

6.06 TIOTROPIUM

Solution for oral inhalation 2.5 µg per actuation, 60 Spiriva® Respimat®, Boehringer Ingelheim Pty Limited

1 Purpose of Application

- 1.1 The submission requested an Authority Required (STREAMLINED) listing for tiotropium solution for inhalation in patients with severe asthma, aged 6 to 17 years who remain uncontrolled despite receiving optimised asthma therapy. This was the first application to the PBAC for tiotropium in this population. Tiotropium was recommended for adult patients with severe asthma in March 2016.
- 1.2 The submission requested listing based on a cost effectiveness analysis, presented as a cost per symptomatic exacerbation (non-severe and severe) avoided compared to placebo. A cost utility analysis was not provided as the submission claimed that there were inherent difficulties in determining utility values in children.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Children aged 6 to 17 years with severe asthma.
Intervention	Tiotropium 5 µg (two puffs of 2.5 µg) once daily plus optimised asthma therapy.
Comparator	Optimised asthma therapy (defined as adherence to the maintenance combination of ICS (≥ 400 µg budesonide/day or equivalent in children aged < 14 years, and ≥ 800 µg budesonide/day or equivalent in children aged ≥ 14 years, and a LABA), plus placebo (two puffs) daily.
Outcomes	Lung function (FEV ₁ peak (0–3h) and trough FEV ₁), asthma exacerbations (post-hoc), adverse events.
Clinical claim	Tiotropium as an add-on to optimised therapy is superior in terms of efficacy and non-inferior in terms of safety compared to optimised asthma therapy alone.

Source: Table 1.1, p14 of the submission

FEV₁ = forced expiratory volume in one second; ICS = inhaled corticosteroid; LABA = long-acting beta₂ agonist

2 Requested listing

Name, restriction, manner of administration and form	Maximum quantity (packs)	No. of Repeats	Dispensed price for maximum quantity ^a	Proprietary Name and manufacturer	
TIOTROPIUM, Authority Required (Streamlined) Solution for oral inhalation, 2.5 µg, 60 actuations	1	5	\$59.42	Spiriva® Respimat®	Boehringer Ingelheim

Public Summary Document – March 2018 PBAC Meeting

Category/Program:	General Schedule
PBS indication:	Severe asthma
Restriction:	<input checked="" type="checkbox"/> Streamlined
Treatment criteria:	<i>Must be treated in consultation with a paediatrician or a respiratory physician or a general physician experienced in the management of patients with severe asthma.</i>
Clinical criteria:	Patient must have failed to achieve adequate control due to frequent episodes of asthma while receiving optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented AND The treatment must be used in combination with a maintenance combination of an inhaled corticosteroid (ICS) and a long acting beta ₂ agonist (LABA) unless contraindicated
Population criteria:	Patient must be aged 6 to less than 18 years
Prescriber criteria:	Optimal asthma therapy includes adherence to the maintenance combination of an ICS (at least 400 micrograms budesonide per day or equivalent in children aged under 14 years, otherwise at least 800 micrograms budesonide per day or equivalent) and a LABA. If LABA therapy is contraindicated, not tolerated or not effective, montelukast, cromoglycate or nedocromil may be used as an alternative

Source: Table 1.8, p44; and Table 1.9, p46 of the submission

AEMP = approved ex-manufacturer price; ICS = inhaled corticosteroid; LABA = long-acting beta₂ agonist; PBS = Pharmaceutical Benefits Scheme

Criteria in *italics* proposed by the pre-PBAC response.

^a The AEMP of tiotropium will be reduced by 14.5% (statutory 10% + 5% price reductions for F1 products listed for 10 and 15 years) on 1 June 2018 as a result of the Strategic Agreement between the Commonwealth and Medicines Australia.

- 2.1 The proposed PBS restriction was largely consistent with the Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention (2017), which recommends a high dose ICS (i.e. > 400 µg budesonide per day for children aged 6 to 12, and > 800 µg budesonide per day for children aged 12 and over) plus a LABA for severe uncontrolled asthma.
- 2.2 The proposed PBS restriction differed from the National Asthma Council Australia, which in the Australian Management Handbook (2017), stated that in children, a low dose ICS (defined as 200-400 µg budesonide (high dose budesonide is defined as 400-800 µg)) should be used in combination with a LABA, before referral to a specialist.
- 2.3 The ESC agreed with the secretariat proposal to model the Prescriber instruction for optimised therapy on the current PBS listing for omalizumab for severe allergic asthma in patients between 6 and 12 years of age.
- 2.4 The ESC was concerned that it was poor medical practice to add another agent to children not adequately adhering to optimised asthma therapy and advised that the restriction should include a clause to require specialist consultations or initiation in hospital to ensure patients are compliant with optimal asthma therapy prior to treatment with tiotropium. However, this may increase the restriction level to a Telephone Authority. The ESC agreed that the children's restriction should be separate from the adult restriction to highlight these issues. The pre-PBAC response noted these issues and proposed an Authority Required (STREAMLINED) listing for all the severe asthma listings in response. It also proposed inclusion of the Treatment Criteria: "Must be treated in consultation with a paediatrician or a respiratory

physician or a general physician experienced in the management of patients with severe asthma”.

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

3 Background

Registration status

- 3.1 The submission was made under TGA/PBAC Parallel Process. The TGA delegate’s file note was not received in time for PBAC consideration. In the pre-PBAC response the sponsor stated it had received notification that the TGA Clinical Delegate would not take this item to the Advisory Committee for Medicines (ACM) and instead will recommend tiotropium as add-on maintenance bronchodilator treatment in patients aged 6 years and older with moderate or severe asthma.
- 3.2 Tiotropium solution is already TGA approved and PBS listed for the treatment of:
 - severe asthma in adults; and
 - bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease (COPD).

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

4 Population and disease

- 4.1 Asthma is a chronic inflammatory disorder of the airways with typical symptoms of recurrent episodes of wheezing, breathlessness, chest tightness and coughing. Asthma symptoms frequently cause sleeplessness, daytime fatigue, reduced activity levels, and school and work absenteeism.
- 4.2 Asthma severity is determined by the type and amount of treatment needed to maintain adequate symptom control, with more serious disease requiring a greater intensity of treatment. Poor symptom control is strongly associated with an increased risk of asthma exacerbations, which may require hospitalisation. The Australian Institute of Health and Welfare (AIHW) 2013 report, ‘Asthma hospitalisation in Australia 2010-11’ estimates that children are hospitalised for asthma management at approximately five times the rate of adults.
- 4.3 The proposed clinical treatment algorithm places tiotropium as an add-on bronchodilator for children aged 6 to 17 years with severe asthma, who remained uncontrolled despite receiving optimised asthma therapy. Optimised asthma therapy was considered to consist of a high-dose inhaled corticosteroid (ICS) used in combination with a long-acting beta₂ agonist (LABA).
- 4.4 The ESC noted that bronchodilators have a history of being associated with an increased risk of death when patients subsequently discontinue their other forms of standard asthma therapy.

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

5 Comparator

- 5.1 The submission nominated placebo plus optimised asthma therapy as the main comparator. This was appropriate.
- 5.2 The PBAC had previously accepted placebo plus optimised asthma therapy as the appropriate comparator for tiotropium in adults with severe asthma (paragraph 7.4, July 2015 and March 2016 Public Summary Documents (PSD)).

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 Asthma Australia via the Consumer Comments facility on the PBS website. Of note, Asthma Australia highlighted that children with symptoms unresponsive to current guideline recommendations should be referred to specialist services for further investigation where they can undergo systematic evaluation. It was further noted many children with asthma are found not to have severe, treatment-refractory asthma after thorough evaluation and approximately 50% of children referred for severe asthma have persistent symptoms and poor control because of inadequate disease management where the addition of another treatment option will not benefit either.
- 6.3 Where deemed appropriate as an additional treatment option, tiotropium was described as having a range of benefits for children unable to achieve adequate control of their asthma with current therapeutic options, including increased quality of life, lower doses of inhaled corticosteroids, lower use of systemic corticosteroids which have side effects, decreased rates of asthma exacerbations, less hospitalisations and a lower risk of mortality.
- 6.4 The PBAC noted the advice received from Asthma Australia clarifying the likely use of tiotropium in clinical practice. The PBAC specifically noted the advice that the use of tiotropium should be included in the Australian Asthma Handbook, that the PBS restriction should specify the stepped approach to treatment of children and adolescents, particularly in regards to the prescribing of ICS/LABA preventer medications, and patients should be under the care of a respiratory specialist who would prescribe tiotropium appropriately and with clear and regular device instruction. The PBAC noted that the clinical evidence did not adequately support the clinical place of tiotropium in children.

Clinical trials

6.5 The submission was based on a meta-analysis of two 12-week head-to-head randomised trials comparing tiotropium plus optimised asthma therapy (i.e. ICS plus LABA) to optimised asthma therapy alone in children aged 6 to 17 years with severe asthma:

- Trial 205.446 recruited patients aged 6 to 11 years (N = 264); and
- Trial 205.456 recruited patients aged 12 to 17 years (N = 265).

6.6 The PBAC noted the pre-PBAC response provided a summary of the outcomes from an additional two 48-week trials which were conducted in children with moderate asthma (as defined by uncontrolled symptoms despite treatment with medium dose ICS either alone or in combination with another controller medication) aged 6-11 years (trial 205.445) or 12-17 years (trial 205.444). These trials were excluded from the submission as they were conducted in a more moderate population, and have therefore not been evaluated or considered by the ESC. In summary, the trials showed tiotropium compared with placebo significantly improved trough FEV₁ response from baseline to 24 and 48 weeks and the incremental difference was consistently above the minimally clinically important difference (MCID) of 0.1 L.

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Trial 205.456 (NCT01277523)	A randomised, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (2.5 mcg and 5 mcg once daily) over 12 weeks as add-on controller therapy on top of usual care in adolescents (12 to 17 years old) with severe persistent asthma. Hamelmann E, Bernstein JA, et al. A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma.	April 2014 Eur Respir J. 2017; 49 (1601100): 1-10
Trial 205.446 (NCT01634152)	A randomised, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution (2.5 µg and 5 µg) delivered via Respimat® inhaler once daily in the evening over 12 weeks as add-on controller therapy on top of usual care in children (6 to 11 years old) with severe persistent asthma. Szeffler SJ, Murphy K, et al. A phase III randomized controlled trial of tiotropium add-on therapy in children with severe symptomatic asthma.	September 2015 J Allergy Clin Immunol 2017; 140 (5): 1277-1287

Source: Table 2.1, pp52-53 of the submission

6.8 Both trials included an arm that received a 2.5 µg daily dose of tiotropium. These were excluded from the analyses as the requested TGA application and PBS listing was for a 5 µg daily dose.

6.9 Baseline characteristics suggested that randomisation was successful in both trials, and the majority of patients were receiving high dose ICS and a LABA. The proportion of patients receiving concomitant leukotriene receptor antagonist (LTRA) therapy was high in both trials (86% in trial 205.446 and 80% in trial 205.456); this was not

consistent with the proposed PBS restriction. The effect of trial patients being more highly treated in terms of efficacy and safety outcomes was uncertain. The Pre-Sub-Committee Response (PSCR) referred to a previous PBAC consideration of a LABA plus LAMA combination for chronic obstructive pulmonary disease (COPD) (indacaterol with glycopyrronium Public Summary Document (PSD) March 2014 para 6.20) where it was acknowledged that the incremental gain associated with add-on therapy would not be as great as the incremental gain associated with monotherapy compared with placebo. However, the proposed restriction for tiotropium was add-on to optimised usual care and hence the benefit needs to be tested within that context. The ESC considered the strong placebo responses suggested adherence to maximal optimal asthma therapy, especially in the 12–17 years group, was poor, and the addition of tiotropium was not the most clinically appropriate solution.

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcomes	Use in modelled evaluation
Tiotropium vs placebo						
204.446	264	R, MC, DB, PC 12 weeks	Low	Children 6-11 years; severe asthma	FEV ₁ peak (0–3h); Trough FEV ₁ ; Rate of symptomatic exacerbations (non-severe and severe) calculated post-hoc	Not used
206.456	265	R, MC, DB, PC 12 weeks	Low	Children 12-17 years; severe asthma	FEV ₁ peak (0–3h); Trough FEV ₁ ; Rate of symptomatic exacerbations (non-severe and severe) calculated post-hoc	Not used
Meta- analysis	529	Included 204.46 and 204.456; Assessed FEV ₁ peak (0–3h); trough FEV ₁ ; rate of symptomatic exacerbations (non-severe and severe)				Rate of symptomatic exacerbations (non-severe and severe)

Source: Compiled during the evaluation based on pp47-159 of the submission

DB = double blind; FEV₁ = forced expiratory volume in one second; MC = multi-centre; PC = placebo controlled; R = randomised

6.11 The primary outcome for both trials was change in the highest forced expiratory volume in one second, observed within three hours after administration (FEV₁ peak (0–3h)) from baseline to 12 weeks. The key secondary outcome was change in trough forced expiratory volume in one second (trough FEV₁) and rate of symptomatic exacerbations (which included non-severe and severe). The PBAC has previously accepted trough FEV₁, which is a surrogate outcome based on lung function, and which was the primary outcome (although presented at 24 weeks) when reviewing tiotropium solution in adults (paragraph 7.5, PSD July 2015). FEV₁ peak (0–3h) was not a key outcome in the consideration of tiotropium in adults. As noted in the Cochrane review on the addition of LABA to ICS in childhood asthma (Chauchan et al 2015), it is not surprising to see a bronchodilator effect in subjects who are selected because they respond to a bronchodilator. The FEV₁ peak (0–3h) is a measure of a short-term bronchodilator effect on top of the trough measure which reflects longer-term lung function. Since LABA and tiotropium are both long-acting

bronchodilators, an effect on trough FEV₁ may include a 24 hour bronchodilator component as well as a longer-term change in lung function.

- 6.12 In the adult submissions (July 2015, March 2016), the PBAC considered that the incremental benefits in trough FEV₁ were likely to be clinically meaningful, but it 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. (paragraph 7.5, PSD July 2015). However, the evaluation considered the use of FEV₁ measures in children might not provide a true representation of the severity of disease. Guilbert (2014) stated that “Extrapolating adult severity classifications to children is difficult.....adults with asthma are more likely to exhibit a persistent pattern; while children may have a pattern of rapidly evolving, frequent and often severe exacerbations....triggered by viral infections and/or allergen exposure....but then often remain asymptomatic between these episodes.” In addition, in children “Lung function measurements also show different patterns, are age-dependent, and may be within normal levels despite significant symptom burden and medication use. The distal airways are more affected, and increased distal lung resistance, in the absence of significant large airway involvement, likely explains the often unimpaired FEV₁ values.” The pre-PBAC response noted the acceptance from the FDA and EMA of the extrapolation of efficacy results from adults to children. The PBAC agreed this may be reasonable for the adolescent patient group. The ESC considered other important outcome measures from longer term trials would include frequency of significant exacerbations, asthma control such as asthma control questionnaire (ACQ), and quality of life.
- 6.13 The economic analysis and financial estimates were informed by the rate of symptomatic exacerbations (non-severe and severe). As the rate of exacerbations was not an outcome of either trial, post-hoc analyses were conducted to provide the number of symptomatic exacerbations (non-severe and severe) from which the rates were calculated.
- 6.14 The table below summarises the definitions for the key outcomes from trials 205.446 and 205.456.

Table 4: Definition of outcomes

Outcome	Definition
FEV ₁ peak (0–3h)	Highest FEV ₁ reading observed within 3 hours after administration of the daily dose (given in the evening) of each randomised treatment. The change from baseline at the end of the 12-week treatment period was measured. The tiotropium in adults with severe asthma submissions presented change in FEV ₁ peak (0–3h) at 24 weeks; however, it was not a key outcome (Table 2, p6 PSD July 2015).
Trough FEV ₁	Trough FEV ₁ was measured in the evening at the end of the dosing interval (24 hours post drug administration), 10 minutes prior to treatment. The change from baseline at the end of the 12-week treatment period was measured. The tiotropium in adults with severe asthma submissions presented change in trough FEV ₁ at 24 weeks as a key outcome (Table 2, p6 PSD July 2015).
Symptomatic (non-severe and severe) asthma exacerbation	All asthma exacerbations excluding those where only a decrease of patient's best morning PEF of $\geq 30\%$ from the patient's mean morning PEF for ≥ 2 consecutive days occurred. This definition has not been presented to the PBAC previously.
Severe asthma exacerbation	All asthma exacerbations that required treatment with systemic corticosteroids for ≥ 3 days or if already receiving systemic corticosteroids, a doubling of the previous daily dose for ≥ 3 days. This definition was consistent with the definition of severe asthma exacerbation in the tiotropium in adults with severe asthma submissions (Table 3, p6 PSD July 2015) and with the definition of clinically significant exacerbations in the omalizumab in children with severe allergic asthma submission (paragraph 6.7, PSD July 2016).
Non-severe symptomatic exacerbation	All asthma exacerbations that were classified as symptomatic but were not considered severe. This definition differed to that presented in the tiotropium in adults with severe asthma submission, which was all exacerbations that were not considered severe (Table 3, p6 PSD July 2015).

Source: Compiled from text, pp85-90; and p189 of the submission

FEV₁ = forced expiratory volume in one second; PBAC = Pharmaceutical Benefits Advisory Committee; PEF = peak expiratory flow; PSD = public summary document

- 6.15 The MCID for trough FEV₁ was 0.10 L. This has previously been accepted by the PBAC in the consideration of tiotropium in adults (paragraph 7.5, tiotropium PSD, July 2015). The PSCR refers to the aforementioned Cochrane review by Chauchan et al 2015 (p23) indicating that “given the smaller lung volumes in children, the observed 80 mL greater improvement in FEV₁ associated with LABA added to ICS in children may be of clinical importance”. However the ESC noted the authors of the review went on to say that a bronchodilator response was not unexpected, given that LABA is a bronchodilator; it was further noted that a longer period of follow-up may be required to detect an effect on exacerbations.
- 6.16 The submission stated that the MCID for FEV₁ peak (0–3h) had not been rigorously established for asthma. In the adult tiotropium submissions, the mean difference in change from baseline in trough FEV₁ and FEV₁ peak (0–3h) responses were 0.10 L and 0.12 L respectively. Therefore, the submission concluded that the previously accepted MCID of 0.10 L for trough FEV₁ corresponded to an incremental benefit of 0.12 L for FEV₁ peak (0–3h), and that this value was therefore clinically meaningful in patients with severe asthma. This might not be reasonable; the PBAC was asked to consider whether a MCID of 0.12 L for FEV₁ peak (0–3h) was considered clinically meaningful. No published data on FEV₁ peak (0–3h) was identified. The ESC considered the outcomes of most interest will be those related to changes in the

chronic aspects of severe asthma, which includes exacerbations and stability in lung function. The FEV₁ peak (0–3h) is a measure of a short-term bronchodilator effect on top of the trough measure which reflects longer-term lung function. The PBAC agreed with the ESC's view that FEV₁ peak was not an appropriate outcome measure for a condition that affects patients over the long term.

Comparative effectiveness

6.17 The results from trials 204.446 and 204.456 for change from baseline in FEV₁ peak (0–3h) and trough FEV₁ at 12 weeks follow-up and the associated meta-analyses are presented in Table 5.

Table 5: Results for change from baseline in FEV₁ peak (0–3h) response and trough FEV₁ response at 12 weeks (mITT populations)

Trial ID	Tiotropium 5 µg		Placebo		Adjusted mean difference (95% CI) ^b
	N	Adjusted mean change at follow-up (SD) ^a	N	Adjusted mean change at follow-up (SD) ^a	
FEV₁ peak (0–3h) response (L)					
205.446 (6-11 years)	128	0.39 (0.35)	130	0.25 (0.29)	0.14 (0.08, 0.20)
205.456 (12-17 years)	130	0.53 (0.51)	132	0.44 (0.52)	0.09 (-0.02, 0.20)
Meta-analysis result (I ² statistic = 0%; Chi ² for heterogeneity = 0.45 (P = 0.50))					0.13 (0.07, 0.19)
Trough FEV₁ response (L)					
205.446 (6-11 years)	128	0.22 (0.31)	130	0.14 (0.31)	0.09 (0.02, 0.15)
205.456 (12-17 years)	130	0.28 (0.55)	132	0.23 (0.55)	0.05 (-0.06, 0.17)
Meta-analysis result (I ² statistic = 0%; Chi ² for heterogeneity = 0.18 (P = 0.67))					0.08 (0.01, 0.14)

Source: Tables 2.19-2.20, pp94-95; and Figures 2.8-2.9, pp119-120 of the submission

CI = confidence interval; FEV₁ = forced expiratory volume in one second; L = litre; mITT = modified intention-to-treat; MMRM = mixed model repeated measures; P = p-value; SD = standard deviation; **Bold** = statistically significant

^a SD calculated post-hoc

^b MMRM with fixed categorical effects of treatment, country, visit, and treatment-by-visit interaction, continuous fixed covariates of baseline and baseline-by-visit interaction, and random effect of patient.

6.18 In trial 205.446 (6-11 years), tiotropium statistically significantly improved FEV₁ peak (0–3h) response compared to placebo (mean difference (MD) = 0.14 L; 95% confidence interval (CI): 0.08, 0.20) at 12 weeks. This result was also considered clinically significant by the submission as the improvement was greater than the nominated MCID (i.e. 0.12 L). In trial 205.456 (12-17 years) tiotropium did not result in a statistically significant or clinically significant improvement in FEV₁ peak (0–3h).

6.19 The results of the meta-analysis demonstrated that tiotropium resulted in a statistically significant improvement in the FEV₁ peak (0–3h) response compared with placebo (MD = 0.13 L; 95% CI: 0.07, 0.19) at 12 weeks. The submission considered this was clinically meaningful as it crossed the nominated MCID threshold of 0.12 L.

6.20 Tiotropium resulted in a statistically significant improvement in trough FEV₁ compared with placebo in trial 205-446 (6-11 years) (MD = 0.09 L; 95% CI: 0.02, 0.15). This response was not clinically significant as it was not greater than the nominated MCID (i.e. 0.10 L). Tiotropium did not result in a statistically or clinically significant improvement in trough FEV₁ in trial 205.456 (12-17 years).

- 6.21 The results of the meta-analysis showed that tiotropium resulted in a statistically significant improvement in trough FEV₁ compared with placebo (MD = 0.08 L; 95% CI: 0.01, 0.14) at 12 weeks; however this response was not considered clinically meaningful.
- 6.22 Overall, the magnitude of the benefit of tiotropium was uncertain, particularly in children aged 12 to 17 years. In this population, tiotropium compared with placebo did not result in any clinically meaningful or statistically significant improvements in FEV₁ peak (0–3h) or trough FEV₁ responses. The significant results in the meta-analysis were due to the effects measured in the 6–11 years trial.
- 6.23 Patients in the placebo arms of both trials experienced improvements from baseline in FEV₁ peak (0–3h) (i.e. ≥ 0.12 L) and in trough FEV₁ (i.e. ≥ 0.10 L) that are greater than the MCID proposed in the submission. The results could suggest that improved adherence to optimised asthma therapy in the trial setting resulted in improvements in these surrogate outcomes for all patients.
- 6.24 Table 6 presents the results of the post-hoc analyses of the number of symptomatic asthma exacerbations, severe symptomatic exacerbations and non-severe symptomatic exacerbations observed in trials 205.446 and 205.456, the estimated rate per patient year and the results of the meta-analyses.

Table 6: Rate of asthma exacerbations per patient year (mITT populations)

Trial	Tiotropium 5 µg			Placebo			Rate ratio (95% CI) ^b
	Events, n	Total exposure, days	Events/patient-year ^a	Events, n	Total exposure, days	Events/patient-year ^a	
Symptomatic exacerbations (non-severe and severe)							
205.446 (6-11 years)		11,156			11,492		
205.456 (12-17 years)		11,162			11,479		
Meta-analysis result (I ² = %; Chi ² = (P =))							
Severe symptomatic exacerbations							
205.446 (6-11 years)		11,156			11,492		
205.456 (12-17 years)		11,162			11,479		
Meta-analysis result (I ² = %; Chi ² = (P =))							
Non-severe symptomatic exacerbations							
205.446 (6-11 years)		11,156			11,492		
205.456 (12-17 years)		11,162			11,479		
Meta-analysis result (I ² = %; Chi ² = (P =))							

Source: Table 2.24, p103; Figure 2.13, p126 of the submission; and calculated during evaluation using Review Manager 5.3

CI = confidence interval; mITT = modified intention-to-treat; P = p-value; SD = standard deviation; **Bold** = statistically significant

^a Calculated post-hoc: events per patient year = total events/ (total exposure days/365.25)

^b 95% CI calculated post-hoc using Review Manager 5.2 software

^c Risk ratio reported

- 6.25 The rates of symptomatic exacerbations (non-severe and severe) per patient year were lower in the tiotropium arms compared to the placebo arms in both trials; however, the difference was only statistically significant for symptomatic

exacerbations in trial 205.446 (6-11 years) (rate ratio (RR) = [REDACTED]; 95% CI: [REDACTED]) and this was due to a reduction in non-severe symptomatic exacerbations. The ESC noted that reduction in non-severe exacerbations may be expected in a 12 week trial. 'Symptomatic exacerbations' is not the usual trial measure for a study of long term treatment for asthma. Severe exacerbations is considered to be the usual outcome measure, which is often the primary outcome measure, for asthma trials across all age groups. The clinical relevance of non-severe exacerbations as an outcome measure is unclear.

- 6.26 The rates of severe asthma exacerbations were marginally higher in the tiotropium arms compared to the placebo arms in both trials.
- 6.27 The results of the meta-analyses suggested that tiotropium resulted in a statistically significant reduction in symptomatic exacerbations (non-severe and severe) for children aged 6 to 17 years (RR = [REDACTED]; 95% CI: [REDACTED]). This was due to the reduction in non-severe symptomatic exacerbations in trial 205.446 (6-11 years) (risk ratio = [REDACTED]; 95% CI: [REDACTED]). As noted above with the FEV₁ responses, the effect identified in the meta-analysis was due to the effect in the 6-11 year trial. It is of concern that in 12-17 year olds there was a non-significant increase in the severe exacerbations (RR [REDACTED]; CI: [REDACTED]). Coupled with the uncertain clinical relevance of non-severe exacerbations and no evidence of an impact in severe exacerbations, the ESC did not consider the data presented were good indicators that tiotropium would work well for children.
- 6.28 The submission stated that neither trial was powered to detect differences in asthma exacerbations. The short 12-week duration of the trials meant that the number of all, symptomatic and severe exacerbations were low and that it was not possible to obtain statistically significant results from the data. The ESC noted the study duration of 12 weeks presented in the submission was not appropriate for long-term treatment of asthma, and the selected primary outcome measure, peak FEV₁ (0–3h), did not have evidence to support its use as a surrogate of long-term control of childhood asthma.

Comparative harms

- 6.29 A summary of the adverse events reported in trials 205.446 and 205.456 are presented below.

Table 7: Summary of adverse events from trials 205.446 and 205.456 at 12 weeks (mITT populations)

	Tiotropium	Placebo	Risk difference (95% CI)
Any adverse event, n/N (%)			
205.446 (6-11 years)	56/130 (43%)	66/134 (49%)	-0.06 (-0.18, 0.06)
205.456 (12-17 years)	43/130 (33%)	48/135 (36%)	-0.02 (-0.14, 0.09)
Meta-analysis result ($I^2 = 0\%$; $Chi^2 = 0.19$ ($P = 0.66$))			-0.04 (-0.13, 0.04)
Serious adverse event, n/N (%)			
205.446 (6-11 years)	4/130 (3%)	2/134 (2%)	0.02 (-0.02, 0.05)
205.456 (12-17 years)	2/130 (2%)	0/135	0.02 (-0.03, 0.04)
Meta-analysis result ($I^2 = 0\%$; $Chi^2 = 0.00$ ($P = 0.98$))			0.02 (-0.01, 0.04)
Leading to discontinuation, n/N (%)			
205.446 (6-11 years)	2/130 (2%)	2/134 (2%)	0.00 (-0.03, 0.03)
205.456 (12-17 years)	0/130	1/135 (1%)	-0.01 (-0.03, 0.01)
Meta-analysis result ($I^2 = 0\%$; $Chi^2 = 0.21$ ($P = 0.65$))			-0.01 (-0.03, 0.01)

Source: Tables 2.27-2.33, pp107-117; and Figures 2.16-2.20, pp133-142 of the submission

CI = confidence interval; mITT = modified intention-to-treat; P = p-value

6.30 The number of adverse events reported in the tiotropium arms of both trials were similar to the number of adverse events reported in the placebo arms. Further, the number of serious adverse events and the number of adverse events leading to discontinuation were low across both trials. None of the differences were statistically significant. This was similar to the response in the adult tiotropium submission, in which there were no differences in the proportion of patients experiencing adverse events resulting in discontinuation, severe adverse events or serious adverse events compared to usual care (paragraph 6.14, PSD July 2015).

Benefits/harms

6.31 A summary of the comparative benefits and harms for tiotropium versus placebo is presented in the table below.

Table 8: Summary of comparative benefits and harms for tiotropium and placebo

Trial	Events per patient year		Rate ratio (95% CI)	Event rate per 100 patient years		Risk difference (95% CI)
	Tiotropium	Placebo		Tiotropium	Placebo	
Benefits						
Symptomatic (severe and non-severe) exacerbations (number per patient year) ^a						
205.446 (6-11 years)	205	446	0.66 (0.51, 0.86)	2.0	3.0	-1.0 (-1.5, -0.5)
205.456 (12-17 years)	205	456	1.0 (0.81, 1.2)	3.0	3.0	0.0 (-0.2, 0.2)
Severe symptomatic exacerbations (number per patient year) ^a						
205.446 (6-11 years)	205	446	0.9 (0.67, 1.2)	0.9	0.9	0.0 (-0.1, 0.1)
205.456 (12-17 years)	205	456	1.0 (0.81, 1.2)	1.0	1.0	0.0 (-0.1, 0.1)
FEV₁ peak (0–3h) response (L) at 12 weeks						
	Tiotropium		Placebo		Adjusted mean difference (95% CI) ^c	
	N	Adjusted mean change (SD) ^b	N	Adjusted mean change (SD) ^b		
205.446 (6-11 years)	128	0.39 (0.35)	130	0.25 (0.29)	0.14 (0.08, 0.20)	
205.456 (12-17 years)	130	0.53 (0.51)	132	0.44 (0.52)	0.09 (-0.02, 0.20)	
Trough FEV₁ response (L) at 12 weeks						
	Tiotropium		Placebo		Adjusted mean difference (95% CI) ^c	
	N	Adjusted mean change (SD) ^b	N	Adjusted mean change (SD) ^b		
205.446 (6-11 years)	128	0.22 (0.31)	130	0.14 (0.31)	0.09 (0.02, 0.15)	
205.456 (12-17 years)	130	0.28 (0.55)	132	0.23 (0.55)	0.05 (-0.06, 0.17)	
Harms						
	Tiotropium	Placebo	Relative risk (95% CI)	Event rate per 100 patients per 12 weeks		Risk difference (95% CI)
				Tiotropium	Placebo	
Nasopharyngitis events per 12 weeks						
205.446 (6-11 years)	6/130	11/134	0.56 (0.21, 1.48)	4.6	8.2	-0.04 (-0.01, 0.02)
205.456 (12-17 years)	5/130	4/135	1.30 (0.36, 4.73)	3.8	3.0	0.01 (-0.04, 0.05)
Respiratory tract infection events per 12 weeks						
205.446 (6-11 years)	3/130	5/134	0.62 (0.15, 2.54)	2.3	3.7	-0.01 (-0.06, 0.03)
205.456 (12-17 years)	1/130	2/135	0.52 (0.05, 5.66)	0.8	1.5	-0.01 (-0.03, 0.02)

Source: Tables 2.19-2.20, pp94-95; Figures 2.8-2.9, pp119-120; Table 2.24, p103; and Tables 2.32-2.33, pp116-117 of the submission
 CI = confidence interval; FEV₁ = forced expiratory volume in one second; L = litre; MMRM = mixed model repeated measures;
 SD = standard deviations; **Bold** = statistically significant

^a Calculated post-hoc: events per patient year = total events/(total exposure days/365.25)

^b SD calculated post-hoc

^c MMRM with fixed categorical effects of treatment, country, visit, and treatment-by-visit interaction, continuous fixed covariates of baseline and baseline-by-visit interaction, and random effect of patient.

6.32 On the basis of the direct comparison evidence presented by the submission, for every 100 patients treated with tiotropium in comparison to placebo and over a duration of exposure of one year:

- Approximately 64 fewer symptomatic exacerbations (due only to a reduction in non-severe exacerbations) would be experienced in patients aged 6 to 11 years.
- There would be no difference in the rate of severe exacerbations.
- There would be no difference in either symptomatic (which includes both non-severe and severe), or severe exacerbations for patients aged 12 to 17 years.

- 6.33 On the basis of the direct comparison evidence presented by the submission, the comparison of tiotropium and placebo, over a duration of follow-up of 12 weeks, resulted in:
- Approximately 0.14 L improvement in lung function, as measured by the forced expiratory volume in one second (FEV₁) peak response (which is measured 0 to 3 hours after dosing by spirometry), in patients aged 6 to 11 years. The submission considered that an improvement of 0.12 L was clinically meaningful.
 - Approximately 0.09 L improvement in lung function, as measured by the trough FEV₁ response (which is measured 24 hours after dosing by spirometry), in patients aged 6 to 11 years. It was considered that an improvement of 0.10 L was clinically meaningful.
 - No clinically meaningful difference lung function, as measured by FEV₁ peak (0–3h) and trough FEV₁ responses, in patients aged 12 to 17 years.
- 6.34 On the basis of the direct comparison evidence presented by the submission, for every 100 patients treated with tiotropium in comparison to placebo and over a duration of follow-up of 12 weeks:
- There would be no difference in the proportion of patients who developed nasopharyngitis.
 - There would be no difference in the proportion of patients who developed a respiratory tract infection.

Clinical claim

- 6.35 The submission described tiotropium plus optimised asthma therapy as superior in terms of effectiveness and non-inferior in terms of safety compared to placebo plus optimised asthma therapy.
- 6.36 The submission's claim that tiotropium was superior in terms of effectiveness compared to placebo was not supported as:
- no primary or secondary outcomes from trial 205.456 (12-17 years) were considered to be clinically meaningful or statistically different, suggesting tiotropium had limited clinical benefit as an add-on to optimised asthma therapy in children aged 12 to 17 years;
 - the incremental benefit for trough FEV₁ was below the nominated MCID of 0.10 L in both trials and in the meta-analysis;
 - the selected primary outcome measure, peak FEV₁ (0–3h), did not have evidence to support its use as a surrogate of long-term control of childhood asthma. The nominated MCID of 0.12 L for FEV₁ peak (0–3h) has not previously been accepted by the PBAC and is not sourced from published literature. Therefore, the improvements observed in trial 205.446 (6-11 years) and in the meta-analysis

might not have been clinically meaningful;

- tiotropium resulted in a statistically significant reduction in the rate of symptomatic exacerbations (non-severe and severe) in trial 205.446 (6-11 years) only, which was due only to the reduction in non-severe symptomatic exacerbations; all other analyses were not statistically different;
- the majority of trial patients were receiving triple therapy, consisting of a high dose ICS, a LABA and a LTRA, whereas the proposed PBS restriction required patients to have uncontrolled severe asthma despite optimal treatment with an ICS and a LABA; and
- the rate of severe exacerbations was marginally higher in the tiotropium arms compared to the placebo arms in both trials. It should be noted that the definition for severe exacerbations aligned with the definition of clinically significant exacerbations in the omalizumab in children with severe allergic asthma submission, which was considered by the PBAC in July 2016.

6.37 Compared to optimised asthma therapy, treatment with tiotropium for 12 weeks did not improve FEV₁ measurements to a clinically important degree and did not reduce clinically important exacerbations. The ESC advised that three aspects of the trials may have caused the uncertainty in the results:

- questions surrounding adherence to maximal optimal asthma therapy, especially in the 12-17 years group. This was apparent by the high placebo responses for trough, peak and bronchodilator response compared to the MCIDs of 0.10 L to 0.12 L.
- the study duration of 12 weeks was not long enough to develop a benefit in lung function or exacerbations.
- the large discrepancies between the two age-based groups; for instance the overall rate of exacerbations in the 6-11 years group was [REDACTED]/patient year, compared to [REDACTED]/patient year in the 12-17 years group. As noted above, this may have been adherence related.

6.38 The ESC considered the submission's claim of non-inferior safety compared to placebo was adequately supported at 12 weeks.

6.39 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data.

6.40 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.41 The submission presented a trial-based cost-effectiveness analysis, based on the direct randomised trials, 205.446 (6-11 years) and 205.456 (12-17 years). The

economic evaluation was in the form of a cost per symptomatic exacerbation avoided, as the submission considered that there was insufficient data to develop a full cost utility model. The primary outcome of FEV₁ peak (0–3h) was not used in the model.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	12 weeks in the model base case versus 12 weeks in the key trials (205.446 and 205.456)
Health outcomes	Symptomatic (non-severe plus severe) asthma exacerbations avoided
Methods used to generate results	Decision tree analysis estimating the cost of treatment and cost of asthma exacerbations for: 1) Tiotropium plus optimised asthma therapy; and 2) Optimised asthma therapy alone.
Transition probabilities	Trial based - rate of symptomatic asthma exacerbations (non-severe and severe) in the tiotropium and placebo arms.

Source: Table 3.1, p163 of the submission

6.42 In the consideration of omalizumab, July 2016, the PBAC accepted a cost per clinically significant exacerbation avoided. The definition for clinically significant exacerbation was ‘a worsening of asthma symptoms requiring doubling of the baseline ICS dose and/or treatment with rescue systemic corticosteroids for at least three days’ (paragraph 6.7, omalizumab PSD, July 2016 PBAC Meeting). This definition aligned with the definition of severe symptomatic exacerbation in trials 205.446 and 205.456.

6.43 The ESC did not consider the outcome used in the economic evaluation for this tiotropium submission was clinically meaningful given the outcomes for symptomatic exacerbations were due only to the effect on non-severe exacerbations and only for the results in trial 205.446 (6-11 years).

6.44 The results of the economic evaluation are presented in the table below.

Table 10: Results of the economic evaluation

	Costs			Exacerbation rate			Result
	Tiotropium	Placebo	Increment	Tiotropium	Placebo	Increment	
Cost per extra symptomatic exacerbation (non-severe and severe) avoided							
Children 6-17 years	\$█	\$█	\$█	█	█	█	\$█ per symptomatic exacerbation avoided
	To provide an ICER of \$█, the QALY loss per symptomatic exacerbation = \$█/\$█ = █						
Cost per extra severe symptomatic exacerbation avoided							
Children 6-17 years	\$█	\$█	\$█	█	█	█	█
Cost per extra non-severe symptomatic exacerbation avoided							
Children 6-17 years	\$█	\$█	\$█	█	█	█	\$█ per non-severe exacerbation avoided

Source: Table 3.22, p203 of the submission; and calculated during evaluation from Att_10_Section 3 Workbook.xls

ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life years

6.45 The submission estimated a cost per symptomatic exacerbation (non-severe and severe) avoided of \$█.

- 6.46 To provide a frame of reference for interpreting the cost per exacerbation avoided, the submission calculated that to achieve an incremental cost-effectiveness ratio (ICER) of \$45,000 - \$75,000 per quality-adjusted life year (QALY), a symptomatic exacerbation (non-severe and severe) must be associated with a loss of [REDACTED] QALYs. The American College of Allergy, Asthma and Immunology suggests that a severe asthma attack can last from hours to days. ESC noted the submission’s proposed QALYs were large considering exacerbations usually only last a few days, and suggested that a [REDACTED] QALY loss for a non-severe exacerbation was implausible.
- 6.47 The submission considered this QALY value demonstrated tiotropium’s cost-effectiveness as similar calculations considered by the PBAC relating to omalizumab, resulted in a 0.28 QALY loss per clinically significant exacerbation (paragraph 6.33, omalizumab PSD, July 2016 PBAC Meeting). The comparison was not appropriate as the outcomes were not equivalent. A comparative QALY value could not be calculated for tiotropium as tiotropium was dominated by placebo in terms of severe exacerbations in both trials.
- 6.48 The results of the sensitivity analyses presented by the submission and conducted during the evaluation are presented in the table below.

Table 11: Results of sensitivity analyses

	Δ cost	Δ exacerbation rate	Cost per exacerbation avoided
Base case	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
COST PER EXTRA SYMPTOMATIC EXACERBATION (non-severe and severe) AVOIDED			
Children aged 6-11 years (trial 205.446)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Children aged 12-17 years (trial 205.456)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Severe exacerbation rate (base case: tiotropium = [REDACTED]; placebo = [REDACTED])			
Rate from 205.446 (tiotropium = [REDACTED]; placebo = [REDACTED])	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Rate from 205.456 (tiotropium = [REDACTED]; placebo = [REDACTED])	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Non-severe exacerbation rate (base case: tiotropium = [REDACTED]; placebo = [REDACTED])			
Rate from 205.446 (tiotropium = [REDACTED]; placebo = [REDACTED])	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Rate from 205.456 (tiotropium = [REDACTED]; placebo = [REDACTED])	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
COST PER EXTRA SEVERE SYMPTOMATIC EXACERBATION AVOIDED			
Base-case: children aged 6-17 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Children aged 6-11 years (trial 205.446)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Children aged 12-17 years (trial 205.456)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
COST PER EXTRA NON-SEVERE SYMPTOMATIC EXACERBATION AVOIDED			
Base-case: children aged 6-17 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Children aged 6-11 years (trial 205.446)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Children aged 12-17 years (trial 205.456)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Table 3.25, p203 of the submission; and compiled during evaluation using Att_10_Section 3 workbook.xlsl

- 6.49 The cost per exacerbation avoided was most sensitive to changes in the rates of symptomatic exacerbations used.
- 6.50 The submission assumed all severe exacerbations would require hospitalisations, and the majority of non-severe exacerbations assumed general practitioner (GP) visits and purchases of medicines. ESC noted this may not be the case, for example

parents usually stockpile asthma medications and may not take their children to the GP each time they had a non-severe exacerbation as defined in the trials. Cost offsets were likely to have been overestimated in the model. The PBAC agreed with the ESC’s view that this cost has been overestimated, as patients would have an asthma action plan in place and parents would know what to do in the case of a non-severe exacerbation and would not need to visit the GP for every event.

Drug cost/patient/year: \$638.21

The annual cost of tiotropium per patient per year was estimated to be \$638.21, based on the proposed DPMQ of \$52.42 (which included the 14.5% price reduction to be applied on 1 June 2018) and assuming 100% compliance (12.18 prescriptions per year).

6.51 If a compliance rate of 80.9% was used, which was the weighted trial-based compliance rate, the annual cost of tiotropium per patient per year was estimated to be \$516.53 (9.85 prescriptions per year).

Estimated PBS usage & financial implications

6.52 This submission was not considered by DUSC.

6.53 The submission presented an epidemiological approach to estimate the financial impact of listing tiotropium on the PBS/RPBS.

Table 12: Estimated use and financial implications

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Estimated extent of use						
Number of patients treated						
Number of scripts dispensed ^a						
Estimated financial implications of tiotropium						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Co-payments	\$	\$	\$	\$	\$	\$
Total cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Estimated financial implications for other PBS medicines						
Cost offset to PBS/RPBS	-\$	-\$	-\$	-\$	-\$	-\$
Co-payments	\$	\$	\$	\$	\$	\$
Total cost offset to PBS/RPBS	-\$	-\$	-\$	-\$	-\$	-\$
Net financial implications						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$

Source: Tables 4.15-4.33, pp217-232; and Att_12_Section 4 Workbook.xlsx

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Assuming 9.85 number of scripts per year as estimated by the submission.

The redacted table shows that at Year 6, the estimated number of patients was 10,000 – 50,000 per year, and the net cost to the PBS would be less than \$10 million per year.

6.54 The estimated financial implications for the PBS/RPBS of listing tiotropium were uncertain as:

- there was uncertainty surrounding the size of the eligible population and the assumed uptake rates (over or underestimate);

- the rate of compliance observed in clinical practice might be lower than that observed in the clinical trials (overestimate);
- the true impact on other service use is highly uncertain; and
- there was potential for use of tiotropium beyond the requested restriction (underestimate).

Quality Use of Medicines

6.55 The submission included proposals for Quality of Use of Medicine information, such as an updated product information document and additional educational resources that would ensure tiotropium would be prescribed as indicated by the TGA. The proposals provided were appropriate, given that a large proportion of asthma patients might not be compliant with their chronic asthma medications and the potential for tiotropium use outside of the PBS restriction.

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

7 PBAC Outcome

- 7.1 The PBAC decided not to recommend the Authority Required (STREAMLINED) listing for tiotropium solution for inhalation in patients aged 6 to 17 years old with severe asthma. The PBAC considered the clinical claim of superior effectiveness in comparison to placebo plus optimised asthma therapy to be questionable as there were several issues with the methodology and conclusions based on the clinical trials presented in the submission. The PBAC also considered the economic model based on a cost per symptomatic exacerbation avoided was problematic.
- 7.2 The PBAC noted the majority of trial patients were receiving triple therapy, consisting of a high dose ICS, a LABA and a LTRA, which was not consistent with the proposed PBS restriction that required patients to have uncontrolled severe asthma despite optimal treatment with an ICS and a LABA.
- 7.3 The PBAC noted both pivotal trials were conducted over short 12 week durations, which was not optimal for a typically long term disease such as severe asthma. As expected from trials of a short duration, low numbers of symptomatic and severe exacerbations were recorded in both the tiotropium and placebo arms, thus it was not possible to obtain reliable estimates for these events from the trials and the differences observed were not statistically significant. Despite this, the submission used these outcomes in the economic analysis.
- 7.4 The PBAC considered FEV₁ peak to be a measure of short term effect, and agreed with the ESC's view that a bronchodilator response was not unexpected given that trial patients had been taking concomitant LABA which is also a bronchodilator, and that a longer period of follow-up may be required to detect an effect on exacerbations. Noting the submission stated that no longer term trials in this

population are expected, the PBAC considered the extrapolation of adult outcomes to the adolescent population may be reasonable. However, PBAC also noted the longer term, 48-week, trials in patients with more moderate disease, may have provided some further support to these claims.

- 7.5 The PBAC noted that the secondary outcome of trough FEV₁ with MCID of 0.10 L had previously been accepted in the consideration of tiotropium in adults as a clinically meaningful outcome. Results of the trough FEV₁ outcome did not show any clinically significant difference in either of the 6-11 or 12-17 year age group trials. The PBAC noted the ESC's view that the strong placebo responses suggested that adherence to maximal optimal asthma therapy was poor prior to the trials, especially in the 12-17 year group, and thus the addition of tiotropium to the dosing regimen was not the most clinically appropriate approach. The PBAC noted the consumer response from Asthma Australia emphasised the importance of patients undergoing systematic evaluation and following the stepped approach to treatment of children and adolescents, particularly in regards to the prescribing of ICS/LABA preventer medications.
- 7.6 The PBAC noted that a statistically significant reduction in the rate of symptomatic exacerbations (non-severe and severe) was only found in trial 205.446 (6-11 years), which was due only to the reduction in non-severe symptomatic exacerbations. The PBAC noted that symptomatic exacerbations was not the usual trial measure for a study of long term treatment for asthma, and that severe exacerbations was used in the consideration of tiotropium in the adult population. The PBAC noted that the rate of severe exacerbations was marginally higher, but not statistically significant, in the tiotropium arms compared to the placebo arms in both trials.
- 7.7 The PBAC noted that the economic evaluation was in the form of a cost per symptomatic exacerbation avoided (non-severe and severe), which was not clinically meaningful given the outcomes for symptomatic exacerbations were due only to the effect on non-severe exacerbations and only for the results in trial 205.446 (6-11 years). As noted above, due to the short trial durations it was not possible to obtain reliable estimates for these events from the trials and the differences observed were not statistically significant, and thus this outcome was an inappropriate basis for an economic analysis.
- 7.8 The PBAC agreed with the ESC's view that the proposed [REDACTED] QALY loss per symptomatic exacerbation (non-severe and severe) was large considering exacerbations only last for a few days, and thought this to be implausible for a non-severe exacerbation. The PBAC noted the submission's claim that patients would visit a GP and purchase medicines for all non-severe exacerbation, however considered that patients are likely to have an asthma action plan in place for these situations and parents would know the protocol to follow when treating their child for a non-severe exacerbation, hence that this cost has been overestimated.

- 7.9 The PBAC noted that the predicted uptake rates were uncertain due to differences in the rate of compliance observed in clinical practice and that observed in the clinical trials, the true impact on other service use for each exacerbation, and the potential for use beyond the requested restriction earlier in the proposed treatment algorithm.
- 7.10 The PBAC noted that currently Australian guidelines for asthma do not include tiotropium in the treatment algorithm, however it is approved for use in the USA and by the EMA, and it has received TGA registration in the paediatric population; thus it may have a place in the treatment of asthma in children. The PBAC advised that the data presented in support of its listing could potentially place it at the end of the therapeutic ladder, or alternatively, based on the 48-week trials (excluded from this submission, as noted in paragraph 6.5) in a more moderate population, with a corresponding applicable price and restriction.
- 7.11 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.