

5.11 OLODATEROL, 2.5 microgram/actuation inhalation: solution for, 60 actuations, Striverdi® Respimat® Boehringer Ingelheim Pty Ltd

1 Purpose of Application

- 1.1 The submission proposed the inclusion of olodaterol 5 microgram on the Pharmaceutical Benefits Scheme (PBS) as a restricted benefit item for treatment of chronic obstructive pulmonary disease (COPD).
- 1.2 Olodaterol 5 microgram is a once daily (2 puffs of 2.5 microgram) maintenance bronchodilator treatment.

2 Requested listing

- 2.1 The submission sought the following listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
OLODATEROL HYDROCHLORIDE Soft mist inhaler, 2.5µg per dose, 60 doses	1	5	\$73.65	Striverdi® Respimat® Boehringer Ingelheim

Restricted benefit: Chronic Obstructive Pulmonary Disease
NOTE: Olodaterol is not listed for the treatment of asthma

- 2.2 The pre-PBAC response proposed an alternative restriction with the clinical criteria: Patient must have a history of significant symptoms despite currently receiving regular long-acting muscarinic antagonist therapy.
- 2.3 Listing was sought on a cost-minimisation basis with olodaterol compared to tiotropium and indacaterol.

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

3 Background

- 3.1 Olodaterol was TGA registered on 20 November 2013 for once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease.
- 3.2 Olodaterol had not previously been considered by the PBAC.
- 3.3 Three monotherapies for COPD are currently listed; tiotropium (a long-acting muscarinic antagonists (LAMA)), indacaterol (a long-acting beta-2 agonist (LABA)) and glycopyrronium (LAMA).
- 3.4 Tiotropium capsules for oral inhalation have been listed on the PBS since 1 February 2003. Indacaterol has been listed on the PBS since 1 December 2011. Glycopyrronium was listed in April 2014 and the PBAC (March 2014) recommended aclidinium (a LAMA) for listing on the PBS.

4 Clinical place for the proposed therapy

- 4.1 The submission proposed that the PBS listing of olodaterol will provide an alternative long acting bronchodilator for the symptomatic relief of mild to severe COPD.

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

5 Comparator

- 5.1 The submission nominates four comparators. The two main comparators were:

- Olodaterol vs. tiotropium;
- Olodaterol + tiotropium vs. fluticasone/salmeterol + tiotropium;

The submission nominated two supplementary comparators.

- Olodaterol vs. indacaterol (150 microgram or 300 microgram);
- Olodaterol + tiotropium vs. indacaterol 150 microgram + tiotropium.

- 5.2 Indacaterol could be considered the main comparator as it is a pharmaceutical analogue and has the same restricted benefit as that proposed for olodaterol.

- 5.3 The ESC considered that indacaterol is the appropriate main comparator. This is consistent with the decision made by the PBAC in November 2010 in consideration of indacaterol when it was decided that replacement of tiotropium for indacaterol is only likely to occur in newly diagnosed patients and that indacaterol is more likely to be added to tiotropium rather than replace it, thus not being considered the most appropriate main comparator. The ESC disagreed with the Pre-Sub-Committee Response (PSCR, p1) that argued that tiotropium should be the principle comparator as it has the greatest potential to be replaced.

- 5.4 The PBAC noted the sponsor’s discussion about the comparator in the PSCR and in the pre-PBAC response. The PBAC agreed with the ESC that indacaterol 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 that no consumer comments were received for this item.

Clinical trials

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

Trial	Protocol title/ Publication title	Publication citation
Direct randomised trials		
1222.39	Boehringer Ingelheim Internal study report: Characterization of 24 Hour Spirometry Profiles of Inhaled BI 1744 CL and Inhaled Tiotropium Bromide in Patients Suffering From Chronic Obstructive Pulmonary Disease II	Date: May 2011 http://clinicaltrials.gov/ct2/show/NCT01040728

1222.40	Boehringer Ingelheim Internal study report: Characterization of 24 Hour Spirometry Profiles of Inhaled BI 1744 CL and Inhaled Tiotropium Bromide in Patients With Chronic Obstructive Pulmonary Disease	Date: May 2011 http://clinicaltrials.gov/ct2/show/NCT01040689
Trials for olodaterol vs placebo (with and without tiotropium)		
1222.11	Randomised, double-blind, placebo-controlled trial comparing Olodaterol 5 µg, 10 µg with placebo in patients with COPD over 48 weeks. Tiotropium was used as concomitant therapy in some patients.	Internal report. 2011
1222.12	Randomised, double-blind, placebo-controlled trial comparing Olodaterol 5 µg, 10 µg with placebo in patients with COPD over 48 weeks. Tiotropium was used as concomitant therapy in some patients.	Internal report. 2012
1222.13	Randomised, double-blind, double dummy, controlled trial comparing Olodaterol 5 µg, 10 µg, placebo and formoterol 12 µg in patients with COPD over 48 weeks. Tiotropium was used as concomitant therapy in some patients.	Internal report. 2012
1222.14	Randomised, double-blind, double dummy, controlled trial comparing Olodaterol 5 µg, 10 µg, placebo and formoterol 12 µg in patients with COPD over 48 weeks. Tiotropium was used as concomitant therapy in some patients.	Internal report. 2012
Trials for indacaterol		
Kinoshita 2012	Efficacy and safety of indacaterol 150 and 300 µg in chronic obstructive pulmonary disease patients from six Asian areas including Japan: A 12-week, placebo-controlled study. Assessing efficacy of indacaterol in moderate and severe COPD patients: a 12-week study in an Asian population.	Kinoshita, M., Lee, S. H., Hang, L. W., <i>et al.</i> 2012 <i>Respirology</i> ; 17 (2): 379-389 To Y, Kinoshita M, Lee SH, <i>et al.</i> 2012 <i>Respir Med.</i> Dec;106 (12):1715-21.
Dahl 2010	Efficacy of a new once-daily long-acting inhaled (beta)2-agonist indacaterol versus twice-daily formoterol in COPD.	Dahl, R., Chung, K. F., Buhl, R <i>et al.</i> 2010 <i>Thorax</i> ; 65 (6): 473-479
Feldman 2010	Efficacy and safety of indacaterol 150 (µg) once-daily in COPD: A double-blind, randomised, 12-week study.	Feldman, G., Siler, T., Prasad, N., <i>et al.</i> 2010. <i>BMC Pulmonary Medicine</i> ; 10
Kornmann 2011)	Once-daily indacaterol vs twice-daily salmeterol for COPD: a placebo controlled comparison.	Kornmann O, Dahl R, Centanni S, <i>et al.</i> 2011. <i>Eur Respir J</i> ; 37:273-279
Donohue 2010	Once-daily bronchodilators for chronic obstructive pulmonary disease: Indacaterol versus tiotropium. 2010	Donohue, J. F., Fogarty, C., Lotvall, J., <i>et al.</i> 2010. <i>American Journal of Respiratory and Critical Care Medicine</i> ; 182 (2): 155-162
NCT00792805	Efficacy and Safety of Indacaterol in Adults (40 Years and Above) With Chronic Obstructive Pulmonary Disease (COPD)	2011 http://clinicaltrials.gov/ct2/show/NCT00792805
Trial for fluticasone/salmeterol combination and tiotropium		
Cazzola et al 2007	A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD.	Cazzola, M., Ando, F., Santus, P., <i>et al.</i> 2007 <i>Pulmonary Pharmacology and Therapeutics</i> ; 20 (5): 556-561
Trials for indacaterol plus tiotropium		
INTRUST1	Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison.	Mahler DA, D'Urzo A, Bateman ED, <i>et al.</i> 2012 <i>Thorax.</i> Sep;67(9):781-8.
INTRUST2		

6.4 The PBAC considered the most informative evidence was the comparison of olodaterol to indacaterol based on an indirect comparison using six relevant

randomised clinical trials for indacaterol versus placebo and four relevant randomised clinical trials for olodaterol versus placebo.

Trial	N	Design/ duration	Risk of bias	Patient population	Primary Outcomes
Olodaterol vs placebo trials used in all indirect comparisons					
1222.11	417	R, DB, MC, (OL ± tiotropium); 48 weeks	Low	COPD	CT FEV ₁ @12 weeks; COPD worsening; Adverse events
1222.12	425	R, DB, MC, (OL ± tiotropium); 48 weeks	Low	COPD	
1222.13	455	R, DB, MC, (OL ± tiotropium); 48 weeks	Low	COPD	
1222.14	467	R, DB, MC, (OL ± tiotropium); 48 weeks	Low	COPD	
Indacaterol vs placebo					
Kinoshita 2012	347	R, DB, MC; 12 weeks	Low	Moderate - severe COPD	CT FEV ₁ @12 weeks COPD worsening Adverse events
Dahl 2010	869	R, DB, MC; 52 weeks	Low		
Feldman 2010	416	R, DB, MC; 12 weeks	Low		
Kornman 2011	665	R, DB, MC; 6 months	Low		
Donohue 2010	1250	R, DB, MC; 26 weeks	Low		
NCT00792805	561	R, DB, MC; 26 weeks	Low		

- 6.5 The submission presented two head-to-head, randomised, double-blind, double-dummy, placebo-controlled, 4-way cross-over trials comparing olodaterol to tiotropium. As the PBAC considered that tiotropium was not the most appropriate main comparator, the head-to-head trials presented in the submission comparing olodaterol to tiotropium were used as supportive evidence but were not the primary source of clinical data used in PBAC decision making.

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

Comparative effectiveness

- 6.6 A summary of comparative benefits for olodaterol versus indacaterol are shown below.

Benefits							
Results of change in trough FEV ₁ at 12 weeks across the indirect randomised trials of olodaterol compared to indacaterol [indirect comparison]							
Trial ID	Olodaterol 5 µg			Indacaterol			Indirect WMD (95% CI)
	WMD (95% CI)	OLO, N [mean (SE)]	PBO, N [mean (SE)]	PBO, N [mean (SE)]	IND, N [mean (SE)]	WMD (95% CI)	
1222.11							
1222.12							
1222.13							
1222.14							
Olodaterol (4 trials)							
Heterogeneity							
				Indacaterol 150 µg			
Donohue 2010				376 [1.30 (0.02)]	389 [1.46 (0.02)]	0.18 (0.14, 0.22)	
Feldman 2010				189 [1.40 (0.02)]	201 [1.48 (0.02)]	0.13 (0.08, 0.18)	
Kinoshita 2012				70 [1.17 (0.03)]	81 [1.34 (0.02)]	0.17 (0.10, 0.24)	
Kornmann 2011				316 [1.28 (0.02)]	320 [1.45 (0.02)]	0.17 (0.12, 0.22)	
NCT00792805				171 [1.17 (0.024)]	176 [1.32 (0.024)]	0.15 (0.08, 0.22)	
Indacaterol 150 µg (5 trials)				1122 [1.27 ±0.3 ^{SD}]	1167 [1.43 ±0.3 ^{SD}]	0.16 (0.14, 0.19)	
Heterogeneity				$I^2 = 0\%$, chi-square p-value = 0.637			
Olodaterol vs Indacaterol 150 µg							
				Indacaterol 300 µg			
Dahl 2010				371 [1.31 (0.01)]	389 [1.48 (0.01)]	0.180 (0.14, 0.22)	
Donohue 2010				376 [1.28 (0.02)]	389 [1.46 (0.02)]	0.130 (0.08, 0.18)	
Kinoshita 2012				70 [1.17 (0.03)]	79 [1.37 (0.02)]	0.17 (0.10, 0.24)	
NCT00792805				171 [1.17 (0.02)]	178 [1.29 (0.02)]	0.170 (0.12, 0.22)	
Indacaterol 300 µg (4 trials)				988 [1.26 ±0.28 ^{SD}]	1034 [1.43 ±0.27 ^{SD}]	0.17 (0.15, 0.2)	
Heterogeneity				$I^2 = 5.8\%$, chi-square p-value = 0.364			
Olodaterol vs Indacaterol 300 µg							

Source: Table B(i).6b.1 p25 of the commentary and Table B(ii).6-2 to Table B(ii).6-6 pp75-85 of Appendix 3 of the submission.

WMD = treatment effect weighted mean difference; CI = confidence interval; N = number in group; SE = standard error; ^{SD} = Standard deviation; PBO = placebo; IND = indacaterol; OLO = olodaterol; Bold = statistically significant; *italic* = performed during evaluation.

6.7 The meta-analysis for olodaterol vs placebo demonstrates that olodaterol provides an improvement of [redacted] more than placebo in trough FEV₁ at 12 weeks.

6.8 The meta-analysis for indacaterol 150 microgram vs placebo demonstrates that indacaterol 150 microgram provides an improvement of 160 mL more than placebo in trough FEV₁ at 12 weeks.

- 6.9 The meta-analysis for indacaterol 300 µg vs placebo demonstrates that indacaterol 300 microgram provides an improvement of 170 mL more than placebo in trough FEV1 at 12 weeks.
- 6.10 On the basis of indirect comparison evidence, the change in trough FEV1 would be approximately [REDACTED] less with olodaterol compared to indacaterol ([REDACTED] in indacaterol 300 microgram) over a maximum duration of follow-up and a maximum duration of exposure of 12 weeks. There should be no difference in trough FEV1 for a claim of non-inferiority to be made.
- 6.11 The PSCR (p1) argues that the indirect comparison of indacaterol and olodaterol is unreliable due to significant methodological issues and on this basis, reliable conclusions cannot be drawn. The ESC noted that the comparison was still informative despite differences between study populations.
- 6.12 The ESC agreed with the commentary that the results of the indirect comparison of olodaterol and indacaterol do not support non-inferiority.
- 6.13 On the basis of the head to head trials, olodaterol appears to have the same effect as tiotropium in the treatment of COPD using change in trough FEV1 after 6 weeks of treatment. However, the design of the study, four sets of six-week treatment periods, could not include comparison of changes in trough FEV1 at 12 weeks which is the accepted standard surrogate outcome of interest for long-acting bronchodilator treatment of COPD. The PSCR (p3) argues that reliance on trough FEV1 at 12 weeks as a surrogate outcome is too narrow and that other trial efficacy endpoints such as FEV1 AUC, change in use of rescue medications, the St George Respiratory Questionnaire and the transition dyspnoea index are also relevant measures of treatment effect. The ESC considered this is reasonable and could have been considered had the trial been designed to show the benefits of long-term treatment with a long-acting bronchodilator.
- 6.14 On the basis of the supplementary indirect comparisons presented, olodaterol + tiotropium appear to have non-inferior efficacy compared to fluticasone/salmeterol + tiotropium and indacaterol + tiotropium.

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

Comparative harms

- 6.15 A summary of comparative harms for olodaterol versus indacaterol are shown below.

Harms								
COPD progression: indirect comparison								
	Olodaterol	PBO	Indacaterol	RR (95% CI)	Event rate/100 patients/12 weeks			RD (95% CI)
					Olodaterol	PBO	Indacaterol	
Olodaterol (4 trials)	[REDACTED]	[REDACTED]	-	[REDACTED]	[REDACTED]	[REDACTED]	-	[REDACTED]
Indacaterol 150 µg (5 trials)		233/1,261	191/1258	0.83 (0.69; 0.98)	-	18	15	-0.03 (-0.06, 0.00)
Indirect comparison: Olodaterol vs. Indacaterol 150 µg				[REDACTED]	-			[REDACTED]
Indacaterol 300 µg (4 trials)		292/1153	262/1157	0.90 (0.78, 1.03)	-	25	23	-0.03 (-0.06, 0.01)
Indirect comparison: Olodaterol vs. Indacaterol 300 µg				[REDACTED]	-			[REDACTED]

Harms								
Any AEs: indirect comparison								
	Olodaterol	PBO	Indacaterol	RR (95% CI)	Event rate/100 patients/12 weeks			RD (95% CI)
					Olodaterol	PBO	Indacaterol	
Olodaterol (4 trials)	456/671	478/677	-		68	71	-	
Indacaterol 150 µg (5 trials)		649/1,261	656/1258	1.01 (0.91; 1.11)	-	51	52	0.01 (-0.03, 0.05)
Indirect comparison: Olodaterol vs. Indacaterol 150 µg					-			
Indacaterol 300 µg (4 trials)		664/1153	702/1157	1.03 (0.92, 1.16)	-	58	61	0.03 (-0.01, 0.07)
Indirect comparison: Olodaterol vs. Indacaterol 300 µg					-			

Source: Table 5, p6 of the ESC advice and Table B(ii).6-2 to Table B(ii).6-6 p75-85 of Appendix 3 of the submission.

WMD = treatment effect weighted mean difference; CI = confidence interval; *N* = number in group; SE = standard error; PBO = placebo; Bold = statistically significant; *italic* = performed during evaluation.

6.16 The ESC noted that there were no concerns raised by the number of relevant adverse events in the trials as they are similar to the baseline drugs.

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

Clinical claim

6.17 The submission claimed:

- Olodaterol is non-inferior to tiotropium;
- The comparison of olodaterol versus indacaterol as monotherapy was inconclusive;
- Olodaterol plus tiotropium is non-inferior to fluticasone/salmeterol plus tiotropium; and
- Olodaterol plus tiotropium is non-inferior to indacaterol plus tiotropium.

6.18 The commentary found that:

- Olodaterol does not show significant clinical superiority to placebo in respect of change in trough FEV₁ at 12 weeks.
- Olodaterol is non-inferior to tiotropium for trough FEV₁ at 6 weeks; no evidence was available for the clinical outcome of change in trough FEV₁ at 12 weeks.
- As monotherapy, olodaterol is inferior to indacaterol for efficacy outcomes using indirect comparisons.
- Olodaterol plus tiotropium is non-inferior to fluticasone/salmeterol plus tiotropium.
- Olodaterol plus tiotropium is non-inferior to indacaterol plus tiotropium.

6.19 The PBAC considered that the claim of non-inferior comparative effectiveness compared to indacaterol was not adequately supported by the data.

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

Economic analysis

- 6.21 The submission considers, based on doses included in the clinical trials, olodaterol 5 microgram is equivalent to:
- tiotropium 18 microgram
 - indacaterol (150 microgram or 300 microgram)
 - fluticasone 500 microgram + salmeterol 50 microgram (with concomitant tiotropium 18 microgram therapy)
 - indacaterol 150 microgram (with concomitant tiotropium 18 microgram therapy)
- 6.22 The ESC noted that on the basis of evidence provided in the indirect comparison, olodaterol 5 microgram may not be equivalent to indacaterol 150 microgram or 300 microgram.

Summary of cost minimisation

Drug	Dose	DPMQ	Difference
Monotherapy			
Olodaterol	5µg	\$73.65	-
Tiotropium	18µg	\$73.65	\$0
Indacaterol	150µg	\$73.65	\$0
	300µg	\$73.65	\$0
Combined with tiotropium 18µg		DPMQ of combination	
Olodaterol	5µg	\$147.30	\$0
Fluticasone/salmeterol	500 µg /50 µg BID	\$152.30	-\$5.00
	250 µg /25 µg BID	\$152.30	-\$5.00
Indacaterol	150µg	\$147.30	\$0
	300µg	\$147.30	\$0

Source: Table D(i).2.1 of the commentary and Table D.2-1 p 121 of the submission.

DPMQ = dispensed price maximum quantity;

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

Estimated PBS usage & financial implications

- 6.23 The submission was not considered by DUSC. The submission uses a market share approach to estimate utilisation and financial implications of olodaterol over a five-year time horizon. The submission’s estimates are presented in the table below. The estimated mono- and combination therapy packs supplied are in the range 100,000-200,000 in Year 1 and over 200,000 per year in the following years. The estimated financial implications of olodaterol are a saving of less than \$10 million per year.

	2014-2015	2015-2016	2016-2017	2017-2018	2018-2019
Estimated extent of use					
Market share	7%	17%	27%	32%	38%
Scripts	109,256	298,216	509,590	644,117	789,850
Estimated net cost to PBS/RPBS/MBS					
Net cost PBS/RPBS olodaterol	\$9,894,265	\$26,869,002	\$46,038,631	\$58,442,883	\$71,944,581
Net saving PBS/RPBS	-\$10,016,699	-\$27,253,226	-\$46,707,208	-\$59,279,021	-\$72,959,561
Net cost to R/PBS					
	-\$122,434	-\$384,224	-\$668,577	-\$836,138	-\$1,014,980

Source: Table E.3-1 p132 and Table E.4-1 to 4-3 pp135-136 of the Submission

- 6.24 The submission’s estimate of the cost of listing seems reasonable if the switching rates and the co-payments as proposed in the submission are accepted.
- 6.25 The market share is uncertain, and may be lower due to the recent PBS listing of glycopyrronium and recommendation for listing acclidinium for the same indication.

- 6.26 The submission states that there will be a cost saving of over five years if olodaterol is listed. However, the DPMQ for fluticasone/salmeterol in the submission is based on both the asthma and COPD listing. A lower cost for the use in COPD is more likely given that the listing of fluticasone/salmeterol has been considered by the PBAC as equivalent to tiotropium for COPD.

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

7 PBAC Outcome

- 7.1 The PBAC rejected the submission requesting PBS-listing for olodaterol for the treatment of COPD. The PBAC did not accept that tiotropium, as presented in the submission, was the appropriate comparator. The clinical evidence available does not support the claim that olodaterol is non-inferior to indacaterol in terms of clinical efficacy.
- 7.2 The PBAC noted that indacaterol was recommended on the basis of cost minimisation compared with fluticasone with salmeterol and tiotropium, but considered with the listing of indacaterol, tiotropium was no longer the appropriate comparator. The PBAC agreed with the ESC that indacaterol was the appropriate comparator, as it is in the same pharmacological class as olodaterol and that a LABA is most likely to be replaced by a LABA.
- 7.3 The PBAC noted that the requested restriction was consistent with that for indacaterol. The PBAC noted the proposed alternate restriction in the pre-PBAC response, but considered that this restriction was not appropriate in the context of treatment of COPD.
- 7.4 The PBAC relied upon clinical trial data from the indirect comparison of olodaterol to indacaterol, the most appropriate comparator. The PBAC rejected the claim of non-inferior comparative effectiveness of olodaterol compared to indacaterol, based on FEV₁, a surrogate outcome in COPD. The PBAC accepted the claim of non-inferior comparative safety of olodaterol compared to indacaterol.
- 7.5 The PBAC considered that patient relative outcomes, such as exacerbations and hospitalisation, may be more informative for assessing the comparative efficacy of inhaled agents used for patients with COPD, including olodaterol.
- 7.6 The PBAC noted the head-to-head comparison of olodaterol and tiotropium which appear to have the same effect after 6 weeks of treatment, and the indirect comparisons of olodaterol + tiotropium to fluticasone/salmeterol + tiotropium and olodaterol + tiotropium to indacaterol + tiotropium which appear to demonstrate non-inferiority. These comparisons were of less weight than the comparison to indacaterol.
- 7.7 The PBAC considered a cost-minimisation approach to be appropriate, however as non-inferiority between olodaterol and indacaterol was not demonstrated, the calculation of equi-effective doses was not informative.
- 7.8 The PBAC questioned whether there was a significant clinical need for another PBS-listed LABA monotherapy for COPD as indacaterol is currently PBS listed.
- 7.9 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.