7.09 TIOTROPIUM
solution for inhalation, 2.5 microgram per actuation (as bromide monohydrate),
Spiriva® Respimat®, Boehringer Ingelheim Pty Limited.

1 Purpose of Application

1.1 The resubmission requested a Restricted Benefit listing for the inclusion of tiotropium 2.5 µg on the Pharmaceutical Benefits Scheme (PBS) for treatment of asthma in adult patients currently treated with the optimised combination of inhaled corticosteroids (ICS) and long-acting β_2 agonist (LABA), unless LABA was contraindicated or not tolerated, and who experienced one or more severe exacerbations in the previous year.

2 Requested listing

2.1 The requested listing is shown below:

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

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Severe
Condition:	Asthma
PBS Indication:	Severe asthma
Treatment phase:	-
Restriction Level / Method:	☒Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐Streamlined

Clinical criteria:	Patient must have experienced at least one severe exacerbation, which has required documented use of systemic corticosteroids, in the previous 12 months 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 and a long acting beta-2 agonist.
Population criteria:	~~Patient must be aged 18 years or older~~
Prescriber Instructions	Optimised asthma therapy includes adherence to the maintenance combination of an inhaled corticosteroid (at least 800 micrograms budesonide per day or equivalent) and a long-acting β2 agonist.
Administrative Advice	Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.humanservices.gov.au or ww.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).

2.2 The Pre-Sub-Committee Response (PSCR) (p4) noted that the Secretariat recommended removal of the age criterion, and stated that it is the Sponsor's preference for this criterion to be included in the restriction as tiotropium is indicated for use in adults.

2.3 The submission presented a cost-effectiveness analysis of tiotropium plus ICS and LABA compared to placebo plus ICS and LABA.

2.4 The resubmission specified that tiotropium must be used in combination with a maintenance combination of ICS and LABA. Furthermore, high-dose budesonide was re-defined as ≥ 800 micrograms of budesonide per day or equivalent. The requested listing is consistent with the PBAC's suggestions and the existing TGA indication.

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

3 Background

3.1 Tiotropium was TGA registered on July 2015 for: "add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥800 microgram budesonide/day or equivalent) and long-acting beta-2 agonists and who experienced one or more severe exacerbations in the previous year."

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

3.3 Tiotropium was rejected by the PBAC in July 2015 for the treatment of patients with asthma. Table 1 presents a summary of the resubmission and the original submission.

Table 1: Summary of the previous submission and current resubmission

	Tiotropium (July 2015)	Current resubmission
Requested PBS listing	Patients who have experienced ≥ 1 exacerbation in the previous 12 months whilst receiving optimised asthma therapy, despite documented formal assessment of, and adherence to, correct inhaler technique. The treatment must be used as an adjunct to a maintenance combination of both ICS and LABA therapy. PBAC Comment: Recommended • exacerbation in the previous 12 months must have been severe • high dose budesonide should be defined as ≥ 800 µg/day rather than ≥ 1600 µg/day. • adding 'consider consultation with a specialist physician' was not necessary.	• Updated in line with PBAC suggestions
Requested price	• $62.73 DPMQ	• 5% price drop per 1 April 2016, as part of the PBS Access and Sustainability Package.
Main comparator	• Placebo plus ICS and LABA PBAC Comment: This was an appropriate comparator.	• Unchanged
Clinical evidence	• Key Trials 205.416 and 205.416, tiotropium plus ICS and LABA vs. placebo plus ICS and LABA, pooled N=912 PBAC Comment: No specific comment.	• Unchanged
Key effectiveness data	Meta-analysis 205.416 and 205.417 – adjusted mean difference between tiotropium and placebo: • trough FEV_1: [redacted] L (95% CI: [redacted]) • ACQ-7: -[redacted] (95% CI: -[redacted]) Pre-specified analysis 205.416 and 205.417 - HR time to first event • exacerbation (any severity): [redacted] (95% CI: [redacted]) • severe exacerbation: [redacted] (95% CI: [redacted]) • hospitalisation for asthma exacerbation: [redacted] (95% CI: [redacted]) PBAC Comment: The claim of superior comparative effectiveness was reasonable.	• No new evidence provided
Key safety data	Meta-analysis 205.416 and 205.417 - RR • any adverse events: [redacted] (95% CI: [redacted]) • respiratory, thoracic and mediastinal disorders: [redacted] ([redacted]) PBAC Comment: There was no difference in RR between tiotropium and placebo for adverse events that led to treatment discontinuation, or severe or serious adverse events.	• No new evidence provided

	Tiotropium (July 2015)	Current resubmission
Clinical claim	•Superior efficacy, non-inferior in safety compared to placebo PBAC Comment: Claim of superior efficacy and non-inferior safety was reasonable.	• Unchanged
Economic evaluation	•Cost-effectiveness analysis, 15 year time horizon. ICER: $15,000 - $45,000/QALY PBAC Comment: The economic evaluation was unreliable and there is a high degree of uncertainty towards the true cost of tiotropium, which might be higher due to: • Issues with transition probabilities in the model • Separation of control and exacerbation states might lead to double-counting in favour of tiotropium • Differences between outcome measures used in the trial and those used in the model	• Cost-effectiveness analysis, 15 year time horizon. ICER: $15,000 - $45,000/QALY
Number of patients	•10,000 – 50,000 in Year 1 increasing to 50,000 – 100,000 in Year 5. PBAC Comment: Uncertainty over eligible population size	• 10,000 – 50,000 in Year 1 increasing to 50,000 – 100,000 in Year 5
Estimated cost to PBS	•Less than $10 million in Year 1 increasing to $30 - $60 million n Year 5 for a total of more than $100 million over the first 5 years of listing. PBAC Comment: The submission's estimated cost to the PBS is uncertain and potentially higher or lower due to: • Differences between the compliant and responsive patients and compliant and non-responsive patients under usual care • A varied range of values in literature was used to determine the proportion of asthmatics with severe asthma, which might not be applicable in an Australian context • A significantly higher eligible population than calculated by the submission • Unclear market uptake for tiotropium • Use of tiotropium in asthma patients with COPD	• $20 - $30 million in Year 1 increasing to $30 - $40 million in Year 5 for a total of more than $100 million over the first 5 years of listing.
PBAC decision	• Reject on the basis that the economic model used was unreliable and that the true cost-effectiveness of tiotropium indicated in asthma management might be highly uncertain and high (July 2015, Public Summary Document, PARA 7.1)	

Source: *Compiled during the evaluation*

ACQ-7 = asthma control questionnaire 7-item version; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; PBAC = Pharmaceutical Benefits Advisory Committee; ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; PBS = Pharmaceutical Benefits Scheme; DPMQ = dispensed price for maximum quantity; HR = hazard ratio; CI = confidence interval; RR = relative risk; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

4 Clinical place for the proposed therapy

4.1 The proposed clinical treatment algorithm placed tiotropium as add-on therapy to ICS and LABA combination therapy for adult patients with uncontrolled asthma who have experienced at least one exacerbation in the previous year. The proposed management algorithm was consistent with the TGA indication.

5 Comparator

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

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from organisations (1) via the Consumer Comments facility on the PBS website. The comment from the National Asthma Council Australia highlighted concern about lack of treatment options for severe asthma and supported PBS listing of tiotropium for this indication.

Clinical trials

6.3 The clinical data were unchanged from the previous submission.

Benefits/harms

6.4 The following summary of benefits and harms for tiotropium versus placebo is reproduced from the PBAC's July 2015 consideration:

6.5 On the basis the head to head trial, the comparison of tiotropium and placebo resulted in:

- Approximately a 100 mL reduction in trough FEV_1 over a median duration of follow-up of exposure of 24 weeks. It was considered that a reduction of 100−140 mL is clinically significant in COPD, a change of 150 mL has been considered to be clinically meaningful in asthma (fluticasone furoate and vilanterol trifenatate Public Summary Document, March 2014).
- Approximately 56 days difference in time until at least 25% of patients experienced a severe exacerbation with a 48 week follow up.
- Approximately 134 days difference in time without an exacerbation (any severity) for 50% of the patients with a 48 week follow-up.

6.6 On the basis of direct comparison evidence presented by the submission, for every 100 patients treated with tiotropium in comparison to placebo with a 48 week follow-up:

- Approximately 13 fewer patients would have had an exacerbation (any severity)
- Approximately 8 fewer patients would have had a respiratory, thoracic or mediastinal disorder.

Clinical claim

6.7 The resubmission described tiotropium 5 µg combination therapy as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over placebo.

- The PBAC has previously accepted this claim as reasonable, based on improved mean forced expiratory volume in one second (FEV_1) and health-related quality of life measured by the asthma control questionnaire – 7-item version (ACQ-7) scores; and,
- The resubmission did not provide any additional clinical claims.

Economic analysis

6.8 Table 2 provides a summary of the model structure and rationale.

Table 2: Summary of model structure and rationale

Component	Summary
Cohort starting age	53 years, based on trials 205.416/205.417
Time horizon	15 years in the model base case versus 48 weeks in trials
Outcomes	Cost per exacerbation avoided, QALYs
Methods used to generate results	Markov model, cohort expected value analysis with univariate, deterministic and probabilistic sensitivity analyses
Health states	Three health states: • Optimal asthma control • Acceptable asthma control • Poor asthma control
Cycle length	2 initial 4-week cycles, 8-week cycles for the rest of the model
Transition probabilities	Trial-based transition probabilities

Source: Compiled during the evaluation
QALYs: quality-adjusted life years

Compared with the original submission, the resubmission used:

- Three health states instead of seven, with exacerbations incorporated within each health state;
- Cycle lengths that mirrored the frequency of visits in the trials, rather than weekly fixed cycle lengths; and
- EuroQoL 5-dimension 3-level instrument (EQ-5D-3L) utility values derived using Australian weights rather than UK weights.
- The resubmission indicated that tiotropium would have a 5% price reduction to the current approved ex-manufacturer price from 1 April 2016. The DPMQ used in the economic evaluation included the 5% price reduction.

6.9 Table 3 summarises the key drivers of the economic model.

Table 3: Key drivers of the model

Description	Method/Value	Impact
Asthma health state utilities	Taken from trial, derived from EQ-5D-3L (Australian weights) based on ACQ-7 cut-points. The use of the EQ-5D-3L might have been inappropriate.	Moderate, favours tiotropium
Transition probabilities	Transition probabilities might have been extrapolated inappropriately over the time horizon. Treatment effect for transition probabilities were assumed to be constant and sustained over the time horizon which is highly uncertain.	High, favours tiotropium

Source: Compiled during the evaluation
ACQ-7 = asthma control questionnaire 7-item version; EQ-5D-3L = EuroQoL 5-dimension 3-level instrument

6.10 Table 4 summarises the results of the stepped economic evaluation.

Table 4: Results of the stepped economic evaluation

Step and component	Tiotropium	Placebo (ICS + LABA)	Increment
Step 1: trial-based costs and outcomes			
Costs	$	$	$
Exacerbations			-
Severe exacerbations			-
Incremental cost/extra exacerbation avoided			$
Incremental cost/severe exacerbation avoided			$
Years free of exacerbation			
Incremental cost/patient year free of exacerbation			$
Step 2: trial results and premodelling (including health resource utilisation results)			
Costs	$	$	$
Exacerbations			-
Severe exacerbations			-
Incremental cost/extra exacerbation avoided			$
Incremental cost/severe exacerbation avoided			$
Years free of exacerbation			
Incremental cost/patient year free of exacerbation			$
Step 3: modelled evaluation (including utilities)			
Costs	$	$	$
Exacerbations			-
Severe exacerbations			-
Incremental cost/extra exacerbation avoided			$
Incremental cost/severe exacerbation avoided			$
Step 4: modelled evaluation (including utilities)			
Costs	$	$	$
QALY			
Incremental cost/extra QALY gained (Base-case)			$
Original submission ICER			
Costs	$	$	$
QALY			
Incremental cost/extra QALY gained			$

Source: Tables D-9 to D-12, pp270-273 of the resubmission; and Table D.5-4, p245 of the original submission
ICER = incremental cost-effectiveness ratio; ICS = inhaled corticosteroid; LABA = long-acting β_2 agonist; QALY = quality-adjusted life year

6.11 The economic evaluation resulted in an incremental cost-effectiveness ratio (ICER) of $15,000 - $45,000 per quality-adjusted life year (QALY) for tiotropium plus usual care versus usual care alone.

6.12 The approach taken to estimating and applying utility values in the resubmission may overestimate QALY gains:

- Cycle specific utility weights were applied, which favoured tiotropium over the extrapolated section of the model because the difference in utility weights between tiotropium and the comparator was greatest in weeks 40 to 48. The Pre-PBAC Response (p.2) argued that if there was no difference in utility weights assumed between tiotropium and usual care in all cycles to week 48 and the final 8-week treatment cycle utility weights are used to extrapolate beyond the trial period, the ICER increases marginally to $15,000/QALY - $45,000/QALY, and that this assumption has only a minor impact on the cost-effectiveness.
- The applied utility weights are higher than values reported in the literature, which may be due to known ceiling effects of the EQ-5D-3L (Australian weights) and lack of sensitivity to small changes in health state. The PSCR (p.3) argued that "As the target population are a group of difficult to treat patients with severe asthma who are at high risk of experiencing exacerbations, a potential ceiling effect is not expected to significantly affect the results compared with a population with milder disease." The issue is more likely to be that most patients completed the EQ-5D survey when not experiencing an exacerbation and the instrument is not sensitive enough to pick up the more minor effects of asthma. The Pre-PBAC Response (p.3) claimed that if patients were able to complete the survey while experiencing an exacerbation, it is expected that lower quality of life scores would have been obtained for these patients, and that the survey scores are likely to be biased in favour of the usual care arm as the negative impact of the exacerbations on quality of life is not likely to have been completely accounted for.

The submission presented various univariate analyses and a probabilistic sensitivity analysis on three variables only (compliance, extrapolation and time horizon), and additional sensitivity analyses were performed during evaluation. Table 5 presents the key sensitivity analyses.

Table 5: Key results of univariate sensitivity analyses

Univariate analyses	Δ costs	Δ QALY	ICER
Base case	$		$
Baseline distribution - trial based	$		$
Compliance - 100%	$		$
Extrapolation using Weeks 32-48	$		$
Time horizon - 48 weeks	$		$
Sensitivity analyses conducted during evaluation			
Time horizon - 5 years	$		$
Time horizon - 10 years	$		$
ITT analysis	$		$
Equivalent extrapolated treatment effect (intvn and control) -deterministic	$		$
Utilities: Gordois et al. (pooled) (2007) AQoL[a]	$		$
Utilities: mean utilities applied for optimal and acceptable control (pooled)	$		$

Source: Table D-13, p275 of the resubmission

AQoL = assessment of quality of life instrument, ITT = intention-to-treat; intvn = intervention; QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio

[a]AQoL values used: 0.86 for optimal control, 0.84 for acceptable control, 0.71 for uncontrolled asthma

The sensitivity analyses conducted by the submission resulted in an ICER range from less than $15,000 per QALY to $15,000/QALY - $45,000/QALY gained. Univariate analyses performed during the evaluation resulted in a higher ICER ranging from $15,000/QALY - $45,000/QALY to $45,000/QALY - $75,000/QALYgained varying time horizon, utility values and transition probabilities. The ESC noted that it would be informative to consider the combined effect of these issues.

6.13 The PSCR (p.3) argued that the 15 year time horizon used in the resubmission represents a highly conservative approach and that "as asthma is a chronic condition, with a patient cohort that has the condition for lifetime and patients are relatively young (average age in the trial is 53 years), a lifetime model might be considered the most appropriate representation of the disease course." The ESC considered that the concern with the 15 year time horizon related to extrapolation of the treatment effect from 48 week data.

Drug cost/patient/year:

6.14 Estimated $ per year continuing for the lifetime of the patient; assumed usage of 2 puffs once daily and a compliance rate of 100%.

Estimated PBS usage & financial implications

6.15 This resubmission was not considered by DUSC.

6.16 The resubmission used an epidemiological approach to forecast the uptake of tiotropium over a five-year period using data from the Australian Bureau of Statistics, the Australian Health Survey (2011-2012) and a review of the literature. The financial estimates were based on tiotropium being used in adult patients with severe uncontrolled asthma, who were also compliant with their prescribed medication. Table 6 presents the estimated use of tiotropium and associated financial implications from the resubmission. The original submission was considered by DUSC.

Table 6: Estimated use and financial implications presented in the resubmission

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate	25%	40%	50%	55%	60%
*Scripts**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/MBS					
Net cost to PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	-	-	-	-	-
Estimated total net cost					
Net cost PBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: *Compiled during the evaluation*

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme

* Assuming [redacted] scripts per year as estimated by the submission

The redacted table above shows that at year 5, the estimated number of patients would be 50,000 – 100,000 and the net cost to the PBS would be $30-$60 million.

6.17 Table 7 summarises sensitivity analyses conducted by the resubmission and additional sensitivity analyses conducted during the evaluation.

Table 7: Results of sensitivity analysis for overall net cost to PBS/RPBS over 5 years

Analysis	Net cost 5 years	Change from base case
Base case	$[redacted]	-
Tiotropium compliance 87.73%	$[redacted]	-$[redacted]
Severe asthma prevalence from literature – lower bound (8.5%)	$[redacted]	-$[redacted]
Severe asthma prevalence from literature – upper bound (23.0%)	$[redacted]	$[redacted]
Uncontrolled asthma prevalence from literature – lower bound (55.7%)	$[redacted]	-$[redacted]
Uncontrolled asthma prevalence from literature – upper bound (80.3%)	$[redacted]	$[redacted]
ICS+LABA compliance from literature – lower bound (50.0%)	$[redacted]	-$[redacted]
ICS+LABA compliance from literature – upper bound (64.2%)	$[redacted]	-$[redacted]
Additional sensitivity analyses during evaluation		
All uncontrolled severe asthma patients eligible for tiotropium treatment	$[redacted]	$[redacted]
Use of Reddel (2015) compliance, i.e. 19.7% of asthma patients uncontrolled while on ICS or ICS and a LABA with compliance ≥ 5 days per week, 75% of these treated with ICS and a LABA	$[redacted]	$[redacted]
Use of Reddel (2015) compliance, i.e. 19.7% of asthma patients uncontrolled while on ICS or ICS and a LABA with compliance ≥ 5 days per week, 50% of these treated with ICS and a LABA	$[redacted]	$[redacted]

Source: Table E.5-1, p296 of the resubmission; and calculated during the evaluation

ICS = inhaled corticosteroids; LABA = long-acting β2 agonist; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

6.18 Based on the sensitivity analyses conducted by the resubmission, the net financial implication to government health budgets remained under $[redacted] million in each of the first five years of listing. However, the additional sensitivity analyses conducted during the evaluation demonstrated that the cost for tiotropium might be significantly greater than that estimated by the resubmission. However, the ESC noted that it is likely that tiotropium is already used in some of the asthma population due to COPD comorbidity, and thus the financial estimates may be overestimated.

Quality Use of Medicines

6.19 The resubmission included proposals for Quality of Use of Medicine information, which was not included in the original submission. The inclusion of Quality of Use of Medicine information was appropriate, given that a large proportion of asthma patients might not be compliant to chronic asthma medication and the potential for tiotropium use outside of PBS restriction.

Financial Management – Risk Sharing Arrangements

6.20 The submission stated that the sponsor would be willing to enter into a Risk Sharing Arrangement to mitigate financial uncertainty to the Commonwealth. The Risk Sharing Arrangement proposal would include a rebate of [redacted]% of all Commonwealth expenditure for a given year if the expenditure exceeds Subsidisation Caps.

6.21 The PBAC considered that at the proposed price, a Risk Sharing Arrangement would be required to manage the high risk of use in patients with less severe asthma or in patients who are not taking their existing medication optimally, implemented in a way that can be effectively managed by the Department. The PBAC considered that the sensitivity analysis in the Commentary highlights the possible financial impact of use outside of the requested restriction. The Risk Sharing Arrangement would require a financial cap with a [redacted]% rebate as offered by the sponsor. The PBAC recommended that the cap be based on the resubmission financial estimates, modified to remove patients with co-morbid COPD (9.1% of all asthma patients), while maintaining the resubmission uptake rates and the compliance rate of [redacted]%.

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

7 PBAC Outcome

7.1 The PBAC recommended the Restricted Benefit listing of tiotropium as add-on therapy for the treatment of severe uncontrolled asthma. The PBAC was satisfied that tiotropium provides, for some patients, a significant improvement in efficacy over placebo.

7.2 The PBAC noted that the resubmission's proposed restriction was consistent with the PBAC's suggestions from the July 2015 meeting, specifying that tiotropium be used in combination with a maintenance combination of ICS and LABA and that high-dose budesonide was redefined as equal to or greater than 800 micrograms per day or equivalent.

7.3 The PBAC reiterated its view from July 2015 that there was a need for additional treatments for severe uncontrolled asthma.

7.4 As previously, the PBAC agreed that placebo plus ICS and LABA was the appropriate comparator.

7.5 The PBAC noted that the clinical evidence in the resubmission remained unchanged from July 2015.

7.6 As previously, the PBAC considered that the claim of superior comparative effectiveness and non-inferior comparative safety was reasonable.

7.7 The PBAC noted that the economic model had substantially changed from the previous submission as per the PBAC's July 2015 advice. Compared with the original submission, the resubmission presented a simpler model structure which used:

- Three health states instead of seven, with exacerbations incorporated within each health state;
- Cycle lengths that mirrored the frequency of visits in the trials, rather than weekly fixed cycle lengths; and
- EuroQoL 5-dimension 3-level instrument (EQ-5D-3L) utility values derived using Australian weights rather than UK weights.

The PBAC considered that overall, the revised model structure was reasonable. The PBAC noted that residual uncertainty remained around the extrapolation of the treatment effect from the 48 week data to the 15 year time horizon. However, the PBAC considered the base case ICER of $15,000/QALY - $45,000/QALY to be a reasonably reliable estimate of the cost-effectiveness.

7.8 The PBAC recalled its previous consideration of tiotropium for severe asthma in July 2015. The PBAC considered that as patients with co-morbid asthma and COPD are already eligible to receive tiotropium under the current Restricted Benefit PBS listing, these patients should be excluded from the financial estimate calculations. According to the Australian Institute of Health and Welfare (Asthma in Australia 2011[1]), 9.1% of all asthma patients have co-morbid COPD. This proportion is higher in older asthma patients, with 22.5% of asthma patients 65 years and over having comorbid COPD.

7.9 The PBAC recalled the DUSC Advice to the July 2015 meeting, which considered it inappropriate to apply a compliance rate to the estimate of eligible patients on 'optimal usual care', as optimal usual care implies that patients are compliant. The resubmission's base case economic model retained [redacted]% compliance, the weighted average compliance from the key clinical trials, but included a sensitivity analysis with 100% compliance. However, the resubmission applied 100% compliance in the financial estimates with a sensitivity analysis conducted using [redacted]% compliance. The PBAC considered that while patients are required to be uncontrolled on optimal therapy before qualifying for tiotropium, which implies compliance to ICS/LABA, the PBAC considered that this does not necessarily translate to 12.17 prescriptions per patient per year of tiotropium. It is unlikely a higher compliance would be achieved in practice in the community setting than in clinical trials where patients are closely monitored. Therefore, the PBAC considered that estimates of tiotropium use should be based on [redacted]% compliance ([redacted] prescriptions per patient per year).

7.10 The PBAC considered the uptake rates in the resubmission of 25% in Year 1 increasing to 60% in Year 5 were reasonable and should be maintained.

7.11 The PBAC considered that a Risk Sharing Arrangement would be required to manage the high risk of use in patients with less severe asthma or in patients who

[1] Australian Centre for Asthma Monitoring 2011. Asthma in Australia 2011. AIHW Asthma Series no. 4. Cat. no. ACM 22. Canberra: AIHW.

are not taking their existing medication optimally.

7.12 The PBAC advised that tiotropium is suitable for prescribing by nurse practitioners.

7.13 The PBAC recommended that the Early Supply Rule should apply.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

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

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Severe
Condition:	Asthma
PBS Indication:	Severe asthma
Treatment phase:	-
Restriction Level / Method:	☒Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must have experienced at least one severe exacerbation, which has required documented use of systemic corticosteroids, in the previous 12 months 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 and a long acting beta-2 agonist.
Prescriber Instructions	Optimised asthma therapy includes adherence to the maintenance combination of an inhaled corticosteroid (at least 800 micrograms budesonide per day or equivalent) and a long-acting β2 agonist.

Administrative Advice	Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.humanservices.gov.au or ww.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).

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.