

Re-Submission

olodaterol 2.5 microgram solution for inhalation (Striverdi[®] Respimat[®])
SMC No. (974/14)

Boehringer Ingelheim Ltd

05 December 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a re-submission

olodaterol (Striverdi[®] Respimat[®]) is accepted for use within NHS Scotland.

Indication under review: maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease.

In two 48-week studies there was no significant difference between olodaterol 5 microgram and another long acting beta₂ agonist for the primary endpoints of trough forced expiratory volume in 1 second (FEV₁) and FEV₁ area under curve (0 to 3 hours) at week 24.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease.

Dosing Information

Olodaterol 5 microgram given as two (2.5 microgram) puffs from the Respimat[®] inhaler once daily, at the same time of the day.

Product availability date

9 June 2014

Summary of evidence on comparative efficacy

Olodaterol is a once daily long acting beta₂ agonist (LABA), where the dose is delivered by the Respimat[®] inhaler.¹ It is the second once daily inhaled LABA licensed for the treatment of chronic obstructive pulmonary disease (COPD).

Four randomised, double-blind, placebo-controlled, parallel group studies (1222.11, 1222.12, 1222.13 and 1222.14) have been conducted in patients aged ≥40 years with COPD who had relatively stable airway obstruction with a post-bronchodilator forced expiratory volume in 1 second (FEV₁) <80% of predicted normal and a post-bronchodilator FEV₁/forced vital capacity (FVC) <70% predicted at the screening visit.^{1,2,3,4} Patients were required to be current or ex-smokers (>10 pack years). Following a two-week run-in period, patients were randomised (stratified by tiotropium use) to 48 weeks treatment with olodaterol (5 micrograms [2 actuations of 2.5 micrograms] once daily, olodaterol 10 micrograms [2 actuations of 5 micrograms] once daily (both via the Respimat[®] inhaler), placebo or, in studies 1222.13/14 only, formoterol 12 micrograms twice daily (via the Aerolizer[®] inhaler). Background therapy with short-acting beta₂-agonists (SABA), inhaled corticosteroids (ICS), oral corticosteroids, long-acting muscarinic antagonists (LAMA), and methylxanthines were permitted in all treatment groups. Efficacy results for the licensed dose of olodaterol (5 micrograms daily) only are reported in this document.

The co-primary endpoints were change from baseline in trough FEV₁ and FEV₁ area under curve (AUC) (0 to 3 hours) at week 12 (studies 1222.11/12) and week 24 (studies 1222.13/14). Trough FEV₁ was defined as the mean of the FEV₁ obtained at 1 hour prior to daily medication and 10 minutes prior to daily study medication. FEV₁ AUC (0 to 3 hours) was defined as AUC from 0 to 3 hours post-dose using the trapezoid rule, divided by the time duration. Additionally, studies 1222.13/14 included the Mahler transition dyspnoea index (TDI) focal score as a co-primary endpoint. The TDI is a validated instrument that measures the impact of dyspnoea on three domains: functional impairment, magnitude of task and magnitude of effort. Results for the pre-specified analyses of FEV₁ and FEV₁ AUC (0 to 3 hours) are presented in Table 1.

Table 1: Pre-specified analysis of primary endpoints (trough FEV₁ and FEV₁ AUC [0 to 3 hours]) for studies 1222.11, 1222.12, 1222.13 and 1222.14 (olodaterol 5 microgram)

	Trough FEV ₁			FEV ₁ AUC (0 to 3 hours)		
	Change from baseline (SE);	Difference; olodaterol versus placebo	Difference; formoterol versus placebo	Change from baseline	Difference; olodaterol versus placebo	Difference; formoterol versus placebo
Study 1222.11; week 12						
Olodaterol (n=208)	0.052L (SE 0.016)	0.084L (SE 0.023), p=0.0002	-	0.167L (SE 0.016)	0.164L (SE 0.023), p<0.0001	-
Placebo (n=209)	-0.032L (SE 0.016).	-	-	0.002L (SE 0.016)	-	-
Study 1222.12; week 12						
Olodaterol (n=209)	0.038L (SE 0.017)	0.033L (SE 0.024), p=0.1624	-	0.155L (SE 0.016)	0.134L (SE 0.022), p<0.0001	-
Placebo (n=216)	0.005L (SE 0.017)	-	-	0.021L (SE 0.016)	-	-
Study 1222.13; week 24						
Olodaterol (n=227)	0.021L (SE 0.015)	0.078L (SE 0.021), p=0.0002	-	0.142L (SE 0.015)	0.151L (SE 0.021), p<0.0001	-
Placebo (n=225)	-0.056L (SE 0.015)	-	-	-0.009L (SE 0.016)	-	-
Formoterol (n=227)	-0.002L (SE 0.015)	-	0.054L (SE 0.021), p=0.0088	0.168L (SE 0.015)	-	0.177L (SE 0.021), p<0.0001
Study 1222.14; week 24						
Olodaterol (n=232)	-0.003L (SE 0.014)	0.053L (SE 0.019), p=0.0055	-	0.116L (SE 0.014)	0.129L (SE 0.019), p<0.0001	-
Placebo (n=235)	-0.055L (SE 0.014)	-	-	-0.013L (SE 0.014)	-	-
Formoterol (n=233)	-0.13L (SE 0.014)	-	0.042L (SE 0.019), p=0.027	0.137L (SE 0.014)	-	0.150L (SE 0.019), p<0.0001

FEV₁; forced expiratory volume in 1 second, L=litre, SE=standard error, AUC=area under curve.

Amended analyses were conducted for the co-primary endpoints in studies 1222.11/12 following database lock and unblinding which involved removal of the treatment-by-tiotropium stratum interaction terms. The treatment effect of olodaterol was of a higher magnitude in these new analyses and all comparisons of olodaterol 5 microgram versus placebo for the co-primary endpoints were statistically significant.

In a pre-specified pooled analysis of studies 1222.13/14 for the co-primary endpoint of Mahler TDI at 24 weeks, the mean difference from placebo was 0.3 (p=0.17) for olodaterol 5 micrograms and 0.2 (p=0.37) for formoterol. However, in a post-hoc analysis that accounted for patient discontinuations, the difference between olodaterol 5 micrograms and placebo was statistically, although not clinically, significant (0.5, p=0.03).¹

In studies 1222.13/14, key secondary endpoints were analysed in a hierarchical manner to protect against type 1 error, unlike in studies 1222.11/12 where analysis was descriptive only. There were no statistically significant differences between olodaterol 5 microgram versus formoterol at week 24 for FEV₁ AUC (0 to 3 hours) (difference -0.026L in study 1222.13 and -0.021L in study 1222.14), and trough FEV₁ (difference 0.023L in study 1222.13 and 0.011L in study 1222.14).² In all studies, the lung function improvements were generally shown in both tiotropium users and non-tiotropium users, and the bronchodilator effects of olodaterol were maintained throughout the 48 week treatment period.

Non-spirometric secondary endpoints included exacerbations and use of rescue medication. In all studies, there were no statistically significant differences between olodaterol and placebo groups for time to first COPD exacerbation, moderate COPD exacerbation, and first COPD exacerbation leading to hospitalisation. In studies 1222.11 and 1222.14, there was a trend towards fewer exacerbations (any and moderate) for olodaterol versus placebo. In studies 1222.11/12 and 1222.13, daily rescue medication use (measured weekly) over the 48 week treatment period was significantly less (and numerically less for study 1222.14) for olodaterol 5 micrograms compared with placebo. St George's Respiratory Questionnaire (SGRQ) total score after 24 weeks treatment was a secondary endpoint in studies 1222.13/14 (minimal clinically important difference is -4.0). In pooled analysis, the mean change from baseline in SGRQ total score was -5.6 for olodaterol 5 micrograms, -4.0 for formoterol and -2.8 for placebo; difference versus placebo was -2.8 (p=0.0034) for olodaterol 5 micrograms (so did not reach the minimal clinically important difference of -4.0) and -1.2 (p=0.20) for formoterol).

Additional efficacy data come from six phase III randomised, double-blind, 6-week cross-over studies (1222.24/25, 1222.37/38 and 1222.39/40) conducted in similar patient populations as the studies described previously.^{1,2} All studies included olodaterol 5 microgram, olodaterol 10 microgram and placebo arms and, in addition, studies 1222.24/25 included formoterol 12 micrograms twice daily and studies 1222.39/40 included tiotropium 18 microgram once daily as comparator arms. Concomitant pulmonary medications were permitted except for other LABA in all studies and, in addition, LAMA in studies 1222.39/40 and 1222.37/38. In studies 1222.24/25 and 1222.39/40, olodaterol was significantly superior to placebo for FEV₁ AUC (0 to 3 hours) and for mean trough FEV₁ response. Improvements in lung function were comparable to twice daily formoterol (studies 1222.24/25) and once daily tiotropium (1222.39/40). Studies 1222.37/38 assessed exercise endurance time during constant work rate cycle ergometry. Following six weeks treatment, the exercise endurance time for olodaterol 5 microgram was greater than placebo by approximately 1 minute in study 1222.37 and 40 seconds in study 1222.38.

Summary of evidence on comparative safety

Safety data were presented from a pooled analysis of the 48-week studies. Common (≥4%) treatment emergent adverse events (AE) in the olodaterol 5 microgram, formoterol and placebo groups included: nasopharyngitis (11%, 10%, 7.7%), upper respiratory tract infection (8.2%, 7.0%, 7.5%), bronchitis (4.7%, 2.8%, 3.6%), COPD (26%, 29%, 29%), cough (4.2%, 5.9%, 4.0%) and dyspnoea (4.0%, 5.4%, 4.2%).

On-treatment deaths occurred in 13, 10 and 13 patients in the olodaterol 5 microgram, formoterol and placebo groups respectively. There was an imbalance in deaths due to COPD exacerbation across treatment arms (9, 3 and 4 patients in the olodaterol 5 microgram, formoterol, and placebo groups respectively) although these may not solely be explained by olodaterol exposure. The proportion of on-treatment serious AE (SAE) was balanced across treatment groups; 16%, 15% and 16% in the olodaterol 5 microgram, formoterol and placebo groups respectively. Overall, across all treatment groups, the most common on-treatment SAE were COPD exacerbation (5.8%) and pneumonia (1.8%) and these occurred in 4.7% and 1.6% of patients on olodaterol 5 microgram (versus 5.9% and 1.5% of patients on formoterol).

Other data were also assessed but remain commercially confidential.*

Summary of clinical effectiveness issues

Olodaterol is the second once daily LABA licensed for the treatment of COPD. Indacaterol (Onbrez[®] Breezhaler[®]) has been accepted by SMC for the maintenance bronchodilator treatment of airflow obstruction in adult patients with COPD. Relevant comparators also include other LABAs, (formoterol and salmeterol, administered twice daily). LAMA therapy is also a treatment option for the indication under review although LABAs are considered to be more relevant comparators. National Institute for Health and Care Excellence (NICE) guidance recommends the use of LABA monotherapy as a treatment option for patients with stable COPD who have FEV₁ \geq 50% predicted and who remain breathless or have exacerbations despite use of SABAs as required. In more severe COPD, inhaled corticosteroids, LAMA or both can be added to LABA therapy. When an inhaled corticosteroid is added to a LABA, a combination inhaler is recommended.⁵

In the pivotal studies, olodaterol was significantly superior to placebo for the primary endpoints of FEV₁ AUC (0 to 3 hours) and for trough FEV₁ (except for study 1222.12), and the effect was maintained up to week 48. However, there were no significant differences between olodaterol and placebo in terms of the secondary endpoint of time to exacerbation (first, moderate or first leading to hospitalisation).

In studies 1222.13/14, there were no statistically significant differences in the co-primary endpoints between olodaterol 5 microgram and formoterol at week 24. Furthermore, results of four six-week cross-over studies showed that improvements in lung function for olodaterol were comparable to formoterol.

The trough FEV₁ response difference from placebo for olodaterol was relatively small compared with study data for other bronchodilators.² This may be explained by the concomitant pulmonary medications permitted for all patients in the olodaterol studies. It is not clear that the study population received treatment that would correspond to NICE recommendations. The evidence for the use of olodaterol as monotherapy (which is the most likely use according to NICE guidance) is all from subgroup analysis. NICE guidance does note the use of LAMA in addition to LABA in situations where an ICS is declined or not tolerated; lung function improvements for olodaterol versus placebo were generally shown in the tiotropium users strata from the pivotal studies. In studies 1222.11/12, alterations were made to the statistical analysis plan following database lock and unblinding. The treatment effect of olodaterol compared with placebo was of lesser magnitude in the pre-specified analysis compared to the amended analysis.

There are no studies comparing olodaterol with indacaterol or salmeterol. Therefore, indirect comparisons were presented by the company for olodaterol versus indacaterol and versus salmeterol.

Indirect comparisons of varying methodology were used to compare olodaterol with indacaterol. The patient population included adults with stable COPD. Six outcomes were analysed: FEV₁, TDI, SGRQ total score, SGRQ responders, rescue medication and percentage of patients with exacerbations. The data used for the FEV₁ outcome are limited; for the LAMA add-on analysis, data for olodaterol were from the stratified sub-groups who received tiotropium, and in the LAMA-free analysis, the data for olodaterol came from two 6-week cross-over studies (compared to 12-week parallel group studies for indacaterol). Other limitations include that the search was conducted up to July 2011, so excluded any later publications. Also, there was heterogeneity in concomitant bronchodilator use across studies. Overall, the relevance and credibility of the analyses are considered insufficient.

For the comparison of olodaterol with salmeterol, a Bucher type indirect comparison was conducted with placebo as the common comparator. The patient population was adults with stable COPD. The outcomes (assessed at weeks 24/26) were trough FEV₁, SGRQ total score and proportion of patients with at least one adverse event. The results showed no significant difference between olodaterol and salmeterol in trough FEV₁ at six months or in the relative risk of experiencing an adverse event, and a significant difference in SGRQ total score in favour of olodaterol for the LAMA free population only. There were differences in COPD severity at baseline and there was considerable variation among the studies in the use of concomitant ICS; however, sensitivity analyses indicated that there was no clinically significant difference between olodaterol and salmeterol for either parameter.

Clinical experts consulted by SMC considered that the place in therapy of olodaterol would be as an option when a once daily LABA is required. Olodaterol also would provide an alternative inhaler device. There have been no head-to-head studies between olodaterol and other LABA to investigate differences in acceptability to the patient of the various inhaler devices.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis over a one year time horizon comparing olodaterol to indacaterol and salmeterol as maintenance bronchodilator treatment in patients with COPD. A weighted average comparison was also provided which included indacaterol, salmeterol and formoterol. The company has positioned olodaterol for use in moderate symptomatic COPD in place of once or twice daily LABA treatment.

The clinical data to support comparable efficacy were taken from two sources: the pooled analysis of direct head to head studies 1222.13/14 and an indirect comparison. The pooled studies, used to inform the comparative efficacy assumption for the formoterol component of the weighted average comparison, examined a number of primary endpoints including FEV₁ AUC (0 to 3 hours) response, trough FEV₁ response and TDI. Results of the analysis indicated comparable efficacy and safety versus formoterol for all primary endpoints. The indirect comparison, which compared olodaterol to salmeterol, indicated comparable efficacy between the two treatments, resulting in a non significant difference for the outcome FEV₁. It should be noted that the economic analysis is dependent on the assumption of comparable efficacy.

Only drug acquisition costs were included in the analysis. As treatments were assumed to incur the same administration costs, resource use estimates were not included. For the weighted average comparison, costs were estimated based on prescription data for the three LABAs (78%, 8%, and 14% for salmeterol, indacaterol and formoterol respectively). The proportion of prescriptions was multiplied by the cost of each LABA and summed in order to determine the weighted average cost of treatment.

The results indicate that olodaterol is cost saving versus salmeterol, resulting in savings of £35.41 per year or £0.10 per day. For the comparison versus indacaterol, olodaterol also resulted in annual savings of £35.41 per year or £0.10 per day. Based on the weighted average comparison the company estimated olodaterol would result in savings of £6.69 per year or £0.02 per day.

A number of weaknesses were noted:

- There are no direct trial data comparing olodaterol to salmeterol so the assumption of comparable efficacy between the treatments is based on the results of an indirect comparison. The results demonstrated no statistically significant differences between olodaterol and salmeterol for the outcome FEV₁.
- The company has not provided an economic analysis versus formoterol alone. As the acquisition cost of formoterol is less than olodaterol (monthly cost of £12.40 versus £26.35 respectively), olodaterol results in an incremental cost of £169.73 per year. However, as salmeterol is considered to be the most appropriate comparator the omission of this comparison is not considered to be a primary concern.

Despite these weaknesses, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published an update to clinical guideline 101; Management of chronic obstructive pulmonary disease in adults in primary and secondary care, in June 2010.⁵ The guideline includes the following recommendations:

- In people with stable COPD who remain breathless or have exacerbations despite use of SABAs as required, offer the following as maintenance therapy:
 - if FEV₁ ≥ 50% predicted: either LABA or LAMA
 - if FEV₁ <50% predicted: either LABA with an ICS in a combination inhaler, or LAMA.
- In people with stable COPD and an FEV₁ ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA:
 - consider LABA+ICS in a combination inhaler
 - consider LAMA in addition to LABA where ICS is declined or not tolerated.
- Offer LAMA in addition to LABA+ICS to people with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV₁.
- Consider LABA+ICS in a combination inhaler in addition to LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with LAMA irrespective of their FEV₁

The following points are also included:

- Choose a drug based on the person's symptomatic response and preference, the drug's side effects, potential to reduce exacerbations and cost.
- Do not use oral corticosteroid reversibility tests to identify patients who will benefit from inhaled corticosteroids.
- Be aware of the potential risk of developing side effects (including non-fatal pneumonia) in people with COPD treated with inhaled corticosteroids and be prepared to discuss this with patients.

The Global initiative for chronic Obstructive Lung Disease (GOLD) updated their global strategy for diagnosis management and prevention of chronic obstructive pulmonary disease in January 2014.⁸ In terms of pharmacological treatment, four patient groups are identified and treatments for these include;

- Group A: In patients with few symptoms and a low risk of exacerbations the use of a short acting bronchodilator when required is recommended as first choice. Alternative choices are a combination of short acting bronchodilators or use of a long acting bronchodilator.
- Group B: In patients with more significant symptoms but at a low risk of exacerbations the use of long acting bronchodilators is recommended with no class recommended over another for initial treatment. In patients with severe breathlessness the use of a combination of long acting bronchodilators is an option.
- Group C: In patients with few symptoms but a high risk of exacerbations a fixed combination of ICS plus LABA or a LAMA is recommended as first choice. Alternative choices are use of two long acting bronchodilators or ICS plus LAMA.
- Group D: In patients with many symptoms and a high risk of exacerbations the first choice is ICS plus LABA or a LAMA. A second choice is ICS plus LABA plus LAMA.

Additional information: comparators

Other LABA : indacaterol, salmeterol and formoterol

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Olodaterol	5 micrograms once daily	320
Indacaterol	150 to 300 micrograms once daily	355
Salmeterol	50 micrograms twice daily	355
Formoterol*	12 micrograms twice daily	144

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from eVadis and MIMS on 1 October 2014. Cost of olodaterol is from the company's submission.* There is some dose variation among different formulations of formoterol.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 106,650 in year 1, rising to 112,310 in year 5. The submitting company's estimates of treatment uptake, gross and net medicines budget impact were stated to be confidential.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission.

1. Boehringer Ingelheim. Summary of product characteristics for olodaterol (Striverdi[®] Respimat[®]).
2. United States Food and Drug Administration briefing package for the Pulmonary-allergy drugs advisory committee meeting. NDA 203108: olodaterol (proposed trade name Striverdi Respimat) for the proposed indication of long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. 29 January 2013.
3. Ferguson GT, Feldman GJ, Hofbauer et al. Efficacy and safety of olodaterol once daily delivered via Respimat(R) in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. *Int J Chron Obstruct Pulmon Dis* 2014;9:629-45.
4. Koch A, Pizzichini E, Hamilton A et al. Lung function efficacy and symptomatic benefit of olodaterol once daily delivered via Respimat(R) versus placebo and formoterol twice daily in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. *Int J Chron Obstruct Pulmon Dis* 2014;9:697-714.
5. National Institute for Health and Care Excellence. Clinical guideline 101; Management of chronic obstructive pulmonary disease in adults in primary and secondary care. June 2010
6. Cope S, Donohue JF, Jansen JP et al. Comparative efficacy of long-acting bronchodilators for COPD - a network meta-analysis. *Respir Res* 2013 Oct 7;14(100).
7. Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. *Cochrane Database Syst Rev* 2014 Apr 26;(3). Plus additional files (supplementary material)
8. *Global Strategy for the Diagnosis, Management and Prevention of COPD*, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014.

This assessment is based on data submitted by the applicant company up to and including 14 November 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.