

5.13 TIOTROPIUM BROMIDE PLUS OLODATEROL HYDROCHLORIDE

solution for inhalation, 2.5 µg plus 2.5 µg per puff, 60 actuations

Spiolto® Respimat®

Boehringer Ingelheim

1 Purpose of Application

- 1.1 The submission requested Authority Required (streamlined) listing for tiotropium plus olodaterol fixed dose combination (FDC) for treatment of chronic obstructive pulmonary disease (COPD).

2 Requested listing

- 2.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed for Max. Qty	Price	Proprietary Manufacturer	Name and
TIOTROPIUM + OLODATEROL Tiotropium 2.5 microgram/actuation + olodaterol 2.5 microgram/actuation inhalation: solution for, 60 actuations	1	5	\$96.38		Spiolto® Respimat®	Boehringer Ingelheim

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Chronic obstructive pulmonary disease (COPD)
PBS Indication:	Chronic obstructive pulmonary disease (COPD)
Restriction Level / Method:	<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
Clinical criteria:	Patient must have been stabilised on a combination of a long acting muscarinic antagonist and long acting beta-2 agonist.

Administrative Advice	<p>The treatment must not be used in combination with an ICS/LABA, or LAMA or LABA monotherapy.</p> <p>A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.</p> <p>A LABA includes indacaterol, salmeterol, eformoterol, <i>vilanterol</i> or <i>olodaterol</i>.</p> <p>This product is not PBS-subsidised for the treatment of asthma.</p> <p>This product is not indicated for the initiation of bronchodilator therapy in COPD.</p>
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- 2.2 The basis of listing is a cost-minimisation to two main comparators; glycopyrronium/indacaterol FDC and umeclidinium/vilanterol FDC.

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

3 Background

- 3.1 TGA status: The submission was made under TGA/PBAC Parallel Process. Tiotropium/olodaterol FDC was included on the Australian Register of Therapeutic Goods (ARTG) on 10 June 2015.
- 3.2 Since 2002, tiotropium (capsule, 18 µg) using the Handihaler has been listed on the PBS. The PBAC recommended listing of the tiotropium Respimat inhaler (inhalation solution, 5 µg) based on a cost-minimisation to the Handihaler in July 2009. Tiotropium 5 µg has not been listed on the PBS and the submission stated that it intends to have the product listed in October 2015, pending supply.
- 3.3 The submission acknowledged that olodaterol would not be listed as a monotherapy agent. The PBAC rejected olodaterol in July 2014. The PBAC considered that the proposed comparator, tiotropium, was inappropriate and the clinical evidence did not support the claim of non-inferiority between olodaterol and indacaterol.

4 Clinical place for the proposed therapy

- 4.1 The submission argued that the listing of tiotropium/olodaterol FDC would provide an alternative to other available long-acting muscarinic receptor antagonist (LAMA)/ long-acting selective β₂ agonist (LABA) FDC inhalers.

5 Comparator

- 5.1 The submission nominated the two following main comparators:
 1) glycopyrronium/indacaterol FDC
 2) umeclidinium/vilanterol FDC
- 5.2 The submission also nominated additional supportive comparators:
 3) tiotropium monotherapy or olodaterol monotherapy
 4) tiotropium plus olodaterol concurrently

5.3 The PBAC considered that these were the appropriate comparators.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on 13 randomised trials informing the four comparisons.

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

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Tiotropium/olodaterol vs. tiotropium trials		
TONADO 1 and TONADO 2	A randomised, double-blind, parallel group study to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 µg / 5 µg; 5 µg / 5 µg) (delivered by the Respimat® Inhaler) compared with the individual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat® Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD) [TONado™ 1]. Clinical trial report.	10 April 2014 NCT01431274
	A randomised, double-blind, parallel group study to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 µg / 5 µg; 5 µg / 5 µg) (delivered by the Respimat® Inhaler) compared with the individual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat® Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD) [TONado™ 2]. Clinical trial report.	10 April 2014 NCT01431287
	Combined analysis of efficacy data obtained in the twin studies 1237.5 and 1237.6 - Randomised, double-blind, parallel group studies to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 µg / 5 µg; 5 µg / 5 µg) (delivered by the Respimat® Inhaler) compared with the individual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat® Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD) [TONado™ 1 and TONado™ 2]. Clinical trial report.	9 April 2014
	Buhl R, Maltais F, Abrahams R et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4).	<i>Eur Resp J</i> 2015 Epub ahead of print doi:10.1183/09031936.00136014

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Trial ID	Protocol title/ Publication title	Publication citation
Glycopyrronium/indacaterol trials		
SHINE	Bateman ED, Ferguson GT, Barnes N <i>et al.</i> Dual bronchodilation with QVA149 versus single bronchodilator therapy: The SHINE study.	Eur Respir J 2013; 42 (6): 1484-1494 NCT01202188
SPARK	Wedzicha JA, Decramer M, Ficker JH <i>et al.</i> Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): A randomised, double-blind, parallel-group study.	Lancet Respir Med 2013; 1 (3): 199-209 NCT01285492^
ARISE	Asai K, Minakata Y, Hirata K <i>et al.</i> QVA149 once-daily is safe and well tolerated and improves lung function and health status in Japanese patients with COPD: The ARISE study. [Abstract] Frampton JE. QVA149 (indacaterol/glycopyrronium fixed-dose combination): A review of its use in patients with chronic obstructive pulmonary disease.	Eur Resp Soc Annual Congress, 2013. 42: 694s Drugs 2014; 74 (4): 465-488 NCT01285492
Umeclidinium/vilanterol FDC		
Decramer 1 and Decramer 2	Decramer M, Anzueto A, Kerwin E <i>et al.</i> Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: Results from two multicentre, blinded, randomised controlled trials.	Lancet Respir Med 2014; 2 (6): 472-486 NCT01316900
Tiotropium plus olodaterol vs. tiotropium		
ANHELTO 1 and ANHELTO 2	A randomised, double blind, parallel group study to assess the efficacy and safety of 12 weeks of once daily, orally inhaled, co-administration of olodaterol 5µg (delivered by the Respimat® Inhaler) and tiotropium 18µg (delivered by the HandiHaler®) compared to once daily, orally inhaled, co-administration of placebo (delivered by the Respimat® Inhaler) and tiotropium 18µg (delivered by the HandiHaler®) in patients with Chronic Obstructive Pulmonary Disease (COPD) [ANHELTO™1]. Clinical trial report A randomised, double blind, parallel group study to assess the efficacy and safety of 12 weeks of once daily, orally inhaled, co-administration of olodaterol 5µg (delivered by the Respimat® Inhaler) and tiotropium 18µg (delivered by the HandiHaler®) compared to once daily, orally inhaled, co-administration of placebo (delivered by the Respimat® Inhaler) and tiotropium 18µg (delivered by the HandiHaler®) in patients with Chronic Obstructive Pulmonary Disease (COPD) [ANHELTO™2] Clinical trial report ZuWallack R, Allen L, Hernandez G <i>et al.</i> Efficacy and safety of combining olodaterol Respimat® and tiotropium HandiHaler® patients with COPD: Results of two randomized, double-blind, active-controlled studies.	3 March 2014 NCT01694771 3 March 2014 NCT01696058 Int J Chron Obstruct Pulmon Dis 2014; (9): 1133-1144

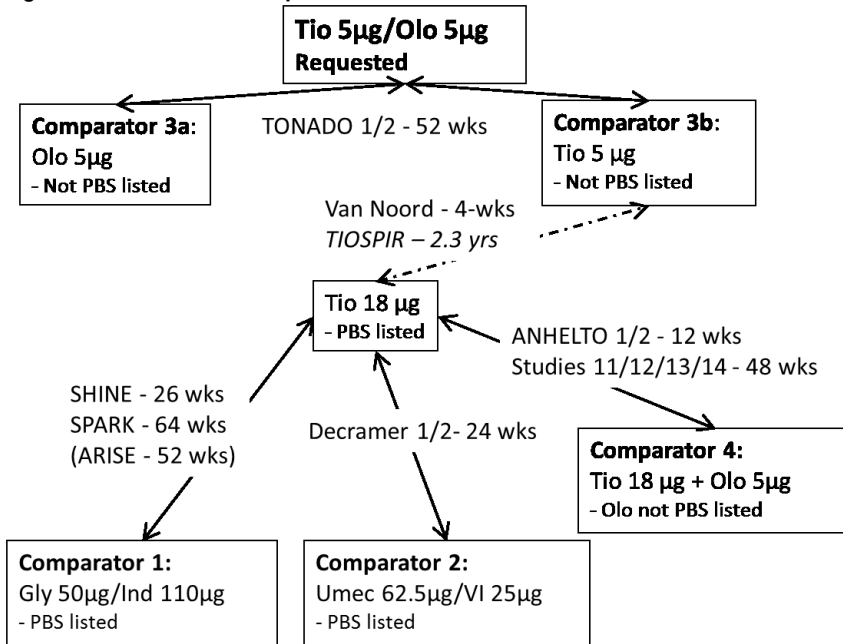
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Trial ID	Protocol title/ Publication title	Publication citation
Study 11 and Study 12	<p>Randomised, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of 48 weeks of once daily treatment of orally inhaled BI 1744 CL (5 µg [2 actuations of 2.5 µg] and 10 µg [2 actuations of 5 µg]) delivered by the Respimat® inhaler, in patients with Chronic Obstructive Pulmonary Disease (COPD). Clinical trial report</p> <p>Randomised, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of 48 weeks of once daily treatment of orally inhaled BI 1744 CL (5 µg [2 actuations of 2.5 µg] and 10 µg [2 actuations of 5 µg]) delivered by the Respimat® inhaler, in patients with Chronic Obstructive Pulmonary Disease (COPD). Clinical trial report</p> <p>Combined analysis of efficacy and safety data obtained in Studies 1222.11 and 1222.12 - Randomised, double-blind, placebo-controlled, parallel group studies to assess the efficacy and safety of 48 weeks of once daily treatment of orally inhaled BI 1744 CL (5 µg [2 actuations of 2.5 µg] and 10 µg [2 actuations of 5 µg]) delivered by the Respimat® inhaler, in patients with chronic obstructive pulmonary disease (COPD). Clinical trial report</p> <p>Ferguson GT, Feldman GJ, Hofbauer P <i>et al.</i> Efficacy and safety of olodaterol once daily delivered via Respimat® in patients with GOLD 2-4 COPD: Results from two replicate 48-week studies</p>	<p>28 December 2011 NCT00782210</p> <p>9 January 2012 NCT00782210</p> <p>9 January 2012</p> <p>Int J Chron Obstruct Pulmon Dis 2014; 9): 629-645</p>
Study 13 and Study 14	<p>A randomised, double-blind, double-dummy, placebo controlled, parallel group study to assess the efficacy and safety of 48 weeks of once daily treatment of orally inhaled BI 1744 CL (5 µg [2 actuations of 2.5 µg] and 10 µg [2 actuations of 5 µg]) delivered by the Respimat® Inhaler, and 48 weeks of twice daily Foradil® (12 µg) delivered by the Aerolizer® Inhaler, in patients with Chronic Obstructive Pulmonary Disease (COPD). Clinical trial report</p> <p>A randomised, double-blind, double-dummy, placebo-controlled, parallel group study to assess the efficacy and safety of 48 weeks of once daily treatment of orally inhaled BI 1744 CL (5 µg [2 actuations of 2.5 µg] and 10 µg [2 actuations of 5 µg]) delivered by the Respimat® Inhaler, and 48 weeks of twice daily Foradil® (12 µg) delivered by the Aerolizer® Inhaler, in patients with Chronic Obstructive Pulmonary Disease (COPD). Clinical trial report</p> <p>Combined analysis of studies 1222.13 and 1222.14: randomised, double-blind, double-dummy, placebo-controlled, parallel group studies to assess the efficacy and safety of 48 weeks of once daily treatment of orally inhaled BI 1744 CL (5 µg [2 actuations of 2.5 µg] and 10 µg [2 actuations of 5 µg]) delivered by the Respimat® Inhaler, and 48 weeks of twice daily Foradil® (12 µg) delivered by the Aerolizer® Inhaler, in patients with chronic obstructive pulmonary disease (COPD). Clinical trial report</p> <p>Koch A, Pizzichini E, Hamilton A <i>et al.</i> Lung function efficacy and symptomatic benefit of olodaterol once daily delivered via Respimat® versus placebo and formoterol twice daily in patients with GOLD 2-4 COPD: Results from two replicate 48-week studies.</p>	<p>27 January 2012 NCT00793624</p> <p>31 January 2012 NCT00796653</p> <p>2 March 2012</p> <p>Int J Chron Obstruct Pulmon Dis 2014; 9): 697-714</p>

Source:

6.5 The clinical evidence presented in the submission is presented diagrammatically in Figure 1.

Figure 1: Clinical evidence presented in the submission



Source: Constructed during evaluation

Tio = tiotropium; Olo = olodaterol; Gly = glycopyrronium; Ind = indacaterol; Umec = umeclidinium; VI = vilanterol; PBS = Pharmaceutical Benefits Scheme; wks = weeks

The ARISE trial was presented in brackets as the submission considered this trial as supplementary. All analyses were performed with and without the inclusion of this trial.

Dashed line indicates assumed non-inferiority by the submission

- 6.6 Comparisons 1, 2, and 4 were based on indirect comparisons while comparison 3 was based on a direct comparison. For the indirect comparisons, tiotropium was used as the common comparator. The submission acknowledged that the tiotropium form was different in the trials for tiotropium/olodaterol FDC and the trials for comparator 1, 2, and 4 (5 µg vs. 18 µg, respectively). The submission argued that the PBAC considered in July 2009 that tiotropium 5 µg (using Respimat) was non-inferior to tiotropium 18 µg (using Handihaler). This was based on a four-week crossover trial (Van Noord, 2009), comparing two doses of tiotropium using Respimat with one dose using Handihaler. During the evaluation, one long-term safety trial (TIOSPIR with a median follow-up of 2.3 years) was identified comparing tiotropium using the Respimat with Handihaler inhaler. This trial found no statistically significant differences in long-term safety, such as cardiovascular death, mortality and COPD exacerbations between the two tiotropium strengths.
- 6.7 The following table presents the key features of the included evidence.

Table 2: Key features of the included evidence – direct and indirect comparisons

Trial	N ^a	Design/ duration	Risk of bias	Patient population	Key outcomes
Comparator 1: Glycopyrronium/indacaterol FDC vs. tiotropium 18 µg					
SHINE	958 ^b	R, OL 26 wks	Unclear	Moderate to severe COPD, FEV ₁ <80%, ≥30%	Trough FEV ₁
SPARK	1,483 ^c	R, OL 64 wks	Unclear	Severe to very severe COPD, FEV ₁ <50%, ≥30%	Trough FEV ₁ exacerbations
ARISE	160 ^d	R, OL, 52 wks	Unclear	Moderate to severe COPD, FEV ₁ <80%,	Trough FEV ₁
Comparator 2: Umeclidinium/vilanterol FDC vs. tiotropium 18 µg					
Decramer 1	421 ^e	R, DB, 24 wks	Low	Moderate to severe COPD FEV ₁ <70%	Trough FEV ₁
Decramer 2	433 ^f	R, DB, 24 wks	Low		
Comparator 3: Tiotropium/olodaterol FDC vs. tiotropium 5 µg or olodaterol 5 µg					
TONADO 1	1,577 ^g	R, DB, 52 wks	Low	Moderate to severe COPD, FEV ₁ <80%,	Trough FEV ₁ exacerbations
TONADO 2	1,524 ^h	R, DB, 52 wks	Low		
Comparator 4: Tiotropium 18 µg plus olodaterol vs. tiotropium 18 µg					
ANHELTO 1	1,132	R, DB, 12 wks	Low	Moderate to severe COPD, FEV ₁ <80%, ≥30%	Trough FEV ₁
ANHELTO 2	1,135	R, DB, 12 wks	Low		
Study 11 ⁱ	96	R, DB, MC, 48 wks	Low	Moderate to severe COPD FEV ₁ <80%	Trough FEV ₁
Study 12 ⁱ	80	R, DB, MC, 48 wks	Low		
Study 13 ⁱ	117	R, DB, MC, 48 wks	Low		
Study 14 ⁱ	120	R, DB, MC, 48 wks	Low		

Source: compiled during the evaluation

DB = double blind; MC = multi-centre; OL = open-label; R = randomised; FDC = fixed dose combination; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in one second; wks = weeks; Gly = glycopyrronium; Ind = indacaterol; Tio = tiotropium; Umecl = umeclidinium; Vi = vilanterol

^a Intention to treat population, N includes only the trial arms relevant for the submission; ^b Gly/Ind = 475, Tio = 483; ^c Gly/Ind = 741, Tio = 742; ^d Gly/Ind = 121, Tio = 39; ^e Umecl/Vi = 212, Tio = 209; ^f Umecl/Vi = 218, Tio = 215; ^g Tio/Olo = 522, Tio = 527; Olo = 528; ^h Tio/Olo = 507; Tio = 507, Olo = 510; ⁱ Patients included in the tiotropium strata of the trial only.

Comparative effectiveness

- 6.8 Table 3 presents the trough forced expiratory volume in one second (FEV₁) at 24 weeks for the indirect comparisons and Table 4 presents the trough FEV₁ at 24 weeks for the direct comparison.

Table 3: The results of change from baseline in trough FEV₁ (L) at 24 weeks (indirect comparisons)

	Tio/Olo FDC vs. Tio			Comparator		Indirect MD (95% CI)
	MD (95% CI)	Tio/Olo Mean (SE)	Tio 5 µg Mean (SE)	Tio 18 µg Mean (SE)	Comp FDC Mean (SE)	
Comparison 1: vs. Gly/Ind FDC				Tio 18 µg	Gly/Ind FDC	
TONADO 1	0.07 (0.05, 0.09)	0.136 (0.008)	0.065 (0.008)			
TONADO 2	0.05 (0.02, 0.07)	0.145 (0.009)	0.096 (0.009)			
SHINE				1.37 (0.01) ^a	1.45 (0.01) ^a	0.08 (0.05, 0.10)
SPARK				1.00 (0.01) ^a	1.07 (0.01) ^a	0.07 (0.04, 0.10)
ARISE				0.115 (0.022)	0.198 (0.016)	0.08 (0.03, 0.14)
Meta-analysis	0.06 (0.04, 0.08) I ² =40%			-ARISE		
				+ARISE		
Comparison 2: vs. Umec/Vi FDC				Tio 18 µg	Umec/Vi FDC	
Decramer 1				0.121 (0.019)	0.211 (0.018)	0.09 (0.04, 0.14)
Decramer 2				0.149 (0.018)	0.208 (0.018)	0.06 (0.01, 0.11)
Meta-analysis						
Comparison 4: vs. Tio 18 µg + Olo 5 µg				Tio 18 µg	Tio + Olo	
Study 11/12				-0.002 (0.021)	0.050 (0.021)	
Study 13/14				-0.054 (0.020)	0.027 (0.019)	
Meta-analysis						

Source:

FDC = fixed dose combination; Tio = tiotropium; Olo = olodaterol; Gly = glycopyrronium; Ind = indacaterol; Umec = umecclidinium; Vi = vilanterol; MD = mean difference; SE = standard error; CI = confidence interval; FEV₁ = forced expiratory volume in one second; Comp = comparator

^a SPARK and SHINE only reported the absolute values not the change from baseline

- 6.9 The ESC noted that several of the trials included in the indirect comparison were assessed as having a low within-trial risk of bias. However, due to exchangeability issues when using these trials in an indirect comparison, there is a high risk of bias in the results of the indirect comparison.

Table 4: The results of change from baseline in trough FEV₁ at 24 weeks (direct comparison vs. tiotropium monotherapy and olodaterol monotherapy)

	Tio/Olo FDC	Tio 5 µg	Olo 5 µg	Tio/Olo vs Tio	Tio/Olo vs. Olo
	Mean (SE)	Mean (SE)	Mean (SE)	MD (95% CI)	MD (95% CI)
TONADO 1	0.136 (0.008)	0.065 (0.008)	0.054 (0.009)	0.071 (0.047, 0.094)	0.082 (0.059, 0.106)
TONADO 2	0.145 (0.009)	0.096 (0.009)	0.057 (0.009)	0.050 (0.024, 0.075)	0.088 (0.063, 0.113)
Meta-analysis				0.06 (0.04, 0.08) I ² = 40%	0.08 (0.07, 0.10) I ² = 0%

Source:

MD = mean difference; CI = confidence interval Tio = tiotropium; Olo = olodaterol; FDC = fixed dose combination; FEV₁ = forced expiratory volume in one second; SE = standard error

- 6.10 There were no statistically significant differences in trough FEV₁ at 24 weeks between tiotropium/olodaterol FDC and glycopyrronium/indacaterol FDC

(comparator 1), umeclidinium/vilanterol FDC (comparator 2) or tiotropium plus olodaterol taken concurrently (comparator 4). Tiotropium/olodaterol FDC was superior to its mono-components (comparator 3a and 3b). See the clinical claim section below for discussion on the clinical relevance.

- 6.11 Data on severe COPD exacerbations were available for comparisons 1 and 3, while data for any COPD exacerbations were available for comparison 2 and 3. The rates of severe COPD exacerbations were higher for tiotropium/olodaterol FDC compared with tiotropium monotherapy in the TONADO trials (5.9% vs. 4.5%, respectively). This difference was not statistically significant and the indirect comparison with glycopyrronium/indacaterol FDC also did not indicate statistically significant differences. This indirect comparison might be invalid, as the event rates in the common comparator arms (tiotropium) were different, with higher event rates in the glycopyrronium/indacaterol FDC trial.
- 6.12 No differences in all COPD exacerbations were observed between tiotropium/olodaterol FDC and tiotropium monotherapy, or olodaterol monotherapy (29.3%, 30.3%, and 33.6%, respectively). The indirect comparison for any COPD exacerbations for tiotropium/olodaterol FDC versus umeclidinium/vilanterol FDC, using tiotropium as common comparator might be invalid. The rates were measured at different points in time due to different trial durations, and the event rates were lower in the umeclidinium/vilanterol FDC trials for the tiotropium arm compared with the tiotropium/olodaterol FDC trials (5-7% vs. 30.3%, for Decramer 1/2 and TONADO 1/2 respectively).

Comparative harms

- 6.13 Tiotropium/olodaterol FDC did not result in higher rates of adverse events than tiotropium monotherapy or olodaterol monotherapy. Similar results were observed for glycopyrronium/indacaterol FDC versus tiotropium and umeclidinium/vilanterol FDC versus tiotropium. The submission performed indirect comparisons, which did not result in statistically significant differences for any of the comparisons. It was inappropriate to perform indirect comparisons for the adverse events, as the durations of the trials were different.

Clinical claim

- 6.14 The PSCR emphasised that the results of the indirect comparisons for the outcome of trough FEV₁ were the basis of the submission's clinical claim.
- 6.15 **Comparison 1: versus glycopyrronium/indacaterol FDC**
Comparison 2: versus umeclidinium/vilanterol FDC
Comparison 4: versus tiotropium plus olodaterol concurrently
The submission described tiotropium/olodaterol FDC as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over glycopyrronium/indacaterol FDC or umeclidinium/vilanterol FDC or tiotropium plus olodaterol concurrently.
- The durations of the trials were different, this might make the indirect comparisons for COPD exacerbation and safety results invalid.
 - The common comparator, tiotropium, was provided in two different doses in the tiotropium/olodaterol FDC trials and the comparators trials. While the data from

Van Noord (2009) and TIOSPIR suggest non-inferiority, there was uncertainty around the point estimate as the confidence intervals were not included in the indirect comparison, which might have underestimated the confidence intervals for the indirect comparisons. The PSCR provided the difference in trough FEV₁ from the Van Noord (2009) analysis between tiotropium 5 µg and 18 µg of 0.029 (95% CI 0.004, 0.055), and argued that the narrow confidence interval was unlikely to result in an underestimation of the confidence intervals for the indirect comparison presented in the submission.

- The efficacy and safety in the common comparator arms were not comparable, limiting the appropriateness of performing an indirect comparison.

6.16 **Comparison 3a: versus tiotropium monotherapy**
Comparison 3b: versus olodaterol monotherapy

The submission described tiotropium/olodaterol FDC as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over tiotropium monotherapy or olodaterol monotherapy. This claim might not be adequately supported.

- While the trough FEV₁ results were significantly better for tiotropium/olodaterol FDC compared with tiotropium (60 mL; 95% confidence interval (CI): 40 to 80 mL) or olodaterol (80 mL; 95% CI: 70 to 100 mL) monotherapy, it did not meet the minimum clinically important difference of 100 to 140 mL. The PSCR argued that applying the minimal clinically important difference (MCID) of 100 to 140 mL to the comparison of tiotropium/olodaterol FDC vs. tiotropium or olodaterol monotherapy is not appropriate, and that the MCID only applies to a claim of non-inferiority, not of superiority. The ESC noted that the MCID values for FEV₁ are anchored and associated with clinical outcomes, and thus seem reasonable to apply to the comparison of FDC with its components. However, the ESC noted discussion in the literature (Jones PW et al., 2014 (American Journal of Respiratory and Critical Care Medicine Vol 189, Iss 3, pp 250–255)) around the fact that mean incremental improvement with multiple therapies may not reach the MCID.
- No differences in severe COPD exacerbations were observed, with numerically higher rates in the tiotropium/olodaterol FDC arm. The PSCR stated that the TONADO trials were not designed to formally evaluate the effect on COPD exacerbations and that it was neither a primary nor secondary outcome of the trials.

Economic analysis

6.17 The submission presented a cost-minimisation analysis. The equi-effective doses were estimated as:

- tiotropium/olodaterol FDC 5 µg / 5 µg;
- glycopyrronium/indacaterol FDC 50 µg / 110 µg; and
- umeclidinium/vilanterol FDC 62.5 µg / 25 µg.

The equi-effective doses were based on the currently PBS listed doses, which were included in the clinical trials. This was considered reasonable.

6.18 The following table presents the cost-minimisation analysis. The submission proposed the same price for tiotropium/olodaterol FDC as for the main comparators glycopyrronium/indacaterol FDC and umeclidinium/vilanterol FDC. This was appropriate.

Table 5: Cost-minimisation analysis

Resource Item	Unit of measurement	Units per year	Cost per unit (DPMQ)	Source
Tio/Olo 5 µg / 5 µg	1 pack	12.17	\$96.38	Proposed
Gly/Ind 50 µg / 110 µg	1 pack	12.17	\$96.38	PBS item 10156M
Umecl/Vi 62.5 µg / 25 µg	1 pack	12.17	\$96.38	PBS item 10188F

Source:

Tio/Olo = tiotropium/olodaterol; Gly/Ind = glycopyrronium/indacaterol; Umecl/Vi = umeclidinium/vilanterol; DPMQ = dispensed price for maximum quantity; PBS = Pharmaceutical Benefits Scheme

Drug cost/patient/year: \$1,173.

6.19 The drug cost per patient per year would be \$1,173 if calculated as 12.17 × 30-day packs per year at a DPMQ of \$96.38. The treatment would be ongoing. The price would be the same as for other LAMA/LABA FDCs.

Estimated PBS usage & financial implications

6.20 This submission was not considered by the DUSC. The submission used a market share approach. First it estimated the future number of prescriptions in the 'World without FDC products', based on a 10% sample of the Department of Health Services data. Then the market share of FDC products was estimated. This was estimated separately as glycopyrronium/indacaterol FDC and umeclidinium/vilanterol FDC were listed in December 2014 and insufficient prescribing data was available. The submission assumed that tiotropium/olodaterol FDC would not change the market share of FDC products, rather it would replace listed FDC products (glycopyrronium/indacaterol FDC and umeclidinium/vilanterol FDC). The market shares were based on assumptions made by the submission.

Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Total FDC scripts					
Uptake Tio/Olo FDC	%	%	%	%	%
Scripts Tio/Olo FDC					
Estimated net cost to PBS/RPBS/MBS					
Net cost PBS/RPBS Tio/Olo FDC	\$	\$	\$	\$	\$
Reduction other FDCs	-\$	-\$	-\$	-\$	-\$
Net cost to MBS	\$0	\$0	\$0	\$0	\$0
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$0	\$0	\$0	\$0	\$0

Source:

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; FDC = fixed dose combination; Tio/Olo = tiotropium/olodaterol; MBS = Medicare Benefits Schedule

The redacted table above shows that in Year 5, the estimated number of tiotropium/olodaterol FDC scripts was over 200,000 and there would be zero net cost to the PBS/RPBS.

6.21 The submission's estimate of the number of prescriptions per year was based on future projections of current co-administration of LAMA with a LABA (± inhaled corticosteroids (ICS)), the expected uptake of LAMA/LABA FDCs and the uptake rate

of tiotropium/olodaterol FDC. Whether this would be an over or underestimate was unknown because:

- the uptake of LAMA/LABA FDC scripts was unclear;
- the uptake of tiotropium/olodaterol FDC was unclear; and
- the submission assumed that the listing of tiotropium/olodaterol FDC would not decrease the number of patients treated with monotherapy (i.e. LABA or LAMA or ICS or LABA/ICS) and therefore increase the number of patients treated with dual therapy for COPD.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of tiotropium/olodaterol FDC as an Authority required (STREAMLINED) benefit for the treatment of chronic obstructive pulmonary disease for patients already stabilised on concomitant LAMA and LABA therapy.
- 7.2 The PBAC recommended the listing on a cost-minimisation basis to the existing LAMA/LABA fixed dose combinations, umeclidinium/vilanterol and glycopyrronium/indacaterol. The equi-effective doses are considered to be tiotropium 5 microgram with olodaterol 5 microgram (two inhalations daily), umeclidinium 62.5 microgram with vilanterol 25 microgram (daily), and glycopyrronium 50 microgram with indacaterol 110 microgram (daily).
- 7.3 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonable. Noting that there was uncertainty due to the limited reliability of the indirect comparisons, the PBAC accepted that the evidence presented in the submission suggested that tiotropium/olodaterol FDC is similar in efficacy and safety to the nominated LAMA/LABA FDC comparators.
- 7.4 The PBAC considered that although the market for fixed dose combination products in COPD is growing, it was unlikely that the listing of tiotropium/olodaterol would result in any substantial additional market growth.
- 7.5 In accordance with subsection 101(3BA) of the *National Health Act* 1953, the PBAC advised that it is of the opinion that tiotropium/olodaterol should be treated as interchangeable on an individual patient basis with indacaterol/glycopyrronium and umeclidium/vilanterol.
- 7.6 In accordance with subsection 101(4AA) of the *National Health Act*, the PBAC advised that it was of the opinion that the Minister should determine a therapeutic group comprising of all LAMA/LABA fixed dose combinations including indacaterol/glycopyrronium, umeclidium/vilanterol, and tiotropium/olodaterol.
- 7.7 The PBAC advised that tiotropium/olodaterol is suitable for prescribing by nurse practitioners.
- 7.8 The PBAC recommended that the Safety Net 20 Day Rule should apply.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
TIOTROPIUM + OLODATEROL			Spiolto® RespiMat® Boehringer Ingelheim
Tiotropium 2.5 microgram/actuation	1	5	
+ olodaterol 2.5 microgram/actuation			
inhalation: solution for, 60 actuations			

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Chronic obstructive pulmonary disease (COPD)
PBS Indication:	Chronic obstructive pulmonary disease (COPD)
Restriction Level / Method:	<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
Clinical criteria:	Patient must have been stabilised on a combination of a long acting muscarinic antagonist and long acting beta-2 agonist.
Administrative Advice	The treatment must not be used in combination with an ICS/LABA, or LAMA or LABA monotherapy. A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium. A LABA includes indacaterol, salmeterol, eformoterol, vilanterol or olodaterol. This product is not PBS-subsidised for the treatment of asthma. This product is not indicated for the initiation of bronchodilator therapy in COPD.

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.