = risk difference; RR = relative risk; nc = not calculable; MD = mean difference; HR = hazard ratio; SD = standard deviation; CI = confidence interval; FEV₁ = forced expiratory volume in one second; **bold** = statistically significant

* Median duration of follow-up/ exposure = 48 weeks

^a 57 patients were excluded from the full analysis set for this outcome, with no further explanation in the clinical trial report

^b Full analysis set

^c Five additional patients were added to the full analysis set, with no further explanation in the clinical trial report

- 6.16 On the basis the head to head trial, the comparison of tiotropium and placebo resulted in:
- Approximately a 100 mL reduction in trough FEV₁ over a median duration of follow-up of exposure of 24 weeks. It was considered that a reduction of 100–140 mL is clinically significant in COPD, a change of 150 mL has been considered to be clinically meaningful in asthma (fluticasone furoate and vilanterol trifenate Public Summary Document, March 2014).
 - Approximately 56 days difference in time until at least 25% of patients experienced a severe exacerbation with a 48 week follow up.
 - Approximately 134 days difference in time without an exacerbation (any severity) for 50% of the patients with a 48 week follow-up.
- 6.17 On the basis of direct comparison evidence presented by the submission, for every 100 patients treated with tiotropium in comparison to placebo with a 48 week follow-up:
- Approximately **■** fewer patients would have had an exacerbation (any severity)
 - Approximately **■** fewer patients would have had a respiratory, thoracic or mediastinal disorder

Clinical claim

- 6.18 The submission described tiotropium 5 µg as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over placebo.
- 6.19 The evaluation considered this claim was adequately supported in terms of statistical measures and tiotropium provided superior efficacy to placebo in terms of trough FEV₁, time to first exacerbation, time to first severe exacerbation and ACQ-7 score. However these may not translate into clinically meaningful differences:
- A value of 150 mL has been used for clinically important difference for detecting non-inferiority in trough FEV₁ in asthma; however the clinical data only demonstrated a 100 mL difference.
 - A clinically meaningful change in ACQ-7 score was a reduction of 0.5 or more⁴, while 12% more patients achieved this in the tiotropium arm, the mean reduction was 0.1.
- 6.20 The PSCR disagreed with the evaluation regarding the clinical significance of the trough FEV₁ difference, stating that ‘it is not appropriate to apply a unidirectional non-inferiority threshold, which is intended to exclude inferiority, in a bidirectional manner to assess superiority’. The ESC disagreed with the PSCR, as the ESC considered that the evaluation was questioning whether a trough FEV₁ difference of 100 mL has clinical meaning for patients (given the non-inferiority threshold of 150 mL is supposed to indicate the point beyond which there is a discernible difference between products), and was not suggesting a trough FEV₁ difference of 150 mL be used to assess superiority.
- 6.21 The Pre-PBAC response noted that the 100 mL improvement in trough FEV₁ was in addition to improvements already achieved with high doses of ICS and LABA as background therapy; with the safety profile of tiotropium as add-on to ICS and LABA being non-inferior to ICS and LABA alone.
- 6.22 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.23 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Economic analysis

- 6.24 The submission presented a modelled economic analysis.

⁴ [Global Initiative for Asthma](#). Global Strategy for Asthma Management and Prevention 2014.

Table 8: Summary of model structure and rationale

Component	Summary		
Time horizon	15 years in the model base case versus 48 weeks in trial		
Outcomes	Exacerbations avoided, patient years free of exacerbation, life years gained and quality-adjusted life-years gained.		
Methods used to generate results	Extrapolated trial data and Markov model		
Health states	Seven health states: 1) optimal asthma control; 2) acceptable asthma control; 3) uncontrolled asthma; 4) non-severe exacerbation; 5) severe exacerbation without hospitalisation; 6) severe exacerbation with hospitalisation; and 7) death (all-cause)		
	Health State	Utility Values	Source
	Optimal control	█	Trial 205.416/205.417, EQ-5D-3L (UK weights)
	Acceptable control	█	
	Uncontrolled	█	
	Non-severe exacerbation	█	Assumption - midpoint uncontrolled and severe
	Severe exacerbation w/o hospital	0.57	Lloyd et al. 2007
Severe exacerbation with hospital	0.33		
Cycle length	1 week		
Transition probabilities	Asthma control states from ACQ-7 from trial 205.416/205.417. Exacerbation health states from trial 205.416/205.417. Mortality from Australian Bureau of Statistics.		

Source: compiled during the evaluation

w/o = without; ACQ-7 = asthma control questionnaire (7-item version); EQ-5D-3L = Euroqol 5-dimension 3-level instrument

6.25 Table 9 presents the key drivers for the economic model.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Time horizon	15 years; assumed from 48 week trial duration	Moderate, favours tiotropium
Asthma health state utilities	Taken from trial. Utility weights for the optimal and acceptable control states were relatively high compared with existing values in the literature.	High, favours tiotropium
Model structure/Transition probabilities	Transition probabilities were estimated inappropriately. Treatment effect for the transition probabilities were not tested for significance and were the key drivers in the model.	High, direction uncertain

Source: compiled during the evaluation, ACQ-7 = asthma control questionnaire (7-item version)

Table 10: Results of the stepped economic evaluation

Step and component	Tiotropium (ICS+LABA)	Placebo (ICS+LABA)	Increment
Step 1: trial-based costs and outcomes			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Exacerbations avoided	[redacted]	[redacted]	[redacted]
Incremental cost/extra exacerbation avoided			\$ [redacted]
Years free of exacerbation	[redacted]	[redacted]	[redacted]
Incremental cost/patient year free of exacerbation			\$ [redacted]
Step 2: trial results and premodelling (including healthcare resource utilisation results)			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Exacerbations avoided	[redacted]	[redacted]	[redacted]
Incremental cost/extra exacerbation avoided			\$ [redacted]
Years free of exacerbation	[redacted]	[redacted]	[redacted]
Incremental cost/patient year free of exacerbation			\$ [redacted]
Step 3: modelled evaluation (including extrapolation results)			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Exacerbations avoided	[redacted]	[redacted]	[redacted]
Incremental cost/extra exacerbation avoided			\$ [redacted]
Step 4: modelled evaluation (including utilities)			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
QALY	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			\$ [redacted]

Source: Tables D.5-1 to D.5-4, pp242-245 of the submission

ICS = inhaled corticosteroid; LABA = long-acting β_2 agonist; QALY = quality-adjusted life year

- 6.26 The economic evaluation presented in the submission resulted in an ICER of \$15,000 - \$45,000 per QALY for tiotropium plus usual care vs. usual care.
- 6.27 There were major issues with the approach taken to estimating and applying transition probabilities in the submission. The ESC noted that the submitted model assumed constant transition probabilities across the full time horizon, which resulted in potentially important differences in the modelled and actual trial distribution of health states at 48 weeks. Optimal and acceptable control was overestimated by 4.3% and 2.1% in the intervention and control groups, respectively. Therefore, the ESC considered the model was not internally valid.
- 6.28 The weekly health state transition probabilities were extrapolated for 15 years, using a fixed matrix. This would not reflect clinical practice and would be likely to favour tiotropium.
- 6.29 The ESC noted that the model was sensitive to small changes in the transition probabilities; for example, changing the intervention transition probability for tiotropium patients from Uncontrolled to Optimal from 0.5% to 0.3% increased the ICER from \$15,000 - \$45,000/QALY to \$75,000 - \$105,000/QALY.
- 6.30 In response to the evaluation, the PSCR presented a revised economic analysis, which used the asthma states observed in the trials over the first 48 weeks, and extrapolated using transition probabilities estimated from the weeks 40 and 48 follow-up points. The PSCR reported that this analysis reduced the ICER from \$15,000 - \$45,000/QALY to \$15,000 - \$45,000/QALY. Without access to the observed data, Evaluator analyses applying the transition matrices generated for

weeks 41 to 48 (inclusive) to the whole model resulted in an ICER of \$15,000 - \$45,000/QALY. However, applying transition matrices generated for weeks 40 to 48 (inclusive), which includes observed data points at weeks 40 and 48, the ICER increases to \$45,000 - \$75,000/QALY.

- 6.31 The ESC noted that sample size was artificially inflated, as the seven follow-up points in the trial were formatted to inform 48 transition probabilities per patient in the model. The real sample size informing some of the transition probabilities was small, especially when using the 40 to 48 week data, which resulted in significant uncertainty around the true value of key transition probabilities.
- 6.32 The ESC considered a better model structure would represent only three health states: optimal, acceptable, and uncontrolled asthma. The costs and quality of life effects of exacerbations could be represented within each state. Separate analyses could assess whether patients receiving the intervention experienced fewer exacerbations within each state. The ESC considered it preferable to use all observed data to week 48, estimating 8-weekly transition probabilities between the asthma control states to extrapolate (with an accompanying Dirichlet distribution⁵ to represent the uncertainty). Alternatively, the ESC considered that time to event analyses could be undertaken to test for time varying transition probabilities, and treatment effects.
- 6.33 The Pre-PBAC response argued that the model structure corresponds with the approaches used in published economic evaluations. This contradicts the view of the Commentary that the majority of published economic evaluations had fewer health states and shorter time horizons.
- 6.34 There were major issues with the approach taken to estimate and apply utility values in the submission. Utility weights for the optimal and acceptable control states were relatively high compared to the literature, whilst the uncontrolled asthma utility weight was consistent with the literature. The model was sensitive to these utility weights and the base case results favoured tiotropium. This may have been due to the use of the EuroQoL 5 dimensions, 3 level (EQ-5D-3L) instrument, which lacks sensitivity to small changes in health states. In this case, EQ-5D-3L may not be sensitive to small decrements in quality of life in patients with controlled asthma.
- 6.35 Additionally, the ESC noted that most exacerbations were experienced by patients with uncontrolled asthma, the effects of which may have been double counted, i.e. reflected in the reported utility values for the 'uncontrolled asthma' group, and the separately defined exacerbation states. This would have favoured tiotropium because fewer exacerbations were experienced in this group. The ESC considered that this issue would also be addressed by the simpler model structure proposed in paragraph 6.32.
- 6.36 The ESC noted that the submission used different cut-points for defining optimal and acceptably controlled asthma to the cut-points for the ACQ-7 used in the literature and in international clinical guidelines. The ESC considered this would not have been

⁵ Briggs AH, Ades AE, Price MJ, Probabilistic Sensitivity Analysis for Decision Trees with Multiple Branches: Use of the Dirichlet Distribution in a Bayesian Framework, *Med Decis Making* July 2003 vol. 23 no. 4 341-350

high impact, but would likely have favoured the intervention, as more intervention patients were in the optimal than the acceptable state.

- 6.37 The submission presented various univariate sensitivity analyses and deterministic sensitivity analyses, and additional sensitivity analyses were performed during evaluation. Table 11 presents the key sensitivity analyses.

Table 11: Key results of univariate and multivariate sensitivity analyses

Univariate analyses	Δ costs	Δ QALY	ICER
Base case	\$		\$
ACQ-6 applied to Health states	\$		\$
Baseline distribution - trial based	\$		\$
Compliance - 100%	\$		\$
Time horizon (base case 15 year)			
48 weeks (trial based)	\$		\$
10 years	\$		\$
20 years	\$		\$
Utility values in ACQ-7 health states (base case: EQ-5D-3L; optimal control 0.96, acceptable: 0.93, uncontrolled 0.76)			
Gordois et al. (2007) AQoL (0.86, 0.84, 0.71)	\$		\$
McTaggart-Cowan et al. (2008) EQ-5D-3L (0.84, 0.81, 0.80)	\$		\$

Source: Table D.6-1, p246 of the submission

QALY = quality-adjusted life year; ICER = incremental cost effectiveness ratio; EQ-5D-3L = EuroQoL 5-dimensions 3-levels; AQoL = assessment of quality of life instrument; ACQ-6 = asthma control questionnaire (6-item version)

- 6.38 The univariate and multivariate deterministic sensitivity analyses conducted by the submission resulted in an ICER range from \$15,000 - \$45,000/QALY to \$45,000 - \$75,000/QALY gained. Analyses performed during evaluation, resulted in higher and lower ICERs (\$15,000 - \$45,000/QALY to \$100,000 - \$200,000/QALY gained), with the key drivers being; utility values, time horizon, and level of compliance. Various structural concerns with the economic model could not be tested during evaluation.
- 6.39 The model implied that severe exacerbations last for two weeks. A crude sensitivity analysis, applying the utility weight for uncontrolled asthma plus half of the difference between the exacerbation and uncontrolled state utility weights, increased the ICER to \$45,000 - \$75,000/QALY.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Drug cost/patient/year

- 6.40 Estimated \$ per year continuing for the lifetime of the patient; assumed usage of two puffs once daily and a compliance rate of %.

Estimated PBS usage & financial implications

- 6.41 The submission was considered by DUSC.
- 6.42 The submission took an epidemiological approach to forecast the uptake of tiotropium over a five year period using data from, the Australian Bureau of Statistics, the Australian Health Survey 2011-2012 and a review of the literature. The financial

estimates were based on tiotropium being used in adult patients with severe uncontrolled asthma and who were compliant with their prescribed medication.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Market share	%	%	%	%	%
Scripts ^a					
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to MBS	-	-	-	-	-
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$

Source: Table E.2-4, p224; Table E.2-6, p225 of the submission

^a Assuming 10.67 per year as estimated by the submission

- 6.43 The redacted table above shows that at year 5, the estimated number of patients was 50,000 – 100,000 and the net cost to the PBS would be \$30 - \$60 million.
- 6.44 The extent of use within the proposed restriction could be higher or lower than the submission estimate due to:
- Differences between “severe or uncontrolled asthma who are compliant with their prescribed medications” estimated in the submission and “severe uncontrolled asthma despite optimal usual care” defined in the restricted benefit. DUSC considered it inappropriate to apply a compliance rate to the estimate of eligible patients on ‘optimal usual care’, as optimal usual care implies that patients are compliant.
 - Sources used to determine the proportion of asthmatics with severe asthma and uncontrolled asthma might not be applicable to the Australian context; and the proportions were derived from a wide range of values in the literature. This introduced uncertainty into the financial estimates.
 - A recent Australian cross-sectional web-based survey⁶ indicated that 19.7% of the asthma patients had inadequate asthma control while compliant to ICS or ICS and LABA treatment. Approximately three times as many patients were on ICS and LABA treatment compared to those on ICS only. This would result in a much larger eligible population than calculated by the submission.
 - Unclear market uptake for tiotropium; and
 - Current use of tiotropium in asthma patients who also have COPD.
- 6.45 The submission presented sensitivity analyses around prevalence of severe and uncontrolled asthma and compliance, with severe asthma prevalence having the largest impact on the overall cost to the PBS/RPBS (\$60 – 100 million to more than \$100 million over five years). The submission did not test different uptake rates. The commentary presented a sensitivity analysis that included all uncontrolled asthma patients eligible for tiotropium treatment with a cost to PBS/RPBS of over \$100 million over five years.

⁶ Reddel HK, Sawyer SM, Everett PW, *et al.* (2015). Asthma control in Australia: a cross-sectional web-based survey in a nationally representative population. *MJA*, 202(9): p. 492-498.

- 6.46 There is a high risk that tiotropium would be used beyond the requested restriction in patients with less severe asthma, or instead of a LABA as add-on to ICS. If asthma medicines continue to be used outside of the guidelines, and if the requested restriction for tiotropium is interpreted liberally, DUSC considered the costs for tiotropium could be higher than the estimates.

Quality Use of Medicines

- 6.47 A recent survey indicated that a large proportion of asthma patients were not compliant to chronic asthma medication.⁶
- 6.48 Tiotropium is a controller that will provide symptomatic relief as an add-on therapy; patients will need to be educated about the need to continue preventer therapy and not substitute this inhaler for their preventer. If patients replace tiotropium for their preventer, this would likely lead to worse clinical outcomes and would likely increase the cost to Government.
- 6.49 This will be a new respiratory device and formulation of a currently approved medicine (tiotropium, Spiriva®). There are already many different inhalers available which require different inhaler techniques. Adding to the number of inhalers available can cause confusion and increases the likelihood of poor inhaler technique.
- 6.50 In the Pre-PBAC response, the sponsor committed to provision of educational resources to address quality use of medicines concerns.

Financial Management – Risk Sharing Arrangements

- 6.51 In the PSCR, the sponsor acknowledged the areas of uncertainty with the financial estimates and was willing to accept a risk sharing arrangement around the financial estimates specific to the severe asthma indication.
- 6.52 In the pre-PBAC response, the sponsor proposed a risk sharing arrangement with subsidisation caps amended from the submission estimates to increase the uptake rate in the first three years of listing, due to the level of poor asthma control identified in a recent study⁶, and with the price adjusted according to future price reductions anticipated by the sponsor.
- 6.53 The PBAC recommended a risk sharing arrangement would be appropriate due to an uncertain patient population for tiotropium in asthma. The PBAC agreed with the DUSC that there is a high risk tiotropium would be used outside of the PBS restriction in patients without severe asthma, or instead of a LABA as add-on to ICS. The PBAC considered it was not appropriate to adjust the financial estimates according to future potential price reductions.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of tiotropium as add-on therapy for the treatment of severe uncontrolled asthma. In making its recommendation, the PBAC

considered that the economic model was not reliable and the true cost-effectiveness of tiotropium in this setting was probably high and highly uncertain.

- 7.2 The PBAC accepted the clinical place for tiotropium as an add-on therapy to an ICS and a LABA for adult patients with severe persistent asthma who have experienced at least one serious exacerbation in the previous year. The PBAC noted the comments from The Lung Foundation and The Centre of Research Excellence in Severe Asthma and agreed that there is a need for additional treatments for severe uncontrolled asthma.
- 7.3 The PBAC agreed with the changes to the restriction wording that were suggested by the Secretariat, ESC and DUSC; including that the exacerbation in the previous 12 months must have been a severe exacerbation, the treatment must be in combination with an ICS and a LABA, and that high dose budesonide should be defined as ≥ 800 $\mu\text{g}/\text{day}$ rather than ≥ 1600 $\mu\text{g}/\text{day}$. The PBAC considered the pre-PBAC suggestion of adding 'consider consultation with a specialist physician' was not necessary.
- 7.4 The PBAC agreed that placebo plus ICS and LABA was the appropriate comparator.
- 7.5 In considering the key trial evidence, a combined analysis of Trials 205.416 and 205.417, the PBAC agreed that the comparative benefit of add-on tiotropium over placebo was adequately supported in terms of statistical measures and tiotropium provided superior efficacy to placebo in terms of trough FEV₁, time to first exacerbation, time to first severe exacerbation and ACQ-7 score. The PBAC considered that the incremental benefit in trough FEV₁ for patients with persistent severe uncontrolled asthma was likely to be clinically meaningful. However, the PBAC questioned the emphasis on the time to first exacerbation (any), which was more convincing statistically than the time to first severe exacerbation, but may not be as clinically or resource meaningful. The PBAC also noted differences in the trough FEV₁ and peak FEV₁ values between the two clinical trials.
- 7.6 The PBAC agreed that tiotropium did not result in any difference in relative risk for adverse events leading to discontinuation, severe adverse events or serious adverse events over placebo controlled usual care.
- 7.7 The PBAC considered the model structure problematic, as separation of control states from exacerbation states created the possibility that the impact of exacerbations could be double counted. The PBAC also noted the disjunct between the trial time horizon and the model duration. The PBAC was concerned that the modelled outcomes were not the clinical outcomes in the key trial and that translating 'any exacerbation' into the economic model rather than 'severe exacerbations' may not have been as clinically meaningful. The PBAC considered the assumption that severe exacerbations last two weeks may have over-represented this health state. The PBAC noted that the model was highly sensitive to small changes in the transition probabilities. Due to these issues with the economic model, the PBAC was not confident in the ICER presented and considered that the true cost-effectiveness was uncertain. The PBAC considered the variability in the ICER resulting from minor changes to the PSCR revised analysis highlighted the uncertainty of the true cost-effectiveness of tiotropium in this setting.

- 7.8 The PBAC considered that while the estimates of use within the requested restriction may be reasonable, the true number of patients who would use tiotropium for asthma was uncertain. The PBAC was concerned that tiotropium could be used beyond the restriction to treat less severe asthma; a population that was not supported by the clinical evidence and in which cost-effectiveness was not tested. However the PBAC noted this could be mitigated through a risk sharing arrangement.
- 7.9 The PBAC considered that any re-submission would need a new economic model based on asthma control states, and would therefore need to be evaluated as a major resubmission.
- 7.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.