

# Chronic obstructive pulmonary disease: olodaterol

## Evidence summary

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[nice.org.uk/guidance/esnm54](https://www.nice.org.uk/guidance/esnm54)

## Key points from the evidence

The content of this evidence summary was up-to-date in February 2015. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

Olodaterol ([Striverdi Respimat](#)) is a new long-acting beta-2 agonist (LABA) for chronic obstructive pulmonary disease (COPD).

In two 48-week studies, olodaterol statistically significantly improved lung function in people with moderate to very severe COPD compared with placebo over 24 weeks, and was not statistically significantly different from formoterol. Statistically significant improvements in health-related quality of life were seen with olodaterol compared with placebo, but the results were less conclusive for dyspnoea (breathlessness) and the studies were not designed to assess exacerbations.

Although olodaterol appears to improve lung function as well as formoterol, little evidence is available comparing it directly with other LABAs and long-acting muscarinic antagonists (LAMAs) for COPD, particularly in terms of patient-oriented outcomes such as exacerbations, breathlessness and quality of life.

Effectiveness	Safety
<ul style="list-style-type: none"> <li>• In 2 RCTs (n=904 and n=934), olodaterol was statistically significantly better than placebo in improving mean FEV<sub>1</sub> AUC<sub>0-3</sub> response (both p&lt;0.0001) and mean trough FEV<sub>1</sub> response (both p&lt;0.01) in people with COPD (92% moderate to severe) at 24 weeks.</li> <li>• When data for the 2 studies were combined, there were no statistically significant differences in lung function between olodaterol 5 micrograms daily and formoterol 12 micrograms twice daily.</li> <li>• Based on combined data, olodaterol statistically significantly improved health-related quality of life scores compared with placebo (p=0.0034) at 24 weeks.</li> <li>• Results were less conclusive for dyspnoea scores and the studies were not designed to assess exacerbations.</li> <li>• Head-to-head data comparing olodaterol and formoterol were not reported for symptomatic end points.</li> <li>• Olodaterol was often co-administered with tiotropium and inhaled corticosteroids (ICS) and only limited data support its use alone.</li> </ul>	<ul style="list-style-type: none"> <li>• In the 2 RCTs, most adverse events were reported to be mild to moderate in severity. The majority of treatment-emergent adverse events were respiratory events, such as exacerbations of COPD, cough and dyspnoea.</li> <li>• The <a href="#">public assessment report for olodaterol</a> notes that, in studies, the adverse effects of olodaterol were as expected for a LABA. However, only about 500 people have been treated for over 48 weeks and data are limited in people with significant cardiac comorbidity.</li> <li>• According to the <a href="#">summary of product characteristics</a>, the most common adverse effects of olodaterol are nasopharyngitis, dizziness and rash (incidence between 1 in 100 and 1 in 1000).</li> </ul>

Patient factors	Resource implications
<ul style="list-style-type: none"> <li>• Olodaterol, indacaterol, glycopyrronium and tiotropium are administered once daily. Formoterol, salmeterol and aclidinium are administered twice daily.</li> <li>• Olodaterol is administered using a Respimat inhaler containing a cartridge of inhalation solution. Other LABAs and LAMAs are available as solutions or dry powder formulations in various different inhaler devices. Some patients may prefer a particular product.</li> <li>• In common with many other devices, the Respimat device cannot be used with a spacer.</li> </ul>	<ul style="list-style-type: none"> <li>• The 30-day cost of olodaterol is £26.35</li> <li>• The 30-day costs of other LABAs and LAMAs range from £27.50 to £34.87, apart from formoterol, the cost of which ranges from £11.87 to £24.80.</li> </ul> <p>(Costs excluding VAT; <a href="#">MIMS</a>, December 2014.)</p>

## *Introduction and current guidance*

According to the NICE guideline on [chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care \(partial update\)](#), in people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, the following should be offered as maintenance therapy:

- if forced expired volume in 1 second (FEV<sub>1</sub>) is 50% predicted or more: either a LABA or LAMA
- if FEV<sub>1</sub> is less than 50% predicted: either a LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or a LAMA. Consider a LAMA in addition to a LABA where an ICS is declined or not tolerated.

See the NICE guideline or the NICE pathway on [COPD](#) for full details.

This evidence summary considers the best available evidence to support the use of olodaterol (a LABA) for COPD.

[Full text of introduction and current guidance.](#)

## Product overview

Olodaterol 2.5 microgram solution for inhalation ([Striverdi Respimat](#); Boehringer Ingelheim) received a marketing authorisation for maintenance bronchodilator treatment in people with COPD in October 2013 and was launched in the UK in June 2014.

The recommended dose of olodaterol is 5 micrograms (2 puffs) once daily, which is administered using a Respimat inhaler containing a cartridge of inhalation solution.

[Full text of product overview.](#)

## Evidence review

- This evidence summary is primarily based on 2 identical [randomised controlled trials](#) of olodaterol that were designed to fulfil EU regulatory requirements ([Koch et al. 2014](#)).
- The studies (n=904 and n=934) investigated the efficacy and safety of olodaterol 5 micrograms and 10 micrograms daily, and formoterol 12 micrograms twice daily compared with placebo over 48 weeks in people with COPD (92% moderate to severe and 8% severe across both studies). Apart from LABAs, usual COPD maintenance treatment was continued (for example, overall, 26% of participants took LAMAs [tiotropium] and 48% took ICS). The 3 co-primary endpoints (measured at 24 weeks) were FEV<sub>1</sub> area under the curve from 0–3 hours (AUC<sub>0-3</sub>) response (change from pre-treatment baseline), trough FEV<sub>1</sub> response, and [Transitional Dyspnoea Index](#) (TDI) focal scores. [St. George's Respiratory Questionnaire](#) (SGRQ; a measure of health-related quality of life) total scores were used as a key secondary endpoint. Efficacy results for the 10 microgram dose are not discussed in this evidence summary because this dose is not licensed in the UK.
- After 24 weeks, in both studies compared with placebo, olodaterol 5 micrograms and formoterol 12 micrograms statistically significantly improved the mean FEV<sub>1</sub> AUC<sub>0-3</sub> response (all p<0.0001) and mean trough FEV<sub>1</sub> response (all p<0.05). The authors report that, when data for the 2 studies were combined, there were no statistically significant differences in lung function outcomes between olodaterol 5 micrograms and formoterol 12 micrograms. However, no data are reported and it is unclear whether this analysis was pre-specified.
- Based on the combined data set, in the pre-specified analysis, there was no statistically significant difference in TDI focal scores between olodaterol 5 micrograms or formoterol 12 micrograms and placebo after 24 weeks. However, a high rate of discontinuations was identified in the placebo group in 1 study (25.3% compared with 15.9–18.9% in active

treatment groups); therefore, a post hoc analysis that accounted for discontinuations was undertaken. It found that the difference between placebo and olodaterol 5 micrograms ( $p=0.0270$ ), but not formoterol 12 micrograms, was statistically significant.

- When data were combined for the 2 studies, olodaterol 5 micrograms, but not formoterol 12 micrograms, statistically significantly improved SGRQ total scores compared with placebo ( $p=0.0034$ ) at 24 weeks. The [hierarchical testing model](#) used in the studies means that the SGRQ results should be considered as descriptive only (because tests ranked above those for SGRQ scores in the model did not demonstrate statistical significance). Nevertheless, around half of people taking olodaterol 5 micrograms saw an improvement of 4 points or more compared with one-third of those taking placebo ( $p<0.0001$ ).
- In the 2 studies, trough FEV<sub>1</sub> response, TDI focal scores and SGRQ total scores were all below the values considered to be the minimum [clinically important](#) differences. However, the improvements in lung function and SGRQ scores seen with olodaterol were comparable to those seen with the established therapy, formoterol, and the [public assessment report for olodaterol](#) states that this demonstrates the clinical relevance of the findings. The [public assessment report](#) also notes that a minimum clinically important difference might not be static, and might be dependent on the patient population studied or the severity of the disease, as well as use of concomitant medication. Patients in the studies were permitted to take background treatment for COPD (except for LABAs) in all of the olodaterol studies, which was not the case in earlier COPD drug development programmes, when minimum clinically important differences were determined.
- Little evidence is available comparing olodaterol directly with other active treatments for COPD, particularly in terms of patient-oriented outcomes. [Koch et al. \(2014\)](#) found there were no statistically significant differences in lung function outcomes between olodaterol 5 micrograms and formoterol 12 micrograms. However, these are disease-orientated outcomes and no comparisons between the active treatments are presented for other, patient-oriented outcomes. In addition, no head-to-head studies have compared olodaterol and the other LABA that is licensed for once-daily (rather than twice-daily) treatment of COPD, indacaterol. An indirect meta-analysis outlined in this evidence summary ([Roskell et al. 2014](#)) found that olodaterol and indacaterol were of similar efficacy but the results should be interpreted with caution because the studies included in the analysis are inherently dissimilar. Comparative efficacy data for tiotropium are limited to 6-week cross over studies ([Lange et al. 2014](#) and [NCT01040728](#)). There are no direct comparisons with other LABAs and LAMAs.
- The [public assessment report for olodaterol](#) advises that 4312 people have been treated with olodaterol monotherapy. Of these, only 265 were treated with olodaterol 5 micrograms, and

258 were treated with olodaterol 10 micrograms, for more than 48 weeks. Data in people with cardiac co-morbidity are limited.

- According to the [summary of product characteristics](#), the most common adverse effects of olodaterol are nasopharyngitis, dizziness and rash (incidence between 1 in 100 and 1 in 1000). Hypertension and arthralgia have been reported rarely (incidence between 1 in 1000 and 1 in 10,000). Adverse effects are usually mild or moderate in intensity. The summary of product characteristics also notes that, as olodaterol is a LABA, the occurrence of adverse effects related to the beta-adrenergic agonist class should be taken into consideration.

[Full text of evidence review.](#)

## Context

The 30-day cost of olodaterol is £26.35. This is lower than the 30-day costs of the other LABAs (indacaterol and salmeterol) and LAMAs (aclidinium, glycopyrronium and tiotropium) which range from £27.50 to £34.87, apart from formoterol, the costs of which range from £11.87 to £24.80. (Costs excluding VAT; [MIMS](#), December 2014).

[Full text of context.](#)

## Estimated impact for the NHS

The NICE guideline on [COPD](#) recommends that the choice of treatment should take into account the person's symptomatic response and preference, and the medicine's potential to reduce exacerbations, side effects and costs.

Specialists involved in the production of this evidence summary consider that olodaterol is likely to be used alone in people with moderate COPD, who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, particularly those who prefer the RespiMat device over other inhaler devices, in line with the NICE guideline on [COPD](#). However, only limited data supports its use alone, rather than in combination with a LAMA or ICS; more evidence is needed comparing olodaterol with other LABAs and LAMAs, such as indacaterol, salmeterol and tiotropium, in terms of patient-oriented outcomes such as breathlessness, exacerbations and quality of life.

Olodaterol is less likely to be used in people with more severe COPD because it is not currently available in combination with an ICS. No inhalers containing an ICS alone are licensed for treating

COPD in the UK because of [safety concerns](#) over using ICS without a LABA. A combination inhaler containing olodaterol and tiotropium is currently in development.

Local decision makers will need to take these factors into account when considering the likely place in therapy of olodaterol.

[Full text of estimated impact for the NHS.](#)

#### About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

## Full evidence summary

### *Introduction and current guidance*

The NICE guideline on [chronic obstructive pulmonary disease](#) (COPD) states that COPD is characterised by airflow obstruction that is usually progressive and not fully reversible; it is predominantly caused by smoking. About 900,000 people in the UK have been diagnosed with COPD, and an estimated 2 million people have COPD that remains undiagnosed. COPD produces symptoms, disability and impaired quality of life, which may respond to pharmacological and other therapies that have limited or no impact on the airflow obstruction. Exacerbations often occur, during which there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations.

The NICE guideline on [COPD](#) advises that all people who are still smoking should be encouraged to stop, and offered help to do so, at every opportunity.

The following are key recommendations from the NICE guideline that relate to this evidence summary and the likely place in therapy of olodaterol ([Striverdi Respimat](#): a long-acting beta-2 agonist [LABA] inhaler). The list is not comprehensive (see the NICE guideline on [COPD](#) for all recommendations).

- Short-acting bronchodilators, as necessary, should be the initial empirical treatment for the relief of breathlessness and exercise limitation.

- In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, offer the following as maintenance therapy:
  - if forced expired volume in 1 second (FEV<sub>1</sub>) is 50% predicted or more: either a LABA or a long-acting muscarinic antagonist (LAMA)
  - if FEV<sub>1</sub> is less than 50% predicted: either a LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or a LAMA. Consider a LAMA in addition to a LABA where an ICS is declined or not tolerated.
- In people with stable COPD and an FEV<sub>1</sub> of 50% predicted or more who remain breathless or have exacerbations despite maintenance therapy with a LABA:
  - consider a LABA with an ICS in a combination inhaler
  - consider a LAMA in addition to a LABA where an ICS is declined or not tolerated.
- Offer a LAMA in addition to a LABA with an ICS to people with COPD who remain breathless or have exacerbations despite taking a LABA with an ICS, irrespective of their FEV<sub>1</sub>.
- Consider a LABA with an ICS in a combination inhaler in addition to a LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with a LAMA, irrespective of their FEV<sub>1</sub>.
- The choice of drug(s) should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and cost.

See the NICE pathway on [COPD](#) for more information.

## Product overview

### Drug action

[Striverdi Respimat](#) (Boehringer Ingelheim) 2.5 microgram solution for inhalation contains the new LABA, olodaterol.

### Licensed therapeutic indication

Olodaterol ([Striverdi Respimat](#)) received a marketing authorisation for maintenance bronchodilator treatment in people with COPD in October 2013. It was launched in the UK in June 2014.

## Course and cost

The recommended dose of olodaterol is 5 micrograms (2 puffs) once daily, which is administered using a Respimat inhaler containing a cartridge of inhalation solution.

The cost of a 60-dose cartridge and Respimat inhaler is £26.35 (excluding VAT; [MIMS](#), December 2014).

## Evidence review

This evidence summary is primarily based on 2 identical [randomised controlled trials](#) (RCTs: [Koch et al. 2014](#), 1222.13 and 1222.14) of olodaterol that were designed to fulfil EU regulatory requirements, including a symptomatic end point. Results of 2 similar RCTs ([Ferguson et al. 2014](#), 1222.11 and 1222.12) that were designed to fulfil US regulatory requirements, and a meta-analysis ([Roskell et al. 2014](#)) indirectly comparing olodaterol and indacaterol are outlined briefly.

### Studies 1222.13 and 1222.14 ([Koch et al. 2014](#))

- **Design:** 2 multicentre, randomised, double-blind, placebo-controlled, parallel-group studies with identical designs compared the efficacy and safety of olodaterol and formoterol with placebo over 48 weeks. The study was designed to reflect clinical practice by adding olodaterol to usual care.
- **Population:** Study 1222.13 included 904 people from 93 centres in 20 countries and study 1222.14 included 934 people from 98 centres in 20 countries. Participants:
  - were aged 40 years or older (mean age 64 years in both studies: 80% male).
  - had a post-bronchodilator FEV<sub>1</sub> less than 80% predicted normal, a post-bronchodilator FEV<sub>1</sub>/forced vital capacity (FVC) less than 70%, and a diagnosis of COPD according to the [Global initiative for chronic Obstructive Lung Disease](#) classification (GOLD: see table 1). About 92% of people in both studies had GOLD stage 2–3 (moderate to severe) COPD and about 8% had GOLD stage 4 (severe) COPD.
  - were current or ex-smokers with a smoking history of more than 10 pack-years (34% and 66% respectively across the studies).

Apart from LABAs, usual COPD maintenance treatment was continued (including short-acting muscarinic antagonists, LAMAs [tiotropium], ICS and xanthines). Patients on LABAs were allowed to switch to short-acting muscarinic antagonists. All patients

were provided with salbutamol for use as rescue medication. Baseline demographics for both studies were broadly similar across the treatment groups.

- **Intervention and comparator:** following an initial screening visit and 2-week baseline period, eligible patients were randomised to receive either placebo, olodaterol (5 or 10 micrograms [2 puffs of 2.5 or 5 micrograms] daily using the Respimat inhaler) or formoterol (12 micrograms [1 puff] twice daily using an Aerolizer inhaler). Efficacy results for the 10 microgram dose are not discussed in this evidence summary because this dose is not licensed in the UK.
- **Outcomes:** the first 2 co-primary end points were FEV<sub>1</sub> area under the curve from 0–3 hours response (AUC<sub>0–3</sub>) and FEV<sub>1</sub> trough response after 24 weeks. Response was defined as change from pre-treatment baseline. The third co-primary end point was [Mahler Transition Dyspnoea Index](#) (TDI) focal score after 24 weeks. Secondary symptomatic end points were [St. George's Respiratory Questionnaire](#) (SGRQ; a measure of health-related quality of life) total scores after 24 weeks, and use of rescue medication. Adverse events were also assessed. The [full NICE guideline on COPD](#) considers a [clinically important](#) change to be 0.100 litres for trough FEV<sub>1</sub>, 1 unit for the TDI focal score and 4 points for the SGRQ total score.
- **Analyses:** although the pre-specified primary comparisons were between olodaterol and placebo, the final sample size was based on the requirements for the comparison between olodaterol and formoterol. Efficacy analyses included all randomised patients who received at least 1 dose of study treatment, who had baseline and at least 1 post-randomisation measurement for any of the co-primary efficacy variables at or before 24 weeks. Safety analyses included all randomised patients who received at least 1 dose of treatment. The studies used a [hierarchical testing model](#). In such a model, no confirmatory claims can be based on tests that have a rank lower than the first test in the hierarchy where statistical significance was not demonstrated. In these studies, olodaterol was required to be statistically significantly superior to placebo for lung functions outcomes before superiority analyses could be undertaken for TDI focal scores and, subsequently, SGRQ total scores.

**Table 1: Classification of severity of airflow obstruction**

	FEV <sub>1</sub> /FVC	FEV <sub>1</sub> %predicted
GOLD 1: mild	<0.7	≥80%
GOLD 2: moderate	<0.7	50–79%
GOLD 3: severe	<0.7	30–49%
GOLD 4: very severe	<0.7	<30%

**Table 2: Summary of Studies 1222.13 and 1222.14 (Koch et al. 2014)**

		Placebo	Olodaterol 5 mcg daily	Formoterol 12 mcg twice daily	Analysis versus placebo	
Randomised	1222.13	n=225	n=227	n=227		
	1222.14	n=235	n=232	n=233		
Efficacy <sup>a,b</sup>	1222.13	n=217	n=222	n=223		
	1222.14	n=233	n=230	n=232		
Primary outcome 1: mean FEV <sub>1</sub> AUC <sub>0-3</sub> response at 24 weeks	1222.13	-0.009 L	0.142 L	0.168 L		Olodaterol: difference 0.151 L p<0.0001 Formoterol: difference 0.177 L p<0.0001
	1222.14	-0.013 L	0.116 L	0.137 L		Olodaterol: difference 0.129 L p<0.0001 Formoterol: difference 0.150 L p<0.0001
Primary outcome 2: mean trough FEV <sub>1</sub> response at 24 weeks	1222.13	-0.056 L	0.021 L	-0.002 L	Olodaterol: difference 0.078 L p<0.001 Formoterol: difference 0.054 L p<0.01	

	1222.14	-0.055 L	-0.003 L	-0.013 L	Olodaterol: difference 0.053 L p<0.01 Formoterol: difference 0.042 L p<0.05
Primary outcome 3: mean TDI focal score at 24 weeks (units)	1222.13 and 1222.14 combined <sup>c</sup>	1.5	1.9	1.8	Olodaterol: difference 0.3 p=0.1704 (NS) Formoterol: difference 0.2 p=0.3718 (NS)
Selected secondary outcome:					
Mean SGRQ total score at 24 weeks (points) <sup>d</sup>	1222.13 and 1222.14 combined <sup>c</sup>	41.6	38.8	40.4	Olodaterol: difference -2.8 p=0.0034 Formoterol: difference -1.2 p=0.2009 (NS)
Safety <sup>e</sup>	1222.13	n=225	n=227	n=227	
	1222.14	n=235	n=232	n=233	
Patients reporting adverse events	1222.13	68.0% (153/ 225)	70.5% (160/227)	65.6% (149/227)	Statistical significance of differences not reported
	1222.14	73.6% (173/ 235)	72.8% (169/232)	72.5% (169/233)	
Patients reporting serious adverse events	1222.13	13.8% (31/ 225)	14.5% (33/ 227)	14.5% (33/ 227)	

	1222.14	20.4% (48/ 235)	14.7% (34/ 232)	15.5% (36/ 233)
Patients reporting treatment-related adverse events	1222.13	7.6% (17/ 225)	7.0% (16/ 227)	11.0% (25/ 227)
	1222.14	10.6% (25/ 235)	5.2% (12/ 232)	11.2% (26/ 233)
Patients reporting adverse events resulting in stopping treatment	1222.13	7.1% (16/ 225)	6.6% (15/ 227)	8.4% (19/ 227)
	1222.14	8.1% (19/ 235)	6.5% (15/ 232)	7.3% (17/ 233)

Abbreviations: AUC<sub>0-3</sub>, area under the curve from 0–3 hours; FEV<sub>1</sub>, forced expired volume in 1 second; L, litre; mcg, micrograms; NS, not significant; p, p value; TDI, transition dyspnoea index.

<sup>a</sup> Efficacy analyses included all randomised patients who received at least 1 dose of study treatment, who had baseline and at least 1 post-randomisation measurement for any of the co-primary efficacy variables at or before 24 weeks.

<sup>b</sup> These numbers refer to primary outcome 1. Numbers of patients are slightly lower for primary outcome 2 in both studies, and are not reported for primary outcome 3.

<sup>c</sup> Data for 1222.13 and 1222.14 are not reported individually.

<sup>d</sup> The hierarchical testing model used in the studies means that the SGRQ results should be considered as descriptive only (because tests ranked above those for SGRQ scores in the model did not demonstrate statistical significance).

<sup>e</sup> Safety analyses included all randomised patients who received at least 1 dose of treatment.

## Clinical effectiveness

### Studies 1222.13 and 1222.14

**Lung function:** after 24 weeks, in both studies compared with placebo, olodaterol 5 micrograms and formoterol 12 micrograms statistically significantly improved the 2 primary lung function

outcomes (mean FEV<sub>1</sub> AUC<sub>0-3</sub> response [all p<0.0001] and mean trough FEV<sub>1</sub> response [all p<0.05]) in people with moderate to very severe COPD (Koch et al. 2014: see table 2 for details). The improvements in trough FEV<sub>1</sub> seen with both drugs are less than the 0.100 litres that the [full NICE guideline on COPD](#) considers to be clinically important (range 0.042 litres to 0.078 litres; see table 2 for details). The evidence strengths and limitations section of this evidence summary discusses the clinical relevance of the study findings in more detail.

Broadly similar results were seen for lung function outcomes after 48 weeks of treatment, although response appeared to decline slightly by this time in all treatment groups.

The authors report that, when data for the 2 studies were combined, there were no statistically significant differences in lung function outcomes between olodaterol 5 micrograms and formoterol 12 micrograms. However, no data are reported and it is unclear whether this analysis was pre-specified.

Subgroup analyses of the studies found no statistically significant differences in lung function outcomes between tiotropium users and non-users.

**Dyspnoea:** based on the combined data set, in the pre-specified analysis, there was no statistically significant difference in TDI focal scores between olodaterol 5 micrograms or formoterol 12 micrograms and placebo after 24 weeks.

The study authors examined the data for TDI scores and found an unexpected improvement in TDI focal scores in the placebo group in study 1222.13. They note that this meant that the pre-specified analysis was unreliable as an estimate of effect size. A high rate of discontinuations was identified in the placebo group in study 1222.13 (25.3% compared with 15.9–18.9% in the active treatment groups); therefore, a post hoc analysis that accounted for discontinuations was undertaken. It found that the difference between placebo and olodaterol 5 micrograms (difference 0.5 units, p=0.0270), but not formoterol 12 micrograms (difference 0.4 units, p=0.1166), was statistically significant. The difference for olodaterol compared with placebo is less than the 1 unit that the [full NICE guideline on COPD](#) considers to be clinically important.

**Health-related quality of life:** when data were combined for the 2 studies, olodaterol 5 micrograms statistically significantly improved SGRQ total scores compared with placebo at 24 weeks (p=0.0034). However, the difference in scores was less than the 4 points that the [full NICE guideline on COPD](#) considers to be clinically important (2.8 points). Around half of people taking olodaterol 5 micrograms did see an improvement of 4 points or more (50.2% compared with 36.4% with placebo p<0.0001). It should be noted that the hierarchical testing model used in the studies

means that the SGRQ results should be considered as descriptive only (because tests ranked above those for SGRQ scores in the model did not demonstrate statistical significance).

There was no statistically significant difference between formoterol 12 micrograms and placebo in SGRQ total scores.

**Rescue medication:** it is reported that the combined dataset showed that olodaterol 5 micrograms and formoterol 12 micrograms statistically significantly reduced weekly mean daytime and night time rescue medication compared to placebo throughout the 48-week treatment period. However, the full dataset is not presented in the paper by [Koch et al.](#)

### ***Studies 1222.11 and 1222.12***

The design of the US regulatory studies (1222.11 and 1222.12: n=624 and n=642 respectively; [Ferguson et al. 2014](#)) was very similar to that of the EU regulatory studies (1222.13 and 1222.14). For example, the inclusion and exclusion criteria and background maintenance therapy were the same, and the study compared olodaterol with placebo over 48 weeks. However, there was no formoterol arm and the co-primary outcomes (mean FEV<sub>1</sub> AUC<sub>0-3</sub> response and trough FEV<sub>1</sub> response) were assessed at 12 weeks, rather than 24 weeks. Also, a symptomatic primary end point was not used in these studies because it is not required for regulatory approval in the US. Secondary symptomatic end points were rescue medication use and Patient Global Rating scores.

**Lung function:** in the US regulatory studies, as in the EU regulatory studies, olodaterol 5 micrograms statistically significantly improved FEV<sub>1</sub> AUC<sub>0-3</sub> response compared with placebo (differences 0.172 litres in study 1222.11 and 0.151 litres in study 1222.12 at week 12, both p<0.0001). Similarly, olodaterol 5 micrograms statistically significantly improved trough FEV<sub>1</sub> response compared with placebo (differences 0.091 litres in study 1222.11, p<0.0001; and 0.047 litres in study 1222.12, p<0.05) at week 12. These results were broadly similar at weeks 24 and 48 in both studies.

**Symptomatic outcomes:** based on combined data from both studies, at week 48, daytime rescue medication was reduced by 0.46 puffs/day and night-time rescue medication was reduced by 0.50 puffs/day with olodaterol 5 micrograms compared with placebo (both p<0.0001).

Based on the combined dataset, compared with placebo, Patient Global Rating scores were statistically significantly improved with olodaterol 5 micrograms (p<0.0001 at weeks 6, 12, and 24, and p=0.0041 at week 48).

It is unclear whether improvements in either of these symptomatic outcomes are clinically important.

### ***Indirect comparison with indacaterol***

No head-to-head RCTs have compared olodaterol and the other LABA that is licensed for once-daily (rather than twice-daily) treatment of COPD, indacaterol. Therefore, [Roskell et al. 2014](#) performed a network meta-analysis to compare the 2 treatments indirectly and provide exploratory insights into their relative efficacy. Eighteen studies were identified, 8 looking at olodaterol and 10 looking at indacaterol. There was considerable [heterogeneity](#) in trial design between the olodaterol and indacaterol studies. For example, the olodaterol studies included patients with moderate to very severe COPD, but the indacaterol studies excluded patients with very severe COPD. Also, concomitant maintenance bronchodilator use was allowed in most of the olodaterol studies, but not in the indacaterol studies.

In order to evaluate lung function, trials or subgroups were selected in order to form indirect treatment comparisons based on patients subject to similar trial conditions. When similarly designed trials and data were analysed for change from baseline in trough FEV<sub>1</sub>, there was no significant difference between olodaterol and indacaterol in studies excluding concomitant LAMAs (tiotropium) or in studies with concomitant or co-administered LAMAs. In sensitivity analyses of the full network indacaterol 150 micrograms (the licensed dose) improved trough FEV<sub>1</sub> statistically significantly more than olodaterol 5 micrograms but this analysis was heterogeneous.

Despite the known heterogeneity, in the full network meta-analyses there were no statistically significant differences between olodaterol and indacaterol in changes from baseline in TDI scores, SGRQ total scores and use of rescue medication, or in the proportions of SGRQ responders and patients experiencing at least 1 exacerbation of COPD.

## **Safety and tolerability**

### ***Studies 1222.13 and 1222.14***

Overall, 80.6% and 82.4% of patients completed the studies, respectively ([Koch et al. 2014](#)). In both studies, the discontinuation rate was higher in the placebo group than the active treatment groups (25.3% compared with 15.9% with olodaterol 5 micrograms, 17.3% with olodaterol 10 micrograms and 18.9% with formoterol 12 micrograms in study 1222.13, and 21.7% compared with 16.0% with olodaterol 5 micrograms, 15.4% with olodaterol 10 micrograms and 17.2% with formoterol 12 micrograms in study 1222.14). The statistical significance of the differences was not reported.

Overall, 69.2% of people in study 1222.13 and 72.8% of people in study 1222.14 reported at least 1 adverse event while on treatment. Of those, 7.7% in study 1222.13 and 8.2% in study 1222.14 were considered treatment-related. The incidence was generally balanced across treatment groups. See table 2 for more details.

The majority of adverse events were reported to be mild to moderate in severity. The majority of treatment-emergent adverse events (events emerging during treatment having been absent pre-treatment or worsening relative to pre-treatment) were respiratory events, such as exacerbations of COPD, cough and dyspnoea.

### ***Public assessment report***

The [public assessment report for olodaterol](#) advises that 4312 people have been treated with olodaterol monotherapy. Of these, only 265 were treated with olodaterol 5 micrograms, and 258 were treated with olodaterol 10 micrograms, for more than 48 weeks. Data in people with cardiac co-morbidity are limited.

The number of people experiencing at least 1 serious adverse event was balanced across the treatment groups in the 48-week RCTs (placebo 16.4%, olodaterol 5 micrograms 15.8%, olodaterol 10 micrograms 16.6% and formoterol 12 micrograms 15.0%). The rate of deaths was comparable between the groups (placebo 1.5%, olodaterol 5 micrograms 1.5%, olodaterol 10 micrograms 1.9% and formoterol 12 micrograms 2.2%).

Adverse events were as expected from a LABA. Nasopharyngitis was reported with a 5% higher frequency with olodaterol 5 micrograms than with placebo.

### ***Summary of product characteristics***

According to the [summary of product characteristics](#), the most common adverse effects of olodaterol are nasopharyngitis, dizziness and rash (incidence between 1 in 100 and 1 in 1000). Hypertension and arthralgia have been reported rarely (incidence between 1 in 1000 and 1 in 10,000). Adverse effects are usually mild or moderate in intensity.

The summary of product characteristics also notes that, as olodaterol is a LABA, the occurrence of adverse effects related to the beta-adrenergic agonist class should be taken into consideration (for example, tachycardia, arrhythmia, palpitations, myocardial ischaemia, angina pectoris, hypertension or hypotension, tremor, headache, nervousness, insomnia, dizziness, dry mouth, nausea, muscle spasms, fatigue, malaise, hypokalemia, hyperglycemia, and metabolic acidosis).

## Evidence strengths and limitations

In the EU regulatory studies (1222.13 and 1222.14), patients were randomised following an initial screening visit and 2-week baseline period; however the reasons for exclusion of a quarter of patients after the 2-week period are not reported. It is also unclear from the paper how patients were randomised or whether [allocation was concealed](#). However, [Roskell et al. 2014](#) report that randomisation was appropriate and allocation concealment was adequate in these studies. Baseline characteristics of participants in the studies were generally well-balanced, although the statistical significance of any differences was not reported. The majority of participants had moderate (53%) or severe (39%) COPD and around 80% were male, limiting applicability to female patients and those with very severe COPD (8%). These limitations also apply to the US regulatory studies (1222.11 and 1222.12). The olodaterol studies discussed in this evidence summary were all funded by Boehringer Ingelheim, the manufacturer of olodaterol.

For olodaterol 5 micrograms (the licensed dose) compared with placebo, the primary end point of trough FEV<sub>1</sub> response was below the minimum clinically important difference of 0.100 litres in all 4 of the regulatory studies. Nevertheless, in the EU regulatory studies, the lung function outcomes seen with olodaterol were comparable to those seen with the established therapy, formoterol and the [public assessment report for olodaterol](#) states that this demonstrates the clinical relevance of the findings. The public assessment report also highlights a review of studies of LABAs ([Donohue JF et al. 2011](#)) that showed that salmeterol and formoterol also did not consistently improve trough FEV<sub>1</sub> by more than 0.100 litres although their clinical benefit is acknowledged in the symptomatic treatment of COPD.

Regarding symptomatic end points, the TDI and SGRQ assessment tools are validated for use in COPD. When data from the EU regulatory studies were combined, olodaterol had no statistically significant effect on TDI scores compared with placebo. However, the results may have been affected by a high rate of discontinuations in the placebo group in study 1222.13. Also, baseline TDI scores were not reported so it is unclear whether patients were breathless at study entry. Other phase III studies of bronchodilators have required patients to report significant breathlessness for enrolment.

The [Medicines Evaluation Board](#) responsible for evaluating olodaterol in the EU considered that the SGRQ could be used as alternative to the TDI to assess symptomatic benefit by demonstrating an improvement in health-related quality of life (see the [public assessment report for olodaterol](#)). However, although there were statistically significant differences between olodaterol 5 micrograms and placebo in SGRQ total scores in the EU regulatory studies, the differences were consistently below the minimum clinically important difference of 4. Nevertheless, around half of

people taking olodaterol 5 micrograms saw an improvement of 4 points or more in SQRQ scores, statistically significantly more than with placebo. Also, the [public assessment report for olodaterol](#) states that more people taking olodaterol achieved a clinically significant improvement in SGRQ score compared with formoterol, substantiating the clinical relevance of the findings.

Amongst other things, the NICE guideline on [COPD](#) recommends that the choice of treatment should take into account the medicine's potential to reduce exacerbations. Although not reported by [Koch et al. \(2014\)](#), the [public assessment report for olodaterol](#) notes that exacerbations were included in the EU regulatory studies as a secondary end point, and neither olodaterol nor formoterol statistically significantly reduced the number of exacerbations or prolonged the time to the first exacerbation compared to placebo. However, the studies were not specifically designed to measure an effect on exacerbations; for example, having an exacerbation in the previous year was not an inclusion criterion.

In summary, although many results were statistically significant, a clinically important improvement with olodaterol 5 mg compared with placebo was not proven for any of these lung function or symptomatic outcomes. Also, the US [FDA briefing information for olodaterol](#) states that, in general, the observed treatment effect for olodaterol is somewhat lower than that observed in most regulatory studies for other LABAs. However, it also notes that patients in the studies were permitted to take background treatment for COPD (except for LABAs) in all of the olodaterol studies, which was not the case in other COPD drug development programs. In the EU regulatory studies, tiotropium was taken by about 26% of patients and ICS were taken by about 48% of patients. Also, the [public assessment report for olodaterol](#) notes that a minimum clinically important difference might not be static, and might be dependent on the patient population studied or the severity of the disease, as well as use of concomitant medication.

Little evidence is available comparing olodaterol directly with other active treatments for COPD. [Koch et al. \(2014\)](#) report that there were no statistically significant differences in lung function outcomes between olodaterol 5 micrograms and formoterol based on the combined data set. However, no head-to-head comparisons between the active treatments are presented for other outcomes.

No head-to-head studies have compared olodaterol and the other LABA that is licensed for once-daily (rather than twice-daily) treatment of COPD, indacaterol. The indirect meta-analysis outlined in this evidence summary ([Roskell et al. 2014](#)) found that olodaterol and indacaterol were of similar efficacy but the results should be interpreted with caution because the studies included in the analysis are inherently dissimilar, particularly with respect to concomitant bronchodilator use and severity of COPD at study entry. Comparative efficacy data for tiotropium are limited to

6-week cross over studies ([Lange et al. 2014](#) and [NCT01040728](#)). There are no direct comparisons with other LABAs and LAMAs.

## Context

### Alternative treatments

In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, the NICE guideline on [COPD](#) advises that the following should be offered as maintenance therapy:

- if FEV<sub>1</sub> is 50% predicted or more: either a LABA or LAMA
- if FEV<sub>1</sub> is less than 50% predicted: either a LABA with an ICS in a combination inhaler, or a LAMA. Consider a LAMA in addition to a LABA where an ICS is declined or not tolerated.

Alternative LABAs to olodaterol, which are licensed for COPD, are indacaterol, formoterol and salmeterol. LAMAs licensed for COPD are aclidinium, glycopyrronium and tiotropium. A variety of formulations are available.

Olodaterol is not currently available in combination with an ICS; therefore, combination LABA/ICS inhalers are not discussed in this evidence summary.

### Costs of alternative treatments

Drug and formulation		Usual dosage <sup>a,b</sup>	30-day cost excluding VAT
<b>LABA inhalers</b>			
Indacaterol 150 microgram/ inhalation	Inhalation solution ( <a href="#">Onbrez</a> <a href="#">Breezhaler</a> )	1 puff daily	£29.26 <sup>c</sup>
Formoterol 12 micrograms/ inhalation	Dry powder inhaler ( <a href="#">Formoterol</a> <a href="#">Easyhaler</a> )	1 puff twice daily	£11.87 <sup>d</sup>

		Inhalation solution ( <a href="#">Atimos Modulite</a> )	1 puff twice daily	£18.04 <sup>c</sup>
		Dry powder capsules ( <a href="#">Foradil</a> )	1 puff twice daily	£23.38 <sup>c</sup>
		Dry powder inhaler ( <a href="#">Oxis Turbohaler</a> )	1 puff twice daily	£24.80 <sup>c</sup>
Olodaterol 2.5 micrograms/ inhalation		Inhalation solution ( <a href="#">Striverdi Respimat</a> )	2 puffs daily	£26.35 <sup>d</sup>
Salmeterol	25 micrograms/ inhalation	Metered dose inhaler ( <a href="#">Serevent Evohaler</a> )	2 puffs twice daily	£29.26 <sup>c</sup>
	50 micrograms/ inhalation	Dry powder inhaler ( <a href="#">Serevent Accuhaler</a> )	1 puff twice daily	£29.26 <sup>c</sup>
<b>LAMA inhalers</b>				
Aclidinium 322 micrograms/ inhalation		Dry powder inhaler ( <a href="#">Eklira Genuair</a> )	1 puff twice daily	£28.60 <sup>d</sup>
Glycopyrronium 44 micrograms/ inhalation		Dry powder capsules ( <a href="#">Seebri Breezhaler</a> )	1 puff daily	£27.50 <sup>d</sup>

Tiotropium	18 micrograms/ inhalation	Dry powder capsules ( <a href="#">Spiriva Handihaler</a> )	1 puff daily	£34.87 <sup>c</sup> Refill £33.50
	2.5 micrograms/dose	Inhalation solution ( <a href="#">Spiriva Respimat</a> )	2 puffs daily	£33.50 <sup>d</sup>

Abbreviations: LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist.

<sup>a</sup> Doses taken from the relevant [summary of product characteristics](#).

<sup>b</sup> The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

<sup>c</sup> Costs taken from the [Drug Tariff](#) (December 2014). All costs include the inhaler device.

<sup>d</sup> Costs taken from [MIMS](#) (December 2014). All costs include the inhaler device.

## Estimated impact for the NHS

### Likely place in therapy

The NICE guideline on [COPD](#) recommends that the choice of treatment should take into account the person's symptomatic response and preference, and the medicine's potential to reduce exacerbations, side effects and costs.

Over 24 weeks, olodaterol 5 micrograms statistically significantly improved lung function in people with mainly moderate to severe COPD compared with placebo, and was not significantly different from formoterol. Nominally statistically significant improvements in health-related quality of life (SGRQ) scores were seen with olodaterol, but not formoterol, compared with placebo. Results were less conclusive for dyspnoea (TDI) scores and the studies were not designed to assess exacerbations.

The adverse effects of olodaterol were as expected for a LABA. However, only around 500 people have been treated for over 48 weeks and data are limited in people with significant cardiac comorbidity.

The NICE guideline on [COPD](#) advises that, if FEV<sub>1</sub> is 50% predicted or more, a LABA or LAMA should be used alone in people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed. There is only limited data to support the use

of olodaterol alone. Although sub group analyses of the EU regulatory studies showed that lung function improved statistically significantly with olodaterol compared with placebo in the 74% of people who weren't taking tiotropium, almost half of patients in the studies were taking ICS. Also, few data are available comparing olodaterol to other LABAs or LAMAs when used alone.

If FEV<sub>1</sub> is less than 50% predicted in people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, NICE advises that either a LABA with an ICS in a combination inhaler, or a LAMA, should be offered. Olodaterol is not available in combination with an ICS and no inhalers containing an ICS alone are licensed for treating COPD in the UK because of [safety concerns](#) over using ICS without a LABA.

According to NICE, a LAMA may be used in addition to a LABA when a LABA/ICS combination is declined or not tolerated. Subgroup analyses of the EU regulatory studies showed that olodaterol statistically significantly improved lung function compared with placebo in the 26% of people who were taking tiotropium. A combination inhaler containing olodaterol and tiotropium is currently in development.

Olodaterol is taken once daily, as is the LABA, indacaterol, and the LAMAs, glycopyrronium and tiotropium. The most established LABAs, salmeterol and formoterol, and the LAMA, aclidinium, are taken twice daily.

Olodaterol is administered using a Respimat inhaler containing a cartridge of inhalation solution and, therefore provides an alternative to dry powder formulations and other inhaler devices, which some people may prefer. In common with many other devices, the Respimat device cannot be used with a spacer.

The 30-day cost of olodaterol (£26.35) is lower than the 30-day costs of the other LABAs and LAMAs (range £27.50 to £34.87), apart from formoterol (range £11.87 to £24.80).

Specialists involved in the production of this evidence summary consider that olodaterol is likely to be used alone in people with moderate COPD, particularly those who prefer the Respimat device over other inhaler devices, because it is not currently available in combination with an ICS. However, before it is used first-line, more evidence is needed comparing olodaterol with other LABAs and LAMAs, such as indacaterol, salmeterol and tiotropium, in terms of patient-oriented outcomes such as breathlessness, exacerbations and quality of life.

Local decision makers will need to take these factors into account when considering the likely place in therapy of olodaterol.

## Estimated usage

It is not possible to provide estimated usage based on the available data.

## *Relevance to NICE guidance programmes*

Olodaterol was not considered appropriate for a NICE technology appraisal and is not currently planned into any other NICE work programme.

In 2010, NICE published a guideline on [chronic obstructive pulmonary disease](#) (NICE guideline CG101), which has been incorporated into a [NICE pathway](#).

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## *Development of this evidence summary*

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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## **Declarations of interest**

Dr John O'Reilly has received expenses to attend medical conferences and payments to attend advisory boards from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline and Novartis.

Professor Dave Singh has received sponsorship to attend international meetings, honoraria for lecturing or attending advisory boards, and research grants from various pharmaceutical companies including Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Genentech,

GlaxoSmithKline, Glenmark, Merck, Napp, Novartis, Pfizer, Respivert, Skypharma, Takeda, Teva, Therevance and Verona.

#### About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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