

## 7.05 TIOTROPIUM, Solution for oral inhalation 2.5 micrograms (as bromide monohydrate) per actuation (60 actuations), Spiriva® Respimat®, Boehringer Ingelheim

### 1 Purpose of Application

- 1.1 The resubmission requested an Authority Required (STREAMLINED) listing for tiotropium solution for inhalation (hereafter referred to as tiotropium) for the treatment of severe asthma in children and adolescents aged 6-17 years who have not achieved adequate asthma control. The original submission was considered by the PBAC at its March 2018 meeting.
- 1.2 The key components presented in the resubmission remained unchanged from the March 2018 submission, except that the resubmission presented a modified restriction and added additional clinical trials from different population groups to the clinical evidence and the meta-analyses. The resubmission claimed that tiotropium plus optimised asthma therapy (i.e. inhaled corticosteroid (ICS) plus long acting beta<sub>2</sub> agonist (LABA)) has superior efficacy and non-inferior safety compared to optimised asthma therapy alone in children and adolescents aged 6-17 years with severe asthma.

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

Component	Description
Population	Children aged 6 to 17 years with severe asthma <sup>a</sup>
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 an ICS and a LABA) <sup>b</sup> , plus placebo (two puffs) daily If a LABA is contraindicated, not tolerated or not effective, montelukast, cromoglycate or nedocromil may be used as an alternative.
Outcomes	Lung function (FEV <sub>1</sub> ), asthma exacerbations, asthma control, adverse events
Clinical claim	Tiotropium, as add-on to optimised asthma therapy, is superior in terms of efficacy and non-inferior in terms of safety compared to optimised asthma therapy alone.

Source: Table 1.2, p15 of the submission and compiled during the evaluation

FEV<sub>1</sub> = Forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long acting beta<sub>2</sub> agonist

<sup>a</sup> Patients with severe asthma were defined as those who remained uncontrolled despite optimised treatment.

<sup>b</sup> Optimised asthma therapy in children with severe asthma was defined in the trial as a high dose ICS plus ≥ 1 other controllers; or a medium dose ICS plus ≥ 2 other controllers.

### 2 Requested listing

- 2.1 The proposed PBS listing was updated from that presented in the March 2018 submission.
- 2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

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Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TIOTROPIUM Solution for oral inhalation, 2.5 µg, 60 actuations	1	5	\$52.41	Spiriva® Respimat®; Boehringer Ingelheim
<b>Category / Program</b>	GENERAL – General Schedule (Code GE)			
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
<b>Condition:</b>	Severe asthma			
<b>PBS Indication:</b>	<i>Severe asthma</i>			
<b>Treatment phase:</b>	-			
<b>Restriction Level / Method:</b>	<input 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 checked="" type="checkbox"/> Streamlined			
<b>Treatment criteria:</b>	Must be treated <del>in consultation with</del> by a respiratory physician, paediatric respiratory physician, clinical immunologist, allergist, <del>or</del> , paediatrician or general physician experienced in the management of patients with severe asthma; <i>or in consultation with one of these specialists</i>			
<b>Clinical criteria:</b>	Patient must have failed to achieve adequate control with optimised asthma therapy, despite formal assessment of <i>and</i> adherence to correct inhaler technique, which has been documented, AND Patient must have <del>While receiving optimised asthma therapy in the previous 12 months,</del> experienced at least <del>one</del> ONE severe asthma exacerbation, <i>which has required requiring</i> documented use of systemic corticosteroids, <del>(oral corticosteroids initiated or increased for at least 3 days, or parenteral corticosteroids)</del> in the previous 12 months while receiving optimised asthma therapy, OR Patient must have <del>e</del> Experienced frequent episodes of moderate asthma exacerbations 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 a LABA is contraindicated.			
<b>Population criteria:</b>	Patient must be aged 6 to <del>less than 18</del> 17 years inclusive.			
<b>Prescriber Instructions</b>	Optimised <del>d</del> asthma therapy includes adherence to the maintenance combination of a medium to high dose ICS and a LABA. If LABA therapy is contraindicated, not tolerated or not effective, montelukast, cromoglycate or nedocromil may be used as an alternative.			
<b>Administrative Advice</b>	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 <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a> or <a href="http://ww.nationalasthma.org.au">ww.nationalasthma.org.au</a> ); 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).  Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before "stepping up" a patient's medication regimen.			

Source: Table ES.2, pii; Table1.13, p54 of the submission

2.3 The PBS restriction was revised to be in line with (but not identical to) the restriction in adults. The Pre-Sub-Committee Response (PSCR) stated that the proposed restriction was revised based on the advice of the ESC during the March 2018 consideration to help ensure that tiotropium is only used in patients adherent to

therapy. The resubmission included clinical criteria that required the patient to be on optimised therapy for 12 months and to have had either a severe asthma exacerbation or to have experienced frequent episodes of moderate asthma exacerbations. The ESC considered that this may not be appropriate for children as they may have severe asthma without having a long history of asthma, and this requirement differed from the clinical trials. The pre-PBAC response argued that the proposed restriction is aligned with that of the adult population and relevant guidelines. The PBAC considered it appropriate that the rationale for the proposed restriction was consistent with the current PBS listing of tiotropium for severe asthma. The PBAC agreed with the changes to the restriction wording that were suggested by the Secretariat.

- 2.4 During the March 2018 consideration of tiotropium the ESC agreed that the children's restriction should be separate from the adult restriction to highlight that it was poor medical practice to add another agent to children not adequately adhering to optimised asthma therapy. The ESC 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 (Paragraph 2.4 Tiotropium Public Summary Document (PSD), March 2018 PBAC meeting). In line with ESC's recommended changes to the restriction, the resubmission included treatment criteria that patients must be treated in consultation with a respiratory physician, paediatric respiratory physician, clinical immunologist, allergist; or paediatrician or general physician experienced in the management of patients with severe asthma. The PBAC noted that tiotropium is currently PBS listed as a restricted benefit and considered that a separate Authority Required (STREAMLINED) listing specifying treatment by or in consultation with a specialist was required for children and adolescents aged 6-17 years to optimise the quality use of tiotropium in this population.
- 2.5 The proposed PBS restriction was largely consistent with the Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention (2018), which recommends a moderate to high dose ICS in combination with a LABA for severe uncontrolled asthma.
- 2.6 The proposed restriction defined optimal asthma therapy as adherence to the maintenance combination of a medium to high dose ICS and a LABA. This is inconsistent with the trial evidence for patients 6-17 years with severe asthma, where optimised asthma therapy was defined as a high dose ICS plus  $\geq 1$  other controllers; or a medium dose ICS plus  $\geq 2$  other controllers. The PSCR stated that the definition of optimised asthma therapy is consistent with the adult restriction, is comparable to the omalizumab restriction in children and aligns with Australian prescribing practice (e.g. leukotriene receptor antagonists (LTRAs) are not PBS listed for use as add-on therapy). The PBAC noted that the proportion of trial patients receiving concomitant LTRA therapy in children/adolescents with severe asthma was high (86% in trial 205.446 and 80% in trial 205.456).

- 2.7 The proposed PBS restriction was more restrictive than the approved TGA indication as it:
- restricts use to patients with severe asthma, whilst the TGA indication includes patients with moderate to severe asthma;
  - requires tiotropium to be co-administered with both an ICS and LABA (unless contraindicated); and
  - requires patients to have failed to achieve adequate control, whilst receiving optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented.

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

### **3 Background**

#### ***Registration status***

- 3.1 Tiotropium was TGA registered in May 2018 for the following indication: 'add-on maintenance bronchodilator treatment in patients aged 6 years and older with moderate to severe asthma'.

#### ***Previous PBAC consideration***

- 3.2 This was the second submission for tiotropium for the treatment of severe asthma in children and adolescents aged 6-17 years. The first major submission was considered by the PBAC in March 2018.
- 3.3 A summary of the outstanding matters of concern to the PBAC following the March 2018 meeting are presented below.
- Based on the randomised trials in children and adolescents (previously seen by PBAC in March 2018), the claim that tiotropium was superior in terms of effectiveness compared to placebo remained uncertain especially in patients aged 11-17 years with severe asthma.
  - The clinical importance of FEV<sub>1</sub> peak as a clinically meaningful outcome measure in patients with severe asthma remained uncertain.
  - The economic model remained unchanged in the resubmission. The resubmission has not addressed the issues previously raised by the PBAC at its March 2018 meeting regarding the economic model.
  - The resubmission has not addressed any of the financial uncertainties raised by the PBAC in March 2018.
- 3.4 The key differences between the current resubmission and the previous March 2018 submission were:
- Tiotropium was approved by the TGA in May 2018 for patients aged 6 years and older with moderate to severe asthma.

- The proposed PBS restriction was revised.
- The clinical evaluation and meta-analyses included trials in adults.
- Trials in patients 6-17 years with more moderate asthma treated for 48 weeks were presented as a supplementary analysis.
- A newly nominated minimal clinically important difference (MCID) of 0.07 L for trough FEV1 in children was presented.
- The resubmission included the outcome of % predicted normal trough FEV1.

*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, which is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning.
- 4.2 Tiotropium is proposed for listing on the PBS as an add-on maintenance bronchodilator treatment for patients aged 6-17 years with severe asthma, who have failed to achieve adequate asthma control despite adherence to a maintenance treatment combination of ICS and a LABA. The proposed population was unchanged from the March 2018 submission.

## **5 Comparator**

- 5.1 As in the March 2018 submission, the nominated comparator was placebo. The PBAC had previously accepted placebo as the appropriate comparator (Paragraph 5.1 Tiotropium PSD, March 2018 PBAC).

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinicians presented information on the Paediatric Investigational Plan for tiotropium, the rationale and development of the newly nominated MCID and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative as it provided a clinical perspective on the Paediatric Investigational Plan for tiotropium.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from health care professionals (2) via the Consumer Comments facility on the PBS website. The comments highlighted the limited number of treatment options for children with severe asthma and the side effect profile of those currently available. The comments described a range of benefits of treatment with tiotropium including improved asthma control and in some cases the weaning of oral steroids. The comments indicated that there was a need for new

treatment options which can be prescribed under specialist advice.

### ***Clinical trials***

- 6.3 The resubmission was based on a meta-analysis of head-to-head randomised trials comparing tiotropium plus optimised asthma therapy (i.e. ICS plus LABA) to optimised asthma therapy alone in children/adolescents aged 6-17 years and adults  $\geq$  18 years with severe asthma:
- Trial 205.446 recruited patients aged 6 to 11 years (N = 264);
  - Trial 205.456 recruited patients aged 12 to 17 years (N = 265); and
  - Trial 205.416 and trial 205.417 recruited adults (N = 912).
- 6.4 Trial 205.446 and trial 205.456 were presented to the March 2018 PBAC meeting as part of the tiotropium submission for use in children/adolescents with severe asthma. Trial 205.416 and trial 205.417 were presented to the July 2015 and March 2016 PBAC meetings as part of the tiotropium submission for use in adults with severe asthma.
- 6.5 The resubmission added the trials in adult patients with severe asthma (205.416/205.417) to the meta-analyses. In addition, trial 205.445 and 205.444 in patients aged 6-17 years (N= 540) (not previously seen by PBAC) with moderate asthma were presented as a supplementary analysis and in a sensitivity meta-analysis.
- 6.6 Details of the trials presented in the resubmission are provided in Table 2.
- 6.7 Paediatric trials included an arm that received a 2.5  $\mu$ g daily dose of tiotropium. These were excluded from the analyses as the TGA indication and the requested PBS listing was for a 5  $\mu$ g daily dose.
- 6.8 Baseline characteristics suggested that randomisation was successful within trials; however, there were differences across trials. There were differences between the trial populations in regard to inclusion criteria, clinical characteristics, disease severity, treatment period, and concomitant treatment at baseline and during treatment. Given the clinical and methodological heterogeneity in the trials it was inappropriate to conduct meta-analyses.
- 6.9 The PBAC previously noted that both pivotal trials (205.446 and 205.456) in children and adolescents with severe asthma were conducted over short 12 week durations, which was not optimal for a typically long term disease such as severe asthma (Paragraph 7.3 Tiotropium PSD, March 2018 PBAC). The ESC considered that the concerns raised by the PBAC in March 2018 regarding the short duration of trials 205.446 and 205.456 remained relevant to the resubmission.

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**Table 2: Trials and associated reports presented in the resubmission of the key trials**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Trials in children (6-17 years) with severe asthma – previously presented at the March 2018 PBAC meeting</b>		
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.	April 2014
	Hamelmann E, Bernstein JA, et al. A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma.	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.	September 2015
	Szeffler SJ, Murphy K, et al. A phase III randomized controlled trial of tiotropium add-on therapy in children with severe symptomatic asthma.	J Allergy Clin Immunol 2017; 140 (5): 1277-1287
<b>Trials in adults (≥ 18 years) with severe asthma – previously presented at the July 2015 PBAC meeting</b>		
205.416 (NCT00772538)	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.	25 April 2013 (revision)
205.417 (NCT00776984)	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.	25 April 2013 (revision)
Combined 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 µg/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma.	31 <sup>st</sup> August 2012
	Kerstjens, H, et al. Tiotropium in asthma poorly controlled with standard combination therapy.	J Allergy Clin Immunol 2011; 128 (2): 308-314
<b>Trials in children (6-17) with moderate asthma – not previously presented to the PBAC</b>		
Trial 205.444 (NCT01257230)	A Phase III, Randomised, Double Blind, Placebo-controlled, Parallel Group Study to Assess the Efficacy and Safety Over 48 Weeks of Orally Inhaled Tiotropium Bromide (2.5 and 5 µg Once Daily ) Delivered by the Respimat® Inhaler in Adolescents (12 to 17 Years Old) With Moderate Persistent Asthma	18 June 2014
	Hamelmann E, et al. Tiotropium add-on therapy in adolescents with moderate asthma: A 1-year randomized controlled trial.	J Allergy Clin Immunol 2016; 138 (2): 441-450
Trial 205.445 (NCT01634139)	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 48 weeks in children (6 to 11 years old) with moderate persistent asthma	11 March 2016

Source: Table 2.2, pp67-68; Table 2.5, pp74-75 of the resubmission and compiled during the evaluation from clinical studies reports: 205.446, 205.456, 205.416, 205.417, 205.445 and 205.444

6.10 The key features of the direct randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

Study ID	N	Study design and follow-up	Risk of bias	Treatment	Outcomes	Use in the modelled-evaluation
<b>Children (6-17 years) with severe asthma considered by the PBAC at the March 2018 meeting)</b>						
205.446 (6-11 years)	264	R, MC, DB, PC 12 weeks	Low	Tio 5 µg + OAT <sup>a</sup> vs. PBO + OAT <sup>a</sup>	FEV <sub>1</sub> peak (0–3h); Trough FEV <sub>1</sub> ; Time to first asthma exacerbation; Rate of symptomatic exacerbations (NS and S) calculated post-hoc	Not used
205.456 (12-17 years)	265	R, MC, DB, PC 12 weeks	Low	Tio 5 µg + OAT <sup>a</sup> vs. PBO + OAT <sup>a</sup>	FEV <sub>1</sub> peak (0–3h); Trough FEV <sub>1</sub> ; Time to first asthma exacerbation; Rate of symptomatic exacerbations (NS and S) calculated post-hoc	Not used
<b>Adults (≥ 18 years) with severe asthma (considered by the PBAC at the July 2015 meeting)</b>						
205.416/205.417	912	R, MC, DB, PC 48 weeks	Low	Tio 5 µg + UC <sup>b</sup> vs. PBO + UC <sup>b</sup>	FEV <sub>1</sub> peak (0–3h); Trough FEV <sub>1</sub> ; Time to first asthma exacerbation; Rate of symptomatic exacerbations (NS and S) calculated post-hoc	Not used
<b>Children (6-17 years) with moderate asthma (not previously considered by the PBAC)</b>						
205.445 (6-11 years)	267	R, MC, DB, PC 48 weeks	Low	Tio 5 µg + UC <sup>c</sup> vs. PBO + UC <sup>c</sup>	FEV <sub>1</sub> peak (0–3h); Trough FEV <sub>1</sub> ; Rate of symptomatic exacerbations (NS and S) calculated post-hoc	Not used
205.444 (12-17 years)	273	R, MC, DB, PC 48 weeks	Low	Tio 5 µg + UC <sup>c</sup> vs. PBO + UC <sup>c</sup>	FEV <sub>1</sub> peak (0–3h); Trough FEV <sub>1</sub> ; Rate of symptomatic exacerbations (NS and S) calculated post-hoc	Not used
<b>Meta-analysis</b>						
Base case (severe asthma trials in adult and children/adolescents)	1441	Included adult and paediatric severe asthma trials. Assessed FEV <sub>1</sub> peak (0–3h); trough FEV <sub>1</sub> ; rate of symptomatic exacerbations (NS and S)				Rate of symptomatic exacerbations (NS and S)
Sensitivity analysis (severe and moderate asthma trials)	1981	Included both severe (children and adults) and moderate (children) asthma trials. Assessed FEV <sub>1</sub> peak (0–3h); trough FEV <sub>1</sub> ; rate of symptomatic exacerbations (NS and S)				Not used

Source: Compiled during the evaluation from text, pp55-208 of the resubmission

CSR = clinical study report; DB = double blind; FEV<sub>1</sub> = forced expiratory volume in one second; ICS = inhaled corticosteroids; LABA = long-acting beta2 agonist; LTRA = leukotriene receptor antagonist; MC = multi-centre; PC = placebo controlled; NS = non-severe; OAT = optimised asthma therapy; PBAC = Pharmaceutical Benefits Advisory Committee; PBO = placebo; R = randomised; S = severe; Tio = tiotropium; UC = usual care

<sup>a</sup> Optimised asthma therapy in children with severe asthma was defined as a high dose ICS plus ≥ 1 other controllers; or a medium dose ICS plus ≥ 2 other controllers.

<sup>b</sup> Optimised asthma therapy in adults with severe asthma was defined as a high dose ICS plus LABA.

<sup>c</sup> Usual care in children with moderate asthma was defined as a medium dose of ICS ± LTRA (LABA were not permitted during the trial).

6.11 The primary outcome for the trials undertaken in children and adolescents (moderate and severe asthma trials) was change in the highest forced expiratory volume in one second, observed within three hours after administration (FEV<sub>1</sub> 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). In the adult trials trough FEV1 and time to severe asthma exacerbations were the primary outcomes. The PBAC has previously accepted trough FEV1, which is a surrogate outcome based on lung function, when reviewing tiotropium in adults with severe asthma (Paragraph 7.5 Tiotropium PSD, July 2015 PBAC).

- 6.12 FEV1 peak (0-3h) was not a key outcome in the consideration of tiotropium in adults with severe asthma. When reviewing tiotropium for use in children and adolescents, the PBAC has previously considered FEV1 peak (0-3h) from baseline to 12 weeks to be a measure of short term effect (Paragraph 7.4 Tiotropium PSD, March 2018 PBAC). It was also noted that peak FEV1 (0-3h) did not have evidence to support its use as a surrogate of long-term control of childhood asthma (Paragraph 6.36 Tiotropium PSD, March 2018 PBAC).
- 6.13 When reviewing tiotropium in adults with severe asthma, the PBAC considered that the incremental benefits in trough FEV1 were likely to be clinically meaningful (Paragraph 7.5 Tiotropium PSD, July 2015 PBAC). During the March 2018 consideration of tiotropium the evaluation considered the use of FEV1 measures in children might not provide a true representation of the severity of disease. However, the PBAC has previously considered that extrapolation of adult outcomes to the adolescent population may be reasonable (Paragraph 6.12 and 7.4 Tiotropium PSD, March 2018 PBAC).
- 6.14 There was, however, uncertainty regarding whether extrapolation of adult results to children (aged 6-11 years) was also reasonable. 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.” (Paragraph 6.12 Tiotropium PSD, March 2018 PBAC).
- 6.15 The resubmission provided a justification for the extrapolating of the results in adults to children with severe asthma, based on:
- acceptance by regulatory bodies;
  - the clinical importance of FEV1 in diagnosis and as an objective endpoint in children; and
  - the consistent treatment effect of tiotropium in children and adults.
- 6.16 The PSCR reiterated its rationale for the extrapolation of results, stating that the tiotropium trials in children were specifically designed to avoid unnecessary clinical

trials in children in line with the regulations in the European Directive (EC) Regulation no. 1901/2006 in force at the time of development. In addition, the pre-PBAC response highlighted that the Paediatric Investigational Plan for tiotropium was based on the concept of partial extrapolation of efficacy from the adult trials and was approved by the European Medicines Agency Paediatric Committee (EMA/PDCO).

6.17 The PBAC considered the rates of ICS and LABA concomitant therapy across trials 205.446 (6-11 years), 205.456 (12-17 years) and 205.416/205.417 during the treatment period were comparable. The PBAC also noted the similarities in baseline FEV1 actual values between trial 205.446 (6-11 years) and trials 205.416/205.417 populations. In addition, the PBAC acknowledged the variation evident in FEV1 predicted values between trials in children/adolescents compared with those conducted in adults. Overall, the PBAC considered it was not unreasonable to consider the concept of extrapolation of efficacy between children/adolescent and adult populations for these trials.

6.18 The table below summarises the definitions for the key outcomes in trials 205.446 (6-11 years), 205.456 (12-17 years) and 205.616/205.417 ( $\geq 18$  years).

**Table 4: Definition of outcomes in trials 205.446 (6-11 years), 205.456 (12-17 years) and 205.616/205.417 ( $\geq 18$  years).**

Outcome	Definition
FEV1 peak (0-3h)	Highest FEV1 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 FEV1 peak (0-3h) at 24 weeks; however, it was not a key outcome (Table 2, paragraph 6 Tiotropium PSD July 2015).
Trough FEV1	Trough FEV1 was measured in the evening at the end of the dosing interval (24 hours post drug administration), 10 min prior to treatment. The change from baseline at the end of the 12-week treatment period was measured in trials 205.446 and 205.456. Trough FEV1 was analysed as an absolute response (in litres L) as the primary outcome and as a percentage of predicted normal FEV1 normal. The tiotropium in adults with severe asthma submissions presented change in trough FEV1 at 24 weeks as a key outcome (Table 2, paragraph 6 Tiotropium PSD July 2015).
% predicted normal Trough FEV1 response	Change from baseline in trough FEV1 response as a percentage of predicted normal FEV1 normal at the end of the 12-week treatment period. The FEV1 predicted normal is the "normal" FEV1 for a person based on their age, sex and height. Measuring trough FEV1 as a percentage of the predicted normal FEV1 takes into account differences in body size and development and therefore enables appropriate comparison between adults and children.
Asthma exacerbation	An episode of progressive increase in $\geq 1$ asthma symptoms outside the patient's usual range of day-to-day asthma symptoms for $\geq 2$ 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. This definition matched the definition of (any) asthma exacerbation in the tiotropium in adults with severe asthma submissions (Table 3, paragraph 6 Tiotropium 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 $\geq 2$ consecutive days occurred. The PBAC previously considered that the clinical relevance of non-severe exacerbations as an outcome measure is unclear (paragraph 6.25 PBAC MIN March 2018).
Severe asthma exacerbation	All asthma exacerbations that required treatment with systemic corticosteroids for $\geq 3$ days or if already receiving systemic corticosteroids, a doubling of the previous daily dose for $\geq 3$ days. This definition was consistent with the definition of severe asthma exacerbation in the tiotropium in adults with severe asthma submissions (Table 3, paragraph 6 Tiotropium PSD July 2015).

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Outcome	Definition
Non-severe symptomatic exacerbation	In trials 205.446 and 204.456 - all asthma exacerbations that were classified as symptomatic but were not considered severe. In trials 205.416 - all exacerbations that were not considered severe (Table 3, paragraph 6 Tiotropium PSD July 2015).
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 FEV1. The score ranges from 0-6, where a higher score represents poorer asthma control and successful treatment will reduce the ACQ-7 score. Responders were defined as patients with an improvement of $\geq 0.5$ from baseline for the total ACQ score at 12 weeks.

Source: Compiled during the evaluation from Section 2.4.3, pp105-111 of the submission and March 2018 PSD

FEV<sub>1</sub> = forced expiratory volume in one second; PBAC = Pharmaceutical Benefits Advisory Committee; PEF = peak expiratory flow; PSD = public summary document

- 6.19 The MCID for trough FEV1 in adults was 0.10 L. This has previously been accepted by the PBAC in the consideration of tiotropium in adults with severe asthma (Paragraph 7.5 Tiotropium PSD, March 2018 PBAC). The resubmission nominated a MCID for trough FEV1 in children of 0.07 L. This MCID was based on children having a reduced lung capacity compared to adults; however, this has not been considered previously and it may not be appropriate.
- 6.20 There was uncertainty regarding the method used to establish 0.07 L as a meaningful MCID for trough FEV1 in children due to:
- Concerns regarding whether the demographic and clinical characteristics used in calculations may be considered representative;
  - Concerns regarding whether a % predicted trough FEV1 of 3.48 % is an appropriate surrogate outcome in children.
  - No evidence was provided regarding the biological link between FEV1 predicted normal and absolute trough FEV1 in children and adults.
  - No epidemiological or observational studies were presented to support the plausibility of such an approach.
- 6.21 The PSCR stated that there is no accepted MCID for FEV1 in children. The PSCR argued that the % predicted normal FEV1 is calculated directly from absolute FEV1 and are therefore directly biologically linked. The PSCR also argued that FEV1 predicted normal regression equations are derived from large population samples and can therefore be considered representative of the general population (Quanjer et al 1993; Wang et al 1993). The ESC considered that the appropriateness of the proposed MCID for trough FEV1 in children remained uncertain due to concerns regarding the clinical validity of the value calculated.

### **Comparative effectiveness**

- 6.22 The results from trials in children, adolescents and adults with severe asthma (205.446, 205.456 and 205.416/205.417) and a pooled meta-analyses of these trials for trough FEV1, % predicted normal response and FEV1 peak (0-3h) response are presented in the table below. The pooled meta-analyses from the March 2018 submission (and represented in the resubmission) is also included for comparison. In

addition, a sensitivity analysis including trials in patients 6-17 years with moderate asthma is presented.

**Table 5: Comparison of trough FEV<sub>1</sub> response and FEV<sub>1</sub> peak results**

Outcomes	Weight <sup>a</sup>	Adjusted mean difference (95% CI)
<b>Trough FEV<sub>1</sub></b>		
<b>Absolute response (L)</b>		
205.446 (6-11 years)	25.2%	<b>0.09 (0.02, 0.15)</b>
205.456 (12-17 years)	8.0%	0.05 (-0.06, 0.17)
205.416/205.417 (adults ≥ 18)	66.8%	<b>0.10 [0.05, 0.15]</b>
Pooled 205.446 & 205.456 (March 2018)		<b>0.08 [0.01, 0.14]</b>
Pooled 205.446, 205.456 & 205.416/205.417 (November 2018)		<b>0.09 (0.06, 0.13)</b>
Heterogeneity (I <sup>2</sup> statistic = 0%; Chi <sup>2</sup> for heterogeneity = 0.70; P = 0.87)		
Sensitivity analysis (including moderate asthma 205.445 and 205.444)		<b>0.10 [0.07, 0.13]</b>
<b>% predicted normal response</b>		
205.446 (6-11 years)	13.9%	<b>3.85 (0.58, 7.12)</b>
205.456 (12-17 years)	13.7%	0.83 (-2.35, 4.01)
205.416/205.417 (adults ≥ 18)	72.4%	<b>3.19 [1.62, 4.76]</b>
Pooled 205.446 & 205.456 (March 2018)		-
Pooled 205.446, 205.456 & 205.416/205.417 (November 2018)		<b>2.96 [1.62, 4.29]</b>
Heterogeneity (I <sup>2</sup> statistic = 0%; Chi <sup>2</sup> for heterogeneity = 1.80; P = 0.61)		
Sensitivity analysis (including moderate asthma 205.445 and 205.444)		<b>3.13 [1.95, 4.30]</b>
<b>FEV<sub>1</sub> peak (0-3h) response (L)</b>		
205.446 (6-11 years)	29.4%	<b>0.14 (0.08, 0.20)</b>
205.456 (12-17 years)	9.4%	0.09 (-0.02, 0.20)
205.416/205.417 (adults ≥ 18)	61.2%	<b>0.12 [0.05, 0.19]</b>
Pooled 205.446 & 205.456 (March 2018)		<b>0.13 [0.07, 0.19]</b>
Pooled 205.446, 205.456 & 205.416/205.417 (November 2018)		<b>0.12 [0.08, 0.16]</b>
Heterogeneity (I <sup>2</sup> statistic = 0%; Chi <sup>2</sup> for heterogeneity = 2.27; P = 0.52)		
Sensitivity analysis (including moderate asthma 205.445 and 205.444)		<b>0.14 [0.10, 0.17]</b>

Source: Table 2.41, p159; Table 2.42, p161; Figure 2.13, p160; Figure 2.14, p162 of the submission and March 2018 commentary

CI = Confidence Interval; FEV<sub>1</sub> = forced expiratory volume in one second; L = litre; **Bold** = statistically significant

<sup>a</sup> These weightings relate to the "Pooled 205.446, 205.456 & 205.416/205.417 (November 2018)" results only

- 6.23 The resubmission considered the trough FEV<sub>1</sub> response in children to be clinically meaningful based on the nominated MCID in children (i.e. 0.07 L). Tiotropium resulted in a statistically significant improvement in trough FEV<sub>1</sub> compared with placebo in trial 205.446 (6-11 years) (MD = 0.09 L; 95% CI: 0.02 to 0.15). While, in trial 205.456 (12-17 years) tiotropium did not result in a statistically significant or clinically meaningful improvement in trough FEV<sub>1</sub>.
- 6.24 The newly calculated trough FEV<sub>1</sub> MCID of 0.07 L has not been previously evaluated or accepted by the PBAC. Further, in trial 205.446 in children 6-11 years with severe asthma the 95% CI lower bound was 0.02 L which is much lower than the MCID of 0.07 L proposed in the resubmission.
- 6.25 The ESC noted that the meta-analysis of trial 205.446 (6-11 years) and trial 205.456 (12-17 years) resulted in a statistically significant improvement in trough FEV<sub>1</sub> compared with placebo (MD = 0.08 L; 95% CI: 0.01 to 0.14). However, the trough FEV<sub>1</sub> was below the previously accepted MCID of 0.10 L.

- 6.26 In addition, the resubmission analysed trough FEV1 response as a percentage of predicted normal FEV1, which the resubmission claimed takes into account differences in body size and development, and therefore enables comparison between adults and children. The results showed that tiotropium has a slightly greater incremental benefit in % predicted normal trough FEV1 response in children in trial 205.446 (3.85%; 95 %CI: 0.58 to 7.12) compared with adults in trials 205.416 /205.417 (3.19%; 95 %CI: 1.62 to 4.76). However, the results from trial 205.456 (12-17 years) (0.83%; 95 %CI: -2.35 to 4.01) showed that there was no incremental benefit in % predicted normal trough FEV1 response compared with adults in trials 205.416/205.417.
- 6.27 In trial 205.446 (6-11 years), tiotropium resulted in a statistically significant improvement in FEV1 peak (0-3h) response compared to placebo (MD = 0.14 L; 95 % CI: 0.08 to 0.20). This result was considered clinically meaningful by the resubmission as the improvement was greater than the nominated MCID (i.e. 0.12 L). However the clinical significance of the improvement was uncertain as FEV1 peak (0-3h) was not accepted as a key outcome by the PBAC previously. In trial 205.456 (12-17 years) tiotropium did not result in a statistically significant or clinically meaningful improvement in FEV1 peak (0-3h).
- 6.28 The ESC noted that meta-analysis of trial 205.446 (6-11 years) and trial 205.456 (12-17 years) resulted in a statistically significant improvement in FEV1 peak (0-3h) response compared to placebo (MD = 0.13 L; 95% CI: 0.07 to 0.19). However, the ESC recalled that the nominated MCID of 0.12 L for FEV1 peak (0-3h) had not previously been accepted by the PBAC (Paragraph 6.36 Tiotropium PSD, March 2018 PBAC).
- 6.29 The resubmission stated that the results of the meta-analysis demonstrated that tiotropium resulted in a statistically significantly improved trough FEV1 response (0.09 L; 95% CI: 0.06 to 0.13;  $p < 0.00001$ ), and FEV1 peak response (0.12 L; 95 % CI: 0.08 to 0.16;  $p < 0.00001$ ) compared with placebo from baseline. However, the presented meta-analyses for each of these outcomes were heavily weighted on the results of the adult trials (> 60%).
- 6.30 The PBAC noted the significant improvements in trough FEV1 response (MD = 0.09 L; 95% CI: 0.02 to 0.15), trough FEV1 response as a percentage of predicted normal FEV1 (3.85%; 95% CI: 0.58 to 7.12) and FEV1 peak (0-3h) (MD = 0.14 L; 95% CI: 0.08 to 0.20) in trial 205.446 (6-11 years). The PBAC considered that the benefits reported were of a similar magnitude to those reported in trials 205.416/205.417 conducted in adults (MD =0.10 L; 95% CI: 0.05 to 0.15, 3.19%; 95% CI: 1.62 to 4.76 and MD = 0.12 L; 95% CI: 0.05 to 0.19 respectively). The PBAC noted that tiotropium did not result in a statistically significant improvement in these outcomes in trial 205.456 (12-17 years). The PBAC considered that the clinical development program in adolescents was hampered by poor compliance in this population. The PBAC agreed with the ESC that there was a large placebo effect, which suggested these patients were not taking their regular medications at the start of the study. The PBAC considered that poor compliance during the study would have reduced the power of trial 205.456 to detect a difference between treatment arms.

- 6.31 The time to first asthma exacerbation was lower for all asthma exacerbations in the tiotropium arms compared to the placebo arms in all trials (trial 205.446 (6-11 years) (HR = 0.69; 95% CI: 0.44 to 1.06); trial 205.456 (12-17 years) (HR = 0.60; 95% CI: 0.32 to 1.14); trials 205.416/205.417 ( $\geq 18$  years) (HR = 0.69; 95% CI: 0.58 to 0.82)). However, the results were not statistically significant in children and adolescents. The PBAC considered that, although not statistically significant, the benefits reported for time to first asthma exacerbation in trials 205.446 (6-11 years) and 205.456 (12-17 years) were of a similar magnitude to those reported in the adult trials.
- 6.32 Table 6 presents the results of the post-hoc analyses of the number of asthma exacerbations, symptomatic exacerbations (severe and non-severe) and severe asthma exacerbations observed in trials in patients with severe asthma (205.446, 205.456 and 205.416/205.417) along with pooled meta-analyses for these outcomes. The pooled meta-analyses from the March 2018 submission are included in the table for comparison. A post-hoc analysis of the rate of exacerbations for moderate asthma trials 205.445 and 205.444 was not performed.

Table 6: Comparison of rate of asthma exacerbations results

Outcomes	Weight <sup>a</sup>	Rate ratio (95%CI)
<b>Asthma exacerbation</b>		
205.446 (6-11 years)	%	
205.456 (12-17 years)	%	
205.416/205.417 (adults $\geq 18$ )	%	<b>0.76 [0.63, 0.91]</b>
Pooled 205.446 & 205.456 (March 2018)		
Pooled 205.446, 205.456 & 205.416/205.417 (November 2018)		
Heterogeneity (I <sup>2</sup> statistic = %; Chi <sup>2</sup> for heterogeneity = ; P = )		
<b>Symptomatic exacerbation (severe and non-severe)</b>		
205.446 (6-11 years)	%	
205.456 (12-17 years)	%	
205.416/205.417 (adults $\geq 18$ )	%	<b>0.79 [0.65, 0.97]</b>
Pooled 205.446 & 205.456 (March 2018)		
Pooled 205.446, 205.456 & 205.416/205.417 (November 2018)		
Heterogeneity (I <sup>2</sup> statistic = %; Chi <sup>2</sup> for heterogeneity = ; P = )		
<b>Severe asthma exacerbation</b>		
205.446 (6-11 years)	%	
205.456 (12-17 years)	%	
205.416/205.417 (adults $\geq 18$ )	%	<b>0.80 [0.64, 1.00]</b>
Pooled 205.446 & 205.456 (March 2018)		
Pooled 205.446, 205.456 & 205.416/205.417 (November 2018)		
Heterogeneity (I <sup>2</sup> statistic = %; Chi <sup>2</sup> for heterogeneity = ; P = )		

Source: Table 2.46, p173; Figure 2.18, p174 of the submission and March 2018 commentary

CI = Confidence Interval; FEV<sub>1</sub> = forced expiratory volume in one second; **Bold** = statistically significant

<sup>a</sup> These weightings relate to the "Pooled 205.446, 205.456 & 205.416/205.417 (November 2018)" results only

- 6.33 The rates of all asthma exacerbations per patient-year were not statistically significant in the trials conducted in children and adolescents with severe asthma. The results were statistically significant in the trials conducted in adults. However, the PBAC considered that the benefits reported for the rate of all asthma exacerbations in trials 205.446 (6-11 years) (RR = ; 95% CI: ) and 205.456 (12-17 years) (RR = ; 95% CI: ) were of a similar magnitude to those reported in the adult trials (205.416/205.417) (RR = 0.76; 95% CI: 0.63 to 0.91).

- 6.34 The rates of symptomatic (severe and non-severe) asthma exacerbations were only statistically significant for symptomatic exacerbations in trial 205.446 (6-11 years) (rate ratio (RR) = [REDACTED]; 95% CI: [REDACTED]). Results were not significant in trial 205.456 conducted in adolescents (12-17 years). The rates for severe asthma exacerbations were marginally higher in the tiotropium arms compared to the placebo arms of both trials in children and adolescents. The PBAC noted that neither trial was powered to detect differences in asthma exacerbations and that the short duration of the trials meant that the number of all, symptomatic and severe exacerbations were low.
- 6.35 The results of the meta-analysis demonstrated statistically significant reductions in the number of all asthma exacerbations (RR = [REDACTED]; 95% CI: [REDACTED]; P = [REDACTED]) and symptomatic asthma exacerbations (RR = [REDACTED]; 95% CI: [REDACTED]; P = [REDACTED]) compared to placebo. The addition of the adult trials to the meta-analysis showed a reduction in rate ratio of severe asthma exacerbation; however, the results were not statistically significant and heavily weighted by the adult trials (94.3%). The benefits of tiotropium on reduction of severe asthma exacerbation in children and adolescents remained uncertain.

### Comparative harms

- 6.36 A summary of key adverse events in reported in trials 205.446 and 205.456 is presented below in Table 7.

**Table 7: Summary of key adverse events in the randomised trials 205.446 & 205.456 at 12 weeks (mITT populations)**

	205.446 (6-11 years)			205.456 (12-17 years)		
	Tiotropium	Placebo	RD (95% CI) <sup>a</sup>	Tiotropium	Placebo	RD (95% CI) <sup>a</sup>
N	130	134	-	130	135	-
Any AE, n (%)	56 (43%)	66 (49%)	-0.06 (-0.18, 0.06)	43 (33%)	48 (36%)	-0.02 (-0.14, 0.09)
Drug-related AE, n (%)	1 (1%)	2 (2%)	-0.01 (-0.03, 0.02)	0	1 (1%)	0.02 (-0.01, 0.04)
Any SAE, n (%)	4 (3%)	2 (2%)	0.02 (-0.02, 0.05)	2 (2%)	0	0.02 (-0.01, 0.04)
Leading to discontinuation, n (%)	2 (2%)	2 (2%)	0.00 (-0.03, 0.03)	0	1 (1%)	-0.01 (-0.03, 0.01)
Deaths, n (%)	0	0	-	0	0	-
AEs of special interest						
Respiratory, thoracic, and mediastinal disorders, n (%)	28 (22%)	34 (25%)	-0.04 (-0.14, 0.06)	16 (12%)	19 (14%)	-0.02 (-0.10, 0.06)
PEF rate decreased, n (%)	15 (12%)	20 (15%)	-0.03 (-0.12, 0.05)	5 (4%)	13 (10%)	-0.06 (-0.12, 0.00)
Infections and infestations, n (%)	25 (19%)	35 (26%)	-0.07 (-0.17, 0.03)	21 (16%)	26 (19%)	-0.04 (-0.13, 0.06)

Source: Tables 2.32-2.38, pp142-152 of the submission

AE = adverse event; CI = confidence interval; mITT = modified intention-to-treat; RD = risk difference; PEF = peak expiratory flow; SAE = serious adverse event

<sup>a</sup> Calculated *post-hoc*

- 6.37 The ESC noted that the PBAC had previously considered that the claim of non-inferior comparative safety compared to placebo to be reasonable (Paragraph 6.40 Tiotropium PSD, March 2018 PBAC) based on the number of adverse events reported being similar between tiotropium and placebo treatment arms.

## Benefits/harms

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

Table 8: Summary of comparative benefits 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	
<b>Benefits</b>						
<b>Symptomatic (severe and non-severe) exacerbations (number per patient year) <sup>a</sup></b>						
205.446 (6-11 years)						
205.456 (12-17 years)						
<b>Severe symptomatic exacerbations (number per patient year) <sup>a</sup></b>						
205.446 (6-11 years)						
205.456 (12-17 years)						
<b>FEV<sub>1</sub> peak (0-3h) response (L) at 12 weeks</b>						
	Tiotropium		Placebo		Adjusted mean difference (95% CI) <sup>c</sup>	
	N	Adjusted mean change (SD) <sup>b</sup>	N	Adjusted mean change (SD) <sup>b</sup>		
205.446 (6-11 years)	128	0.39 (0.35)	130	0.25 (0.29)	<b>0.14 (0.08, 0.20)</b>	
205.456 (12-17 years)	130	0.53 (0.51)	132	0.44 (0.52)	0.09 (-0.02, 0.20)	
<b>Trough FEV<sub>1</sub> response (L) at 12 weeks</b>						
	Tiotropium		Placebo		Adjusted mean difference (95% CI) <sup>c</sup>	
	N	Adjusted mean change (SD) <sup>b</sup>	N	Adjusted mean change (SD) <sup>b</sup>		
205.446 (6-11 years)	128	0.22 (0.31)	130	0.14 (0.31)	<b>0.09 (0.02, 0.15)</b>	
205.456 (12-17 years)	130	0.28 (0.55)	132	0.23 (0.55)	0.05 (-0.06, 0.17)	
<b>Harms</b>						
	Tiotropium	Placebo	Relative risk (95% CI)	Event rate per 100 patients per 12 weeks		Risk difference (95% CI)
				Tiotropium	Placebo	
<b>Infections and infestations events per 12 weeks</b>						
205.446 (6-11 years)	25/130	35/134	0.74 (0.47, 1.16)	19	25	-0.07 (-0.17, 0.03)
205.456 (12-17 years)	21/130	26/135	0.84 (0.50, 1.41)	16	19	-0.03 (-0.12, 0.06)
<b>Respiratory, thoracic, and mediastinal disorders events per 12 weeks</b>						
205.446 (6-11 years)	28/130	34/134	0.85 (0.55, 1.32)	22	25	-0.04 (-0.14, 0.06)
205.456 (12-17 years)	16/130	19/135	0.87 (0.47, 1.63)	12	14	-0.02 (-0.10, 0.06)

Source: Tables 2.24-2.25, pp122-123; Table 2.29, p137 Tables 2.32-2.40, pp142-155 of the submission

CI = confidence interval; FEV<sub>1</sub> = forced expiratory volume in one second; L = litre; MMRM = mixed model repeated measures; SD = standard deviations; **Bold** = statistically significant

<sup>a</sup> Calculated *post-hoc*: events per patient year = total events/(total exposure days/365.25)

<sup>b</sup> SD calculated *post-hoc*

<sup>c</sup> 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.

6.39 On the basis of the direct comparison evidence presented by the resubmission, 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 (which includes both non-severe and severe) would be experienced in patients aged 6-11 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 12-17 years.
- 6.40 On the basis of the direct comparison evidence between tiotropium and placebo presented by the resubmission, 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 (FEV<sub>1</sub>) peak response (which is measured by spirometry 0 to 3 hours after dosing), in patients aged 6-11 years.
  - Approximately 0.09 L improvement in lung function, as measured by the trough FEV<sub>1</sub> response (which is measured by spirometry 24 hours after dosing), in patients aged 6-11 years.
  - No difference in lung function, as measured by FEV<sub>1</sub> peak (0-3h) and trough FEV<sub>1</sub> responses, in patients aged 12-17 years.

### ***Clinical claim***

- 6.41 The resubmission 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. This was unchanged from the previous submission.
- 6.42 In March 2018 the PBAC assessed the evidence from the trials in children and adolescents aged 6-17 years with severe asthma (205.446 and 205.456) and found 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” (Paragraph 7.1 Tiotropium PSD, March 2018 PBAC).
- 6.43 In March 2018 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 (Paragraph 7.3 Tiotropium PSD, March 2018 PBAC).
- 6.44 For the trials conducted in children and adolescents with severe asthma (205.446 and 205.456) the resubmission’s claim that tiotropium was superior in terms of effectiveness compared to placebo based on these trials alone was not supported as:
- All primary and secondary outcomes from trial 205.456 (12-17 years) were not clinically meaningful nor statistically significant, suggesting tiotropium had limited clinical benefit in children aged 12-17 years;
  - the mean trough FEV<sub>1</sub> for children was met according to the new recalculated MCID of 0.07 L; However, the 95% CI fell well below the MCID and it was unclear if the MCID was a valid value;

- the nominated MCID of 0.12 L for FEV1 peak (0–3h) response might not be clinically meaningful;
  - there was a strong placebo response observed in both trials, with patients in the placebo arms experiencing clinically meaningful improvements in FEV1 peak (0–3h) response, trough FEV1 response and mean ACQ scores;
  - in terms of a reduction in the rates of exacerbations, 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; all other analyses were not statistically significant;
  - the number of severe exacerbations was marginally higher in the tiotropium arms compared to the placebo arms in both trials; and
  - all time to first exacerbation, time to first symptomatic exacerbation and time to first severe exacerbation analyses were not statistically significant.
- 6.45 In addition to the reasons outlined above the ESC noted the short 12 week duration of trials 205.446 (6-11 years) and 205.456 (12-17 years) and concerns regarding poor adherence to treatment prior to starting in the trials. The ESC considered that evidence for the effectiveness of tiotropium compared to placebo in children with severe asthma was poor, especially in patients aged 12 to 17 years. The PSCR argued that trials 205.446 (6-11 years) and 205.456 (12-17 years) were specifically designed to avoid unnecessary clinical trials in children and that the paediatric development program for tiotropium was accepted by all major authorities and led to its approval. The PSCR also stated that the Australian Asthma Management Handbook, GINA and Canadian Asthma guidelines also recommend tiotropium in adults and adolescents as an add-on therapy option in patients uncontrolled on ICS plus a LABA. The ESC considered that, while the clinical trial evidence was poor, a possible potential benefit may be seen with the use of tiotropium as a late add-on treatment in some children and adolescents with severe asthma who are unable to achieve adequate control of their asthma with current optimised therapy.
- 6.46 The pre-PBAC response argued that the Paediatric Investigational Plan for tiotropium was based on the concept of partial extrapolation of efficacy from adult trials, and that data for tiotropium confirms its bronchodilating effect across both adults and children. Hence, the pre-PBAC response argued that the results in children and adolescents need to be considered within the context of the entire clinical development program. The pre-PBAC response highlighted that the clinical trials in children were powered for lung function as a sensitive endpoint for a bronchodilator and as an anchor point to the adult programme.
- 6.47 The PBAC acknowledged the limitations of trials 205.446 (6-11 years) and 205.456 (12-17 years). However, the PBAC considered that the similar magnitude of benefit observed across trials 205.446 (6-11 years), 205.456 (12-17 years) and 205.416/205.417 supported the premise that age is not a treatment effect modifier for tiotropium in severe asthma. As such, the PBAC considered that the claim of

superior comparative effectiveness of tiotropium plus optimised asthma therapy over placebo plus optimised asthma therapy in children and adolescents aged (6-17 years) with severe asthma was reasonable.

- 6.48 The PBAC reaffirmed its previous advice that the claim of non-inferior comparative safety was reasonable.

### **Economic analysis**

- 6.49 The resubmission 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 resubmission considered that there was insufficient data to develop a full cost utility model. The primary outcome of FEV<sub>1</sub> peak (0–3h) was not used in the model. This was unchanged from the previous submission in March 2018.

- 6.50 Overall, the base case economic evaluation remained unchanged. The resubmission updated the drug, hospitalisation and ED visits costs from the previous March 2018 submission.

**Table 9: Summary of model structure and rationale**

<b>Component</b>	<b>Summary</b>
Time horizon	12 weeks in the model base case versus 12 weeks in the key trials (205.446 and 205.456)
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, p213 of the submission

- 6.51 The PBAC has previously 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)” (Paragraph 7.7 Tiotropium PSD, March 2018 PBAC). The PSCR contended that symptomatic (non-severe and severe) exacerbations were clinically relevant and therefore appropriate as an outcome for the economic evaluation. The ESC considered the resubmission and the PSCR did not provide supporting evidence of a quality of life/utility decrement associated with a symptomatic exacerbation. Hence, the ESC considered that the issue highlighted by the PBAC in their March 2018 consideration of tiotropium remained.

- 6.52 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	
<b>Cost per extra symptomatic exacerbation (non-severe and severe) avoided</b>							
Children 6-17 years	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]	[REDACTED]	- [REDACTED]	\$ [REDACTED] per symptomatic exacerbation avoided
	To provide an ICER of \$ [REDACTED], the QALY loss per symptomatic exacerbation = \$ [REDACTED]/\$ [REDACTED] = 0.027						
<b>Cost per extra severe symptomatic exacerbation avoided</b>							
Children 6-17 years	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Source: Table 3.26, p264 and Compiled during the evaluation from Att\_13\_Section 3 Workbook.xls  
 ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life years

- 6.53 The submission estimated a cost per symptomatic exacerbation (non-severe and severe) avoided of less than \$15,000. The ESC noted that the cost per severe symptomatic exacerbation avoided for children aged 6-17 treated with tiotropium [REDACTED] by placebo.
- 6.54 Consistent with the March 2018 submission, the resubmission calculated the implied QALY loss required to generate an ICER of \$45,000 – \$75,000 per QALY. This involved: assuming no mortality effect, an exacerbation must be associated with a loss of [REDACTED] QALYs to achieve an ICER of \$45,000 – \$75,000 per QALY. This was unchanged from the March 2018 submission.
- 6.55 At the March 2018 meeting the PBAC considered 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 (Paragraph 7.8 Tiotropium PSD, March 2018 PBAC).
- 6.56 The resubmission considered this implied 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). The comparison was not appropriate as the outcomes were not equivalent (clinically significant exacerbations<sup>1</sup> for omalizumab vs symptomatic (non-severe and severe) exacerbations for tiotropium). The ESC noted a comparative QALY value could not be calculated for tiotropium as it was dominated by placebo in terms of severe symptomatic exacerbations avoided in both trials and as such this approach was not appropriate.
- 6.57 The resubmission argued that the plausibility of the [REDACTED] QALY loss was supported by a review of the published literature which indicated that the utility decrement for a symptomatic non-severe exacerbation ranged from 0.026 to 0.63. In addition, the PSCR proposed that the utility decrement of [REDACTED] estimated from the threshold analysis implicitly accounts for the element of time and as such represented the QALY loss of a symptomatic (non-severe and severe) exacerbation. The ESC considered that it was difficult to interpret the utility decrements from the published literature and

<sup>1</sup> This definition aligned with the definition of severe symptomatic exacerbations in trials 205.446 and 205.456.

how they relate to the current setting, given the range and the sources of information. The ESC noted that the approach outlined in the PSCR assumed a QALY was generated via quality of life changes only with no change in survival. The ESC considered that the concerns raised by the PBAC in March 2018 regarding the plausibility of the proposed [REDACTED] QALY loss per symptomatic exacerbation (non-severe and severe) remained.

6.58 The results of the sensitivity analyses presented by the resubmission and conducted during the evaluation are presented in the table below.

**Table 11: Results of sensitivity analyses**

Analyses	Incremental cost	Change in exacerbation rate	ICER (\$/exacerbation avoided)
<b>Base case</b> Marks (2007) GP = 67.7%; ED = 32.3%	\$ [REDACTED]	- [REDACTED]	\$ [REDACTED]
Reddel HK <i>et al.</i> (2015) GP = 78.6%; ED = 21.4%	\$ [REDACTED]	- [REDACTED]	\$ [REDACTED]
<i>Compliance (base case = 80.9%)</i> 90%	\$ [REDACTED]	- [REDACTED]	\$ [REDACTED]
70%	\$ [REDACTED]	- [REDACTED]	\$ [REDACTED]
<b>Rate from 205.446 (6-11 years)</b> Severe exacerbation rate (tiotropium = [REDACTED]; placebo = [REDACTED]) Non-severe exacerbation rate (tiotropium = [REDACTED]; placebo = [REDACTED])	\$ [REDACTED]	- [REDACTED]	\$ [REDACTED]
<b>Rate from 205.456 (12-17 years)</b> Severe exacerbation rate (tiotropium = [REDACTED]; placebo = [REDACTED]) Non-severe exacerbation rate (tiotropium = [REDACTED]; placebo = [REDACTED])	\$ [REDACTED]	- [REDACTED]	\$ [REDACTED]

Source: Table 3.30, p266 of the submission and compiled during evaluation using Att\_13\_Section 3 workbook.xlsx  
ED = emergency department; GP = general practitioner; ICER = incremental cost-effective ratio; QALY = quality-adjusted life years

6.59 The ESC noted the cost per symptomatic exacerbation (non-severe and severe) avoided in each of the trials was \$ [REDACTED] and \$ [REDACTED] for trial 205.446 (6-11 years) and trial 205.456 (12-17 years) respectively.

6.60 The cost per exacerbation avoided was sensitive to using different trial exacerbation rates; this demonstrated that the economic evaluation is reliant on data that may not be robust considering the limited benefit of tiotropium evident in trial 205.456 (12-17 years).

6.61 The March 2018 submission had claimed that patients would visit a GP and purchase medicines for all non-severe exacerbations. The PBAC had 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 and hence this cost had been overestimated (Paragraph 7.8 Tiotropium PSD, March 2018 PBAC). The PSCR argued that the resubmission had provided the results of an Asthma Exacerbation Treatment Survey which justified the cost offsets applied. The ESC noted the survey had a small sample size (N=11) with the majority of participants being GPs (n=8), not respiratory specialists. The ESC considered the survey was subject to recall bias and noted differences in the definitions used in the survey and those used in the trials.

6.62 The resubmission also presented a scenario analysis based on the model presented in the March 2016 consideration of tiotropium for adults with severe asthma. This was modified to include the results from the trials in children and adolescents with severe

asthma (205.446 and 205.456). These modifications were largely applied inappropriately as the children/adolescent data was only used up to week 16 and only adult data was used in the rest of the extrapolation.

6.63 The results of the scenario analyses presented by the resubmission and conducted during the evaluation are presented in the table below.

Table 12: Results of the scenario analysis

	QALYs	Exacerbations	Severe exacerbations	Cost	ICER (\$/QALYs)	ICER (\$/exacerbation avoided)	ICER (\$/severe exacerbation avoided)
<b>Trial 205.416 and 205.417</b>							
Tiotropium				\$			
Usual care				\$			
Incremental				\$			
<b>Trial 205.446 and 205.456</b>							
Tiotropium				\$			
Usual care				\$			
Incremental				\$			
<b>Trial 205.416, 205.417, 205.446 and 205.456</b>							
Tiotropium				\$			
Usual care				\$			
Incremental				\$			
<b>Sensitivity analysis (Trial 205.416 and 205.417) – Time horizon 48 weeks</b>							
Tiotropium				\$			
Usual care				\$			
Incremental				\$			

Source: Table 3.27, p264 of the submission and compiled during evaluation using scenario analysis\_Section 3 workbook.xls  
 ICER = incremental cost-effective ratio; QALY = quality-adjusted life years

6.64 The results of the scenario analysis provided by the resubmission showed that patients treated with tiotropium as add-on to usual care experience [redacted] exacerbations, including [redacted] severe exacerbations, while those treated with usual care alone experience a total of [redacted] exacerbations, including [redacted] severe exacerbations; a difference of [redacted] exacerbations and [redacted] severe exacerbations. The ICERs for the outcomes of exacerbation avoided, severe exacerbation avoided and QALY gained were less than \$15,000, \$15,000 - \$45,000 and \$15,000 - \$45,000, respectively.

6.65 When, health states and transitions probabilities used in the supplementary data from trials 205.446 and 205.456 were used, the ICERs for the outcomes of exacerbation avoided, severe exacerbation avoided and QALY gained were less than \$15,000, \$15,000 - \$45,000 and \$15,000 - \$45,000, respectively. When the pooled results from trials 205.416, 205.417, 205.446 and 205.456 were used the ICERs for the outcomes of exacerbation avoided, severe exacerbation avoided and QALY gained were less than \$15,000, \$15,000 - \$45,000 and \$15,000 - \$45,000, respectively.

6.66 In all scenarios the number of patients defaulted back to only the adult data for the remainder of the model. This was not appropriate and unrealistic. This was particularly noticeable when only pooled children and adolescent trials were used: in the placebo arm, 47 patients were uncontrolled at week 8-16, which dramatically jumped to 268

patients at week 16-24. Similarly, when the pooled transition probabilities and exacerbations were used, the model failed to account for all patients beyond week 16. This meant that in the tiotropium arm, 319 patients were uncontrolled at week 8-16, which dropped to 268 patients at week 16-24.

- 6.67 The ESC considered the scenario analysis presented in the resubmission was not appropriate as it combined results from trial 205.446 (6-11) and trial 205.456 (12-17) with the adult trials (205.416/205.417), and the data driving the model was mostly based on the adult trials. The ESC considered that the scenario analysis did not address concerns regarding the finding that the rates of severe exacerbations were not significantly different in those treated with tiotropium compared with placebo over the 12 week duration of trials 205.446 (6-11) and 205.456 (12-17).
- 6.68 The PBAC reiterated its March 2018 advice that the economic evaluation in the form of a cost per symptomatic exacerbation avoided (non-severe and severe) was not clinically meaningful. In addition, the PBAC agreed with the ESC that scenario analysis presented in the resubmission did not assist decision making due to the concerns raised. However, the PBAC recalled its acceptance that the benefits of tiotropium reported across children and adolescents aged 6-17 years with severe asthma were of a similar magnitude to those reported in adults. The PBAC also noted that the resubmission proposed the same DPMQ for tiotropium regardless of age. Hence, the PBAC concluded that it was reasonable to accept the cost-effectiveness of tiotropium in this population as per its March 2016 recommendation for the use of tiotropium in adults with severe asthma.

***Drug cost/patient/year: \$638.09***

- 6.69 The annual cost of tiotropium per patient per year was estimated to be \$638.09, based on the proposed DPMQ of \$52.41. The resubmission assumed a compliance rate of 100% was used, resulting in a total of 12.18 prescriptions per year and an annual cost of \$638.09.
- 6.70 The financial estimates assumed a compliance rate of 80.88%, which was the weighted trial-based compliance rate. Based on this compliance the annual cost of tiotropium per patient per year was estimated to be \$516.09 (9.85 prescriptions per year).

***Estimated PBS usage & financial implications***

- 6.71 This resubmission was not considered by DUSC.
- 6.72 The resubmission presented an epidemiological approach to estimate the financial impact of listing tiotropium on the PBS/RPBS. The approach taken was the same as that presented in the March 2018 submission.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	██████	██████	██████	██████	██████	██████
Number of scripts dispensed <sup>a</sup>	██████	██████	██████	██████	██████	██████
<b>Estimated financial implications of tiotropium</b>						
Cost to PBS/RPBS	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████
Co-payments	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████
Cost to PBS/RPBS less Co-payments	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████
<b>Estimated financial implications for other PBS medicines</b>						
Cost to PBS/RPBS	-\$ ██████	-\$ ██████	-\$ ██████	-\$ ██████	-\$ ██████	-\$ ██████
Co-payments	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████
Cost to PBS/RPBS less Co-payments	-\$ ██████	-\$ ██████	-\$ ██████	-\$ ██████	-\$ ██████	-\$ ██████
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████	\$ ██████

Source: Compiled from Att\_20\_Section 4 Workbook.xlsx

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

<sup>a</sup> Assuming 9.85 number of scripts per year as estimated by the submission

6.73 The PBAC has previously considered that there was uncertainty regarding the financial implications for the PBS/RPBS of listing tiotropium (Paragraph 6.54 Tiotropium PSD, March 2018 PBAC) 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)”.

6.74 Overall, the ESC noted the resubmission had not addressed any of the issues raised by the PBAC in its March 2018 consideration.

6.75 At Year 6, the estimated number of patients was 15,000 – 45,000 per year, and the net cost to the PBS would be less than \$10 million per year.

6.76 The PBAC considered that the financial estimates were overestimated. As part of its consideration the PBAC noted data provided by the Drug Utilisation Sub Committee (DUSC) Secretariat on tiotropium extracted from the Department of Human Services prescription database for date of supply between July 2017 and June 2018. The data indicated that, although the current PBS listing for tiotropium for severe asthma is not restricted by age, 240 children and adolescents aged 6-17 years were dispensed a prescription for tiotropium over this period.

6.77 The PBAC also noted data from the *Evaluation of the 2014 Post-Market Review of PBS Medicines Used to Treat Asthma in Children* final report which stated that based on analysis of complete PBS data for children aged 0 to 18 years in 2015-2016:

- There is still high use of LABA/ICS without prior trial of other asthma therapies. Of those who initiated preventer medicines, 34% initiated a LABA/ICS combination without prior use of inhaled corticosteroids or LTRA (inappropriate practice). This compares to 42% in the 2012-2013 analysis.
- There is still high use of LABA/ICS without prior trial of inhaled or oral corticosteroids. Of those who initiated a LABA/ICS combination, 60% had had no prior use of inhaled or oral corticosteroids. This compares with 79% in 2012-2013.
- There is still one off or episodic use of LABA/ICS therapy. Of those who initiated a LABA/ICS combination, 67% who had had no prior use of inhaled or oral corticosteroids received only one supply in the 12 months of follow-up, and 54% who had had prior inhaled or oral corticosteroids received only one supply in the 12 months of follow-up. This is similar to the pattern observed in 2012-2013 and reflects poor persistence with use or use for conditions other than asthma.
- GPs continue to initiate the majority of therapy, initiating 95% of patients. This compares with 94% in the 2012-2013 analysis.

The PBAC considered that use of the proportion of the paediatric population using a combination of an ICS and LABA in the estimate calculations would likely inflate the total number of eligible patients due to the common use of this combination earlier in the treatment algorithm than intended by Australian asthma guidelines.

6.78 The PBAC considered that based on published prevalence data for severe asthma reported by Nordlund et al 2014<sup>2</sup> the annual total eligible patients numbers reported in the resubmission are likely to be a three-fold overestimate. However, the PBAC considered that a risk sharing arrangement (RSA) would still be required to manage the risk of use in patients with less severe asthma, use in patients who are not taking their existing medicines optimally or use that is not in consultation with a specialist.

### ***Quality Use of Medicines***

6.79 The resubmission included proposals for Quality of Use of Medicine initiatives. These included the provision of consumer and health care professional information on tiotropium and correct inhaler technique to ensure the appropriate usage of tiotropium and the Respimat® device in patients with severe asthma. The proposals provided were appropriate.

### ***Financial management – risk sharing arrangements***

6.80 The PSCR stated there is currently a RSA for tiotropium in adults with severe asthma. If the PBAC recommended tiotropium on the PBS for children with severe asthma, the

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<sup>2</sup> Nordlund B et al. Prevalence of severe childhood asthma according to the WHO. *Respir Med* 2014;108:1234-7

sponsor proposed that the current RSA be modified to include the use of tiotropium in children.

- 6.81 The PBAC noted the RSA in place for the current PBS listing of tiotropium for severe asthma and that utilisation to date was lower than that estimated in March 2016 and subsequently significantly below the current RSA cap.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing for tiotropium for the treatment of severe asthma in children and adolescents aged 6-17 years who have not achieved adequate asthma control while treated with optimised asthma therapy. The PBAC was satisfied that tiotropium plus optimised asthma therapy provides, for some patients, a significant improvement in efficacy over placebo plus optimised asthma therapy.
- 7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of tiotropium would be acceptable at an equivalent price to tiotropium in severe asthma in adults.
- 7.3 The PBAC noted that tiotropium is currently PBS listed as a restricted benefit and considered that a separate Authority Required (STREAMLINED) listing specifying treatment by or in consultation with a specialist was appropriate for children and adolescents aged 6-17 years to optimise the quality use of tiotropium in this population. The PBAC further noted that the current restriction for tiotropium for adults will need to be concurrently amended to include an age criteria for use in patients 18 years and older. The PBAC agreed with the changes to the restriction wording that were suggested by the Secretariat.
- 7.4 The PBAC recalled that it had previously accepted placebo as the appropriate comparator (Paragraph 5.1 Tiotropium PSD, March 2018 PBAC).
- 7.5 The PBAC noted that trials 205.446 (6-11 years) and 205.456 (12-17 years) were part of the Paediatric Investigational Plan for tiotropium. The Paediatric Investigational Plan was based on the concept of partial extrapolation of efficacy from the trial 205.416 and trial 205.417 in adults with severe asthma. The PBAC had previously agreed that, based on a combined analysis of trials 205.416/205.417, the comparative benefit of add-on tiotropium over placebo was adequately supported in terms of statistical measures and that tiotropium provided superior efficacy to placebo in terms of trough FEV1 and time to first exacerbation in adult patients (Paragraph 7.5 Tiotropium PSD, July 2015 PBAC). Overall, the PBAC considered it was not unreasonable to accept the extrapolation of efficacy for these trials based on rates of ICS and LABA concomitant therapy across the trials during the treatment period and similarities in baseline FEV1 actual values.
- 7.6 The PBAC considered that the benefits reported in terms of improvements in trough FEV1 response, trough FEV1 response as a percentage of predicted normal FEV1, and

FEV1 peak in trial 205.446 (6-11 years) were of a similar magnitude to those reported in trials 205.416/205.417 conducted in adults. While tiotropium did not result in a statistically significant improvement in these outcomes in trial 205.456 (12-17 years), the PBAC considered that the clinical development program in adolescents was hampered by poor compliance in this population contributing to the large placebo effect observed. The PBAC agreed with ESC that this result suggested adolescent patients were not taking their regular medications at the start of the study, and that this poor compliance during the study would have reduced the power of trial 205.456 to detect a difference between treatment arms.

- 7.7 The PBAC considered that the benefits reported in the child and adolescent trials for time to first asthma exacerbation and rate of all asthma exacerbations were of a similar magnitude to those reported in the adult trials.
- 7.8 Overall, the PBAC considered that the similar magnitude of benefit observed across trials 205.446 (6-11 years), 205.456 (12-17 years) and 205.416/205.417 ( $\geq 18$  years) supported the premise that age is not a treatment effect modifier for tiotropium in severe asthma. As such, the PBAC considered that the comparative benefit of add-on tiotropium over placebo in children and adolescents aged (6-17 years) with severe asthma was adequately supported by the evidence provided in the resubmission.
- 7.9 The PBAC reaffirmed its March 2018 recommendation that the claim of non-inferior comparative safety of tiotropium compared to placebo in children and adolescents with severe asthma was reasonable.
- 7.10 The PBAC reiterated its March 2018 advice that the economic evaluation in the form of a cost per symptomatic exacerbation avoided (non-severe and severe) was not clinically meaningful. However, as the benefits reported across children and adolescents aged 6-17 years were of a similar magnitude to those reported in adults, and the resubmission proposed the same DPMQ for tiotropium regardless of age, the PBAC concluded that it was reasonable to accept the cost-effectiveness of tiotropium in this population.
- 7.11 The PBAC considered that the financial estimates were overestimated. The PBAC considered that use of the proportion of the paediatric population using a combination of an ICS and LABA as reflective of asthma severity likely inflated the total number of eligible patients due to the common use of this combination earlier in the treatment algorithm than intended by Australian asthma guidelines. In addition, the PBAC noted that, although the current PBS listing for tiotropium for severe asthma is not restricted by age, data provided by the DUSC Secretariat indicated current PBS subsidised tiotropium use in children and adolescents aged 6-17 years was low.
- 7.12 The PBAC also noted that current PBS subsidised tiotropium use for severe asthma in adults is lower than the estimated use proposed in the March 2016 submission. The PBAC considered that based on published prevalence data for severe asthma in children (Nordlund et al. 2014) the total eligible population is likely to be a three-fold overestimate. The PBAC considered that while the financial estimates were uncertain it was reasonable to accept a three-fold reduction in the total eligible patient numbers

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proposed in the resubmission as the maximum number of PBS eligible children and adolescents aged 6-17 years with severe asthma to be treated per annum.

- 7.13 The PBAC considered that a RSA was required to manage the risk of use in patients with less severe asthma, use in patients who are not taking their existing medicines optimally, or use that is not in consultation with a specialist. The PBAC noted that a RSA was in place for the current PBS listing of tiotropium for severe asthma with utilisation to date significantly below the current RSA cap. The PBAC considered that as the financial estimates are likely to be significantly lower than that proposed in the resubmission, the extension of tiotropium use in this context to children and adolescents aged 6-17 years could be incorporated in the existing RSA. Further, the PBAC was of the view that the current Subsidisation Caps under the existing RSA should not be increased or amended as appropriate utilisation in children and adolescents aged 6-17 years would likely be contained under the current Subsidisation Cap.
- 7.14 The PBAC considered that higher than expected use may occur due to the risk of use beyond the restriction outlined above and recommended that DUSC undertake a review of utilisation after an appropriate period post listing.
- 7.15 The PBAC advised that tiotropium is suitable for prescribing by nurse practitioners for continuing therapy only.
- 7.16 The PBAC recommended that the Early Supply Rule should apply.
- 7.17 The resubmission is not eligible for an Independent Review, because the PBAC has made a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Proprietary Name and Manufacturer
TIOTROPIUM Solution for oral inhalation, 2.5 µg, 60 actuations	1	5	Spiriva® Respimat®; Boehringer Ingelheim
<b>Category / Program</b>	GENERAL – General Schedule (Code GE)		
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives		
<b>Condition:</b>	Severe asthma		
<b>PBS Indication:</b>	Severe asthma		
<b>Restriction Level / Method:</b>	<input 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 checked="" type="checkbox"/> Streamlined		

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<b>Treatment criteria:</b>	Must be treated by a respiratory physician, paediatric respiratory physician, clinical immunologist, allergist, paediatrician or general physician experienced in the management of patients with severe asthma; or in consultation with one of these specialists.
<b>Clinical criteria:</b>	<p>Patient must have failed to achieve adequate control with optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented,</p> <p>AND</p> <p>Patient must have experienced at least one severe exacerbation prior to receiving PBS-subsidised treatment with this drug for this condition, which has required documented use of systemic corticosteroids in the previous 12 months while receiving optimised asthma therapy,</p> <p>OR</p> <p>Patient must have experienced frequent episodes of moderate asthma exacerbations prior to receiving PBS-subsidised treatment with this drug for this condition,</p> <p>AND</p> <p>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 a LABA is contraindicated.</p>
<b>Population criteria:</b>	Patient must be aged 6 to 17 years inclusive.
<b>Prescriber Instructions</b>	Optimised asthma therapy includes adherence to the maintenance combination of a medium to high dose ICS and a LABA. If LABA therapy is contraindicated, not tolerated or not effective, montelukast, cromoglycate or nedocromil may be used as an alternative.
<b>Administrative Advice</b>	<p>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 <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a> or <a href="http://www.nationalasthma.org.au">www.nationalasthma.org.au</a>); 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).</p> <p>Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before "stepping up" a patient's medication regimen.</p> <p>Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p>

## 9 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.

## 10 Sponsor's Comment

The sponsor had no comment.