

Chronic obstructive pulmonary disease: tiotropium/olodaterol (Spiolto Respimat)

Evidence summary

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[nice.org.uk/guidance/esnm72](https://www.nice.org.uk/guidance/esnm72)

Key points from the evidence

The content of this evidence summary was up-to-date in May 2016. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

Compared with its individual mono-components, a combination of tiotropium/olodaterol ([Spiolto Respimat](#)) has shown statistically significant improvements in lung function and health-related quality of life outcomes, although the clinical relevance of these improvements is unclear. There are no published studies which directly compare the efficacy and safety of tiotropium/olodaterol with other long-acting muscarinic antagonist (LAMA) and long-acting beta-2 agonist (LABA) combination inhalers or with combination treatment with tiotropium plus an individual component LABA inhaler.

Regulatory status: Tiotropium/olodaterol ([Spiolto Respimat](#)) was launched in the UK in June 2015 and is the fourth LAMA/LABA combination inhaler to be available in the UK.

<p>Effectiveness</p> <ul style="list-style-type: none"> • Statistically significant improvement in trough FEV₁ of 0.071 and 0.050 litres with tiotropium/olodaterol compared with tiotropium in 2 RCTs of 24 weeks' treatment (n=2,624 and 2,539). • Statistically significant improvement in trough FEV₁ of 0.082 and 0.088 litres with tiotropium/olodaterol compared with olodaterol in 2 RCTs of 24 weeks' treatment (n=2,624 and 2,539). • Statistically significant improvement in St George's Respiratory Questionnaire (SGRQ) with tiotropium/olodaterol compared with tiotropium (-1.233 points) and olodaterol (-1.693 points) from a combined analysis (2 RCTs; 24 weeks' treatment; n=5,163). • The clinical relevance of all of these differences is unclear. 	<p>Safety</p> <ul style="list-style-type: none"> • The risk of cardiovascular side effects should be taken into account when prescribing tiotropium delivered via the Respimat or Handihaler to people with certain cardiac conditions (Drug Safety Update). Olodaterol may also have cardiovascular side effects. • The safety profile of the 2 mono-components (tiotropium and olodaterol) is well described. There is no evidence as yet from the clinical trial programme that there are any additive adverse effects when these are combined in 1 inhaler (Dutch Public Assessment Report [PAR]).
<p>Patient factors</p> <ul style="list-style-type: none"> • Spiolto Respimat is provided as an inhaler and a separate cartridge that needs to be inserted into the inhaler before it is first used. • Tiotropium/olodaterol is used once daily. • Some people may prefer a particular device. Spiolto Respimat is an inhalation solution. Other LAMA/LABA combination inhalers are dry powder inhalers. 	<p>Resource implications</p> <ul style="list-style-type: none"> • The annual cost of treatment with Spiolto Respimat is £390 (MIMS; March 2016, excluding VAT), which is the same cost as the 3 other currently available LAMA/LABA combination inhalers. • Spiolto Respimat costs less than combination treatment with tiotropium and available LABA individual component inhalers.

Introduction and current guidance

The NICE guideline on [chronic obstructive pulmonary disease](#) (COPD; which is being [updated](#), publication date to be confirmed) makes several recommendations about inhaled treatments for managing stable COPD. See the NICE guideline or the [NICE pathway on COPD](#) for full details.

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

Product overview

Spiolto Respimat inhalation solution contains tiotropium (a LAMA) and olodaterol (a LABA). It is licensed as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. Spiolto Respimat contains 2.5 micrograms of tiotropium and 2.5 micrograms of olodaterol per delivered dose (the dose that leaves the mouthpiece of the inhaler). The recommended dose is 5 micrograms of tiotropium and 5 micrograms of olodaterol given as 2 puffs once a day, at the same time of day (summary of product characteristics [SPC]: [Spiolto Respimat](#)).

[Full text of product overview.](#)

Evidence review

This evidence summary discusses the best available evidence on the efficacy and safety of tiotropium/olodaterol. This consists of 2 replicate 52-week double-[blind, randomised controlled trials](#) (RCTs) comparing tiotropium/olodaterol with the individual mono-components tiotropium and olodaterol in 5,163 people with COPD ([Buhl et al. 2015](#)). The main efficacy outcomes in these trials were assessed after 24 weeks' treatment. An additional two 12-week RCTs comparing tiotropium/olodaterol with tiotropium and placebo in 1,623 people with COPD ([Singh et al. 2015](#)) and a 6-week crossover study (n=229) comparing tiotropium/olodaterol with fluticasone propionate/salmeterol ([Beeh et al. 2016](#)) are also briefly discussed.

Buhl et al. (2015) and Singh et al. (2015) included groups randomised to unlicensed doses of tiotropium and tiotropium/olodaterol. This evidence summary only discusses results from the groups given the licensed doses which is tiotropium/olodaterol 5/5 micrograms once daily. For all of the results the clinical relevance of the differences between tiotropium/olodaterol and the individual mono-components is unclear.

- In the 2 RCTs in Buhl et al. (2015) tiotropium/olodaterol statistically significantly improved trough FEV₁ (a measure of the 24-hour bronchodilation profile) after 24 weeks' treatment

compared with the individual components. The mean treatment difference for change from baseline in trough FEV₁ with tiotropium/olodaterol compared with tiotropium was 0.071 litres (95% [confidence interval](#) [CI] 0.047 to 0.094; $p < 0.0001$) in 1 RCT (n=2,624) and 0.050 litres (95% CI 0.024 to 0.075; $p = 0.0001$) in the other RCT (n=2,539). For tiotropium/olodaterol compared with olodaterol the mean treatment difference for change from baseline in trough FEV₁ was 0.082 litres (95% CI 0.059 to 0.106; $p < 0.0001$) and 0.088 litres (95% CI 0.063 to 0.113; $p < 0.0001$).

- In the combined analysis of the 2 RCTs in Buhl et al. (2015), tiotropium/olodaterol statistically significantly improved [SGRQ](#) total score (a health-related quality of life measure ranging from 0 to 100 points) compared with the individual components. The mean treatment difference for the SGRQ total score after 24 weeks' treatment with tiotropium/olodaterol was -1.233 (95% CI -2.313 to -0.153; $p = 0.0252$) compared with tiotropium and -1.693 (95% CI -2.778 to -0.608; $p = 0.0022$) compared with olodaterol. For the same outcome, in the combined analysis of both RCTs reported by Singh et al. (2015), the mean treatment difference after 12 weeks' treatment with tiotropium/olodaterol compared with tiotropium was -2.10 (95% CI -3.47 to -0.72; $p < 0.01$).
- In the combined analysis of the 2 RCTs in Buhl et al. (2015) the mean treatment difference for transition dyspnoea index ([TDI](#)) focal score (a measure of dyspnoea which ranges from -9 to +9) after 24 weeks' treatment with tiotropium/olodaterol was 0.356 (95% CI 0.092 to 0.619; $p < 0.05$) compared with tiotropium and 0.420 (95% CI 0.155 to 0.684; $p < 0.005$) compared with olodaterol. Although statistical analysis is provided for this outcome, it is not strictly inferential due to the hierarchical testing method used in the study. For the same outcome, in the combined analysis of both RCTs reported by Singh et al. (2015), the mean treatment difference after 12 weeks' treatment with tiotropium/olodaterol compared with tiotropium was 0.59 (95% CI 0.22 to 0.97; $p < 0.01$).
- In Buhl et al. (2015) and Singh et al. (2015) the treatment difference between tiotropium/olodaterol and the individual mono-components for trough FEV₁, SGRQ total score and TDI focal score was less than what is generally considered to be the minimum clinically important difference for these outcomes (which is: 0.100 litres for FEV₁, -4 points for SGRQ total score and 1 unit for TDI focal score) [see the [full NICE guideline on COPD](#)]. However, it is unclear if these minimum clinical important differences are appropriate as a benchmark for clinical significance for comparisons between a combination of 2 bronchodilators (LAMA/LABA) and 1 bronchodilator (either a LAMA or a LABA).
- Limited data on exacerbations were reported in Buhl et al. (2015), see the full text section of this [evidence review](#) for details. However, the study was not designed to assess the effect of tiotropium/olodaterol on exacerbation rates. In all of the studies discussed in this evidence

summary participants were allowed to have concomitant treatment with an inhaled corticosteroid.

- In Beeh et al. (2016) tiotropium/olodaterol 5/5 microgram once daily statistically significantly improved FEV₁ area under the curve from 0 to 12 hours (AUC₀₋₁₂) compared with fluticasone propionate/salmeterol 500/50 micrograms twice daily; adjusted mean treatment difference for change from baseline 0.129 litres (95% CI 0.107 to 0.150, p<0.0001). For the same comparison, there was also a statistically significant improvement in trough FEV₁ (a secondary outcome measure); adjusted mean treatment difference for the change from baseline 0.058 litres (95% CI 0.032 to 0.082, p<0.0001).
- In Buhl et al. (2015), 16.4% (169/1029) of people in the tiotropium/olodaterol group, 16.7% (172/1033) of people in the tiotropium group and 17.4% (181/1038) of people in the olodaterol group reported serious adverse events. The Dutch [PAR](#) for Spiolto Respimat inhalation solution concludes that, as yet, there is no evidence from the clinical trial programme that there is an additive effect in terms of the safety profile when the individual drugs (tiotropium and olodaterol) are combined in 1 inhaler. Both tiotropium and olodaterol may have cardiovascular side effects. The [February 2015 Drug Safety Update](#) issued advice to take the risk of cardiovascular side effects into account when prescribing tiotropium delivered via the Respimat or Handihaler for the treatment of COPD to people with certain cardiac conditions. See the [SPC](#) for further information on contraindications, warnings and precautions for use, potential interactions and adverse effects of tiotropium/olodaterol.

[Full text of evidence review.](#)

Context

Tiotropium/olodaterol is the fourth LAMA/LABA combination inhaler to be launched in the UK for treating COPD, following umeclidinium/vilanterol ([Anoro Ellipta](#): see the evidence summary on [chronic obstructive pulmonary disease: umeclidinium/vilanterol](#)), indacaterol/glycopyrronium ([Ultibro Breezhaler](#): see the evidence summary on [chronic obstructive pulmonary disease: indacaterol/glycopyrronium](#)) and aclidinium/formoterol ([Duaklir Genuair](#): see the evidence summary on [chronic obstructive pulmonary disease: aclidinium/formoterol](#)). The annual cost of Spiolto Respimat is £390 (excluding VAT; costs taken from [MIMS](#), March 2016), which is the same cost as the 3 other currently available LAMA/LABA combination inhalers. It costs less than combination treatment with tiotropium and available LABA individual component inhalers.

[Full text of context.](#)

Estimated impact for the NHS

The NICE guideline on [COPD](#) (which is currently being [updated](#), publication date to be confirmed) recommends that the choice of drug treatment should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and its costs. Tiotropium/olodaterol is an inhalation solution delivered by the Respimat soft mist inhaler. Aclidinium/formoterol and umeclidinium/vilanterol are both multi-dose breath-activated dry powder inhalers (Genuair and Ellipta devices respectively). Indacaterol/glycopyrronium is a single dose breath-activated dry powder inhaler (Breezhaler device). Some people may prefer a particular device or be able to use one device better than another. Tiotropium/olodaterol is used once daily. Two of the other currently available LAMA/LABA combination inhalers are also used once daily. Costs for the 4 currently available LAMA/LABA inhalers are the same. However there are no published RCTs which directly compare their efficacy and safety.

[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; which is being [updated](#), publication date to be confirmed) states that COPD is characterised by airflow obstruction that is usually progressive and not fully reversible; it is predominantly caused by smoking. COPD produces symptoms, disability and impaired quality of life, which may respond to pharmacological and other therapies that have limited or no measurable 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 current NICE guideline includes the following recommendations on the use of inhaled therapy for managing stable COPD:

- 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 (FEV₁) is 50% predicted or more: either a LABA or a LAMA
 - if FEV₁ 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 FEV₁ 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 FEV₁.
- 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 FEV₁.
- 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 its cost.

The NICE guideline on COPD was published in 2010 which was before any of the LABA/LAMA combination inhalers were available in the UK. Following a recent review, the guideline is to be updated (publication date to be confirmed).

Product overview

Drug action

Spiolto Respimat inhalation solution contains tiotropium (a long-acting muscarinic antagonist [LAMA]) and olodaterol (a long-acting beta-2 agonist [LABA]) (summary of product characteristics [SPC]: [Spiolto Respimat](#)).

Licensed therapeutic indication

Tiotropium/olodaterol is licensed as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD (SPC: [Spiolto Respimat](#)).

Course and cost

Spiolto Respimat is provided as a Spiolto Respimat inhaler and a Spiolto Respimat cartridge. The cartridge needs to be inserted into the inhaler before it is first used. Spiolto Respimat contains 2.5 micrograms of tiotropium and 2.5 micrograms of olodaterol per delivered dose (the dose that leaves the mouthpiece of the inhaler). The recommended dose is 5 micrograms of tiotropium and 5 micrograms of olodaterol given as 2 puffs once a day, at the same time of day (SPC). Each inhaler pack contains 60 puffs (30 doses), the cost of which is £32.50 (1 month of treatment; excluding VAT; costs taken from [MIMS](#), March 2016). Based on this, the cost per year is £390.

Evidence review

This evidence summary discusses the [best available evidence](#) on the efficacy and safety of tiotropium/olodaterol (Spiolto Respimat), which is 2 replicate 52-week double-[blind, randomised controlled trials](#) (RCTs) comparing tiotropium/olodaterol with the individual mono-components tiotropium and olodaterol in people with COPD ([Buhl et al. 2015](#)). An additional two 12-week RCTs comparing tiotropium/olodaterol with tiotropium and placebo ([Singh et al. 2015](#)) and a 6-week crossover study comparing tiotropium/olodaterol with fluticasone propionate/salmeterol ([Beeh et al. 2016](#)) are also briefly discussed. Information from these studies has been supplemented and clarified using the Dutch Public Assessment Report (PAR) for [Spiolto Respimat inhalation solution](#).

[Buhl et al. 2015](#)

- Design: two 52-week, multicentre, double-blind, parallel-group RCTs conducted in 25 countries. [Allocation was concealed](#).
- Population: for both RCTs participants were aged 40 years and over (mean age 64 years) and had moderate to very severe COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage 2 to 4). Participants were current or former smokers with a smoking history of at least 10 pack-years (37.5% of participants in study 1 and 36.4% in study 2 were current smokers). They had a post-bronchodilator FEV₁ of 80% or less of predicted normal (mean FEV₁ approximately 50%), an FEV₁ to FVC (forced vital capacity) ratio of less than 0.7 (mean FEV₁ to FVC ratio approximately 45%). Exclusion criteria included clinically relevant abnormal baseline laboratory parameters, any other significant disease (although approximately 86% of

participants in study 1 and 87% in study 2 were recorded as having a comorbidity), a history of asthma, myocardial infarction within the previous year, unstable or life threatening cardiac arrhythmia, hospitalisation for heart failure within the previous year or current enrolment in a pulmonary rehabilitation programme. Study 1 included 2,624 randomised participants and study 2 included 2,539 randomised participants.

- **Intervention and comparison:** in both trials after an initial screening visit and 2-week baseline period, participants were randomised to either: tiotropium/olodaterol 5/5 micrograms once daily, tiotropium/olodaterol 2.5/5 micrograms once daily, tiotropium 5 micrograms once daily, tiotropium 2.5 micrograms once daily or olodaterol 5 micrograms once daily. All of the study drugs were delivered via the Respimat soft mist inhaler. Use of inhaled salbutamol for symptom relief was allowed throughout both studies. Inhaled corticosteroids (ICS) were also allowed to be continued throughout the studies. Temporary increases in ICS dose or addition of oral steroids were allowed during the treatment portion of the study. At baseline, in study 1 approximately 36.5% of participants were taking tiotropium, approximately 48.1% were taking a LABA and approximately 48.0% were taking an ICS. In study 2 approximately 34.7% of participants were taking tiotropium, approximately 44.6% were taking a LABA and approximately 46.7% were taking an ICS at baseline. The results from the tiotropium/olodaterol 2.5/5 microgram once daily and tiotropium 2.5 micrograms once daily groups are not discussed in this evidence summary because these are not licensed doses.
- **Outcomes:** both trials had 3 primary outcomes (2 lung function outcomes and 1 health-related quality of life outcome) which were all evaluated after 24 weeks' treatment:
 - trough FEV₁ change from baseline (mean of values 1 hour and 10 minutes prior to the first dose of study medication) in each individual trial
 - FEV₁ area under the curve from 0 to 3 hours (AUC₀₋₃) change from baseline in each individual trial
 - St George's Respiratory Questionnaire (SGRQ) total score (a measure of health-related quality of life. Scores range from 0 to 100 with higher scores indicating more limitations) for study 1 and 2 combined.

Secondary and additional outcomes included transition dyspnoea index (TDI) focal score (a measure of dyspnoea) for study 1 and 2 combined at 24 weeks and probability of moderate or severe COPD exacerbations. Analysis for the primary and secondary outcomes used a hierarchical testing method split into several levels pre-specified by the authors to avoid spurious statistically significant findings arising through chance, given the number of possible comparisons. Safety outcomes included adverse event reporting, vital signs and ECG measurements.

Table 1 Summary of lung function primary outcomes from study 1 and 2 from [Buhl et al. 2015](#)

For all of the results the clinical relevance of the differences between tiotropium/olodaterol and the individual mono-components is unclear – see the [clinical effectiveness](#) section for more details.

	Tiotropium/ olodaterol 5/ 5 micrograms once daily	Tiotropium 5 micrograms once daily	Olodaterol 5 micrograms once daily	Analysis
Randomised (study 1)	n=522	n=527	n=528	
Efficacy (full analysis set)^a (study 1)	The number of participants included in the analysis varied depending on the outcome and are specified below			
Primary outcome: adjusted mean trough FEV ₁ change from baseline ^b after 24 weeks' treatment (litres)	0.136 (n=521)	0.065 (n=520)	0.054 (n=519)	Tiotropium/ olodaterol treatment difference (SE) compared with: tiotropium: 0.071 (0.012); 95% CI 0.047 to 0.094; p<0.0001 olodaterol: 0.082 (0.012); 95% CI 0.059 to 0.106; p<0.0001

Primary outcome: adjusted mean FEV ₁ AUC ₀₋₃ change from baseline ^b after 24 weeks' treatment (litres)	0.256 (n=522)	0.139 (n=526)	0.133 (n=525)	Tiotropium/ olodaterol treatment difference (SE) compared with: tiotropium: 0.117 (0.012); 95% CI 0.094 to 0.140; p<0.0001 olodaterol: 0.123 (0.012); 95% CI 0.100 to 0.146; p<0.0001
Randomised (study 2) ^c	n=507	n=506	n=510	
Efficacy (full analysis set) ^a (Study 2)	The number of participants included in the analysis varied depending on the outcome and are specified below			
Primary outcome: adjusted mean trough FEV ₁ change from baseline ^b after 24 weeks' treatment (litres)	0.145 (n=497)	0.96 (n=498)	0.57 (n=503)	Tiotropium/ olodaterol treatment difference (SE) compared with: tiotropium: 0.050 (0.013); 95% CI 0.024 to 0.075; p=0.0001 olodaterol: 0.088 (0.013); 95% CI 0.063 to 0.113; p<0.0001

Primary outcome: adjusted mean FEV ₁ AUC ₀₋₃ change from baseline ^b after 24 weeks' treatment (litres)	0.268 (n=502)	0.165 (n=500)	0.136 (n=507)	Tiotropium/ olodaterol treatment difference (SE) compared with: tiotropium: 0.103 (0.012); 95% CI 0.078 to 0.127; p<0.0001 olodaterol: 0.132 (0.013); 95% CI 0.108 to 0.157; p<0.0001
Abbreviations: AUC ₀₋₃ , area under the curve from 0 to 3 hours; CI, <u>confidence interval</u> ; SE, standard error				
^a Full analysis set defined as all randomised participants who received at least 1 dose of study medication and had baseline and at least 1 post-baseline measurement for any primary efficacy endpoint. The number of participants included in the analysis varied depending on the outcome.				
^b In study 1 common study baseline trough FEV ₁ (litres) was 1.161 (SE:0.010) and common study FEV ₁ AUC ₀₋₃ was 1.158 (0.010). In study 2 common study baseline trough FEV ₁ and FEV ₁ AUC ₀₋₃ were both 1.150 (0.010).				
^c One participant who was randomised did not receive treatment; however it was not reported which group this participant was in.				

Table 2 Summary of combined analysis for health-related quality of life primary outcome, secondary and additional outcomes and safety from [Buhl et al. 2015](#)

	Tiotropium/ olodaterol 5/ 5 micrograms once daily	Tiotropium 5 micrograms once daily	Olodaterol 5 micrograms once daily	Analysis
Randomised ^a	n=1,029	n=1,033	n=1,038	
Efficacy (full analysis set) ^b	n=979	n=954	n=954	

Primary outcome: adjusted mean SGRQ total score (SE) after 24 weeks' treatment ^c	36.674 (0.386)	37.907 (0.393)	38.366 (0.396)	Tiotropium/olodaterol treatment difference (SE) compared with: tiotropium: -1.233 (0.551); 95% CI -2.313 to -0.153; p=0.0252 olodaterol: -1.693 (0.553); 95% CI -2.778 to -0.608; p=0.0022
Selected secondary and additional outcomes:				
Efficacy (full analysis set) ^b	The number of participants included in the analysis varied depending on the outcome and are specified below			
Adjusted mean TDI focal score (SE) at 24 weeks ^d	1.983 (0.095) [n=992]	1.627 (0.096) [n=978]	1.564 (0.096) [n=984]	Tiotropium/olodaterol treatment difference (SE) compared with: tiotropium: 0.356 (0.135); 95% CI 0.092 to 0.619; p<0.05 ^e olodaterol: 0.420 (0.135); 95% CI 0.155 to 0.684; p<0.005 ^e
Percentage of participants with at least 1 moderate to severe COPD exacerbation over 52 weeks ^f	27.7% [n=1029]	28.8% [n=1033]	31.9% [n=1038]	Annual rate (exacerbations per patient years) risk ratio (SE) tiotropium/ olodaterol compared with: tiotropium: 0.92 (0.08); p=0.3631 olodaterol: 0.83 (0.07); p=0.0332

Percentage of participants with at least 1 severe COPD exacerbation over 52 weeks ^f	5.9% (61/1029)	4.5% (46/1033)	5.4% (56/1038)	Annual rate (exacerbations per patient years) risk ratio (SE) tiotropium/olodaterol compared with: tiotropium: 1.14 (0.24); p=0.5406 olodaterol: 0.93 (0.19); p=0.7210
Safety^g	n=1029	n=1033	n=1038	No statistical analysis reported
Patients reporting serious adverse events	16.4% (169/1029)	16.7% (172/1033)	17.4% (181/1038)	
Adverse events leading to discontinuation	7.4% (76/1029)	9.0% (93/1033)	9.9% (103/1038)	
Adverse events requiring hospitalisation	14.9% (153/1029)	15.0% (155/1033)	15.6% (162/1038)	
Fatal adverse events	1.7% (18/1029)	1.6% (17/1033)	1.3% (14/1038)	

Abbreviations: CI, confidence interval; SE, standard error; SGRQ, St George's Respiratory Questionnaire; TDI, transition dyspnoea index.

^a One participant who was randomised did not receive treatment; however it was not reported which group this participant was in.

^b Full analysis set defined as all randomised participants who received at least 1 dose of study medication and had baseline and at least 1 post-baseline measurement for any primary efficacy endpoint. The number of participants included in the analysis varied depending on the outcome.

^c St George's Respiratory Questionnaire: a measure of health-related quality of life. Scores range from 0 to 100 with higher scores indicating more limitations.

^d Transition dyspnoea index: a measure of dyspnoea which ranges from -9 to +9. The lower the score, the more deterioration in severity of dyspnoea.

^e p values were provided however they are not strictly inferential due to the hierarchical testing method used as previous comparisons in the hierarchy (with the tiotropium/olodaterol 2.5/5 microgram inhaler) were not statistically significant. The study used a hierarchical testing method split into several levels pre-specified by the authors to avoid spurious statistically significant findings arising through chance, given the number of possible comparisons.

^f Data on percentages of participants with at least 1 moderate to severe or at least 1 severe COPD exacerbation taken from the Dutch PAR for Spiolto Respimat inhalation solution. A moderate exacerbation was defined by the need for systemic steroids or antibiotics. A severe exacerbation required hospitalisation. Exacerbations were reported in Buhl et al. (2015), although the study was not designed to assess the effect of tiotropium/olodaterol on exacerbation rates.

^g Safety population: all participants who received at least 1 dose of study medication. No statistical analysis was conducted for the safety outcomes.

Clinical effectiveness

Buhl et al. 2015 was designed according to regulatory authority COPD guidelines, which state that each drug in a fixed-dose combination must make a documented contribution within the combination to the claimed effects (Dutch Public Assessment Report [PAR] for Spiolto Respimat inhalation solution). These regulatory guidelines require at least 2 co-primary outcome measures: a lung function improvement and a symptomatic improvement. The fixed-dose combination must therefore show a clinically relevant improvement in lung function and symptomatic improvement over the mono-components.

Lung function

For both of the RCTs in [Buhl et al. 2015](#), tiotropium/olodaterol statistically significantly improved trough FEV₁ and FEV₁ AUC₀₋₃ change from baseline to week 24 compared with tiotropium and olodaterol monotherapy (see [table 1](#) for details). Trough FEV₁ is used as a measure to assess the 24-hour bronchodilation profile. In the individual studies the mean treatment difference for the change from baseline in trough FEV₁ for tiotropium/olodaterol compared with tiotropium was 0.071 litres (95% CI 0.047 to 0.094; p<0.0001) and 0.050 litres (95% CI 0.024 to 0.075; p=0.0001). For tiotropium/olodaterol compared with olodaterol the mean treatment difference in the change from baseline in trough FEV₁ was 0.082 litres (95% CI 0.059 to 0.106; p<0.0001) and 0.088 litres (95% CI 0.063 to 0.113; p<0.0001).

The minimum clinically important difference for change in FEV₁ is generally considered to be 0.100 litres (see the [full NICE guideline on COPD](#)). However, it is unclear if this is appropriate as a benchmark for clinical significance for comparisons between a combination of 2 bronchodilators (LAMA/LABA) with 1 bronchodilator (either a LAMA or a LABA).

[Beeh et al. 2016](#) was a crossover study with lung function outcomes comparing tiotropium/olodaterol (at 2 different strengths) with fluticasone propionate/salmeterol (at 2 different strengths) in 229 people with moderate to severe COPD ([GOLD](#) stage 2 or 3). Each treatment period lasted 6 weeks with a 3 week washout period in-between. Tiotropium/olodaterol 5/5 microgram once daily statistically significantly improved FEV₁ area under the curve from 0 to 12 hours (AUC₀₋₁₂; the primary outcome) compared with fluticasone propionate/salmeterol 500/50 micrograms twice daily; adjusted mean treatment difference for change from baseline 0.129 litres (95% CI 0.107 to 0.150, p<0.0001). For the same comparison, there was also a statistically significant improvement in trough FEV₁ (a secondary outcome measure); adjusted mean treatment difference for the change from baseline 0.058 litres (95% CI 0.034 to 0.082, p<0.0001).

Health-related quality of life

The third primary outcome in [Buhl et al. 2015](#) was adjusted mean SGRQ total score (a measure of health-related quality of life) for both studies combined after 24 weeks' treatment (see [table 2](#) for details). The minimum clinically important difference for change in SGRQ total score is generally considered to be -4 units (see the [full NICE guideline on COPD](#))

The mean treatment difference for the SGRQ total score after 24 weeks' treatment for tiotropium/olodaterol compared with tiotropium was -1.233 (95% CI -2.313 to -0.153; p=0.0252); compared with olodaterol it was -1.693 (95% CI -2.778 to -0.608; p=0.0022). Percentages of treatment

responders (defined as a reduction in SGRQ total score of 4 or more points after 24 weeks) were 57.5% (563/979) in the tiotropium/olodaterol group, 48.7% (465/955) in the tiotropium group and 44.8% (427/954) in the olodaterol group.

[Singh et al. 2015](#) reported on two 12-week RCTs which compared tiotropium/olodaterol (at either 2.5/5 or 5/5 microgram strengths) with tiotropium 5 microgram and placebo in 1,623 adults with moderate to severe COPD ([GOLD](#) stage 2 or 3). Both RCTs included a primary outcome of SGRQ total score after 12 weeks' treatment. The results discussed in this evidence summary are for tiotropium/olodaterol 5/5 microgram (the licensed dose). For the combined analysis of both studies the mean treatment difference for tiotropium/olodaterol (n=393) compared with tiotropium (n=384) was -2.10 (95% CI -3.47 to -0.72; p<0.01); compared with placebo (n=370) it was -4.67 (95% CI -6.06 to -3.28; p<0.0001).

Breathlessness

[Buhl et al. 2015](#) included adjusted mean TDI focal score (a measure of dyspnoea) at week 24 for the combined analysis as a secondary outcome. The mean treatment difference after 24 weeks' treatment with tiotropium/olodaterol compared with tiotropium was 0.356 (95% CI 0.092 to 0.619; p<0.05); compared with olodaterol it was 0.420 (95% CI 0.155 to 0.684; p<0.005). Although statistical analysis is provided for this outcome, it is not strictly inferential due to the hierarchical testing method used.

[Singh et al. 2015](#) also included TDI focal score after 12 weeks' treatment as a secondary outcome. For the combined analysis of both studies the mean treatment difference for tiotropium/olodaterol (n=393) compared with tiotropium (n=385) was 0.59 (95% CI 0.22 to 0.97; p<0.01); compared with placebo (n=370) it was 1.62 (95% CI 1.25 to 2.00; p<0.0001).

The minimum clinically important difference for change in TDI focal score is generally considered to be 1 unit (see the [full NICE guideline on COPD](#)).

Exacerbations

Exacerbations were reported in [Buhl et al. 2015](#) although the study was not designed to assess the effect of tiotropium/olodaterol on exacerbation rates, and limited data were provided. Further information on exacerbations is given in the Dutch [PAR](#) for Spiolto Respimat inhalation solution. For the combined analysis for both studies the percentage of participants who had at least 1 severe exacerbation (requiring hospitalisation) over 52 weeks was 5.9% (61/1029) in the tiotropium/olodaterol group, 4.5% (46/1033) in the tiotropium group and 5.4% (56/1038) in the olodaterol group. The PAR stated that the combined risk ratio showed comparable incidences for severe

exacerbations between tiotropium/olodaterol and the individual mono-components (see [table 2](#) for details). However, the risk of having a severe exacerbation with tiotropium/olodaterol was inconsistent between the 2 trials (data not provided).

Exercise endurance

The Dutch [PAR](#) for Spiolto Respimat inhalation solution also discussed the results from 3 RCTs (2 replicate 6-week crossover studies and one 12-week parallel study) which compared tiotropium/olodaterol with placebo for exercise endurance. The PAR stated that improvements in endurance exercise time compared with placebo were in-line with previous studies conducted with other LABA/LAMA combination inhalers.

Safety and tolerability

The Dutch [PAR](#) for Spiolto Respimat inhalation solution concludes that there is no evidence from the clinical trial programme that there is an additive effect in terms of the safety profile when the individual drugs (tiotropium and olodaterol) are combined in 1 inhaler.

In [Buhl et al. 2015](#) the proportion of people who reported at least 1 adverse event while on treatment was 74% (761/1029) in the tiotropium/olodaterol group, 73% (757/1033) in the tiotropium group and 77% (795/1038) in the olodaterol group. The proportion of people reporting serious adverse events, adverse events leading to discontinuation, adverse events requiring hospitalisation and fatal adverse events are reported in table 2. The most commonly reported adverse events were respiratory, thoracic and mediastinal disorders: 39% (405/1029) in the tiotropium/olodaterol group, 43% (441/1033) in the tiotropium group and 45% (470/1038) in the olodaterol group. Pneumonia occurred in 3.3% (34/1029) of the tiotropium/olodaterol group, 2.5% (26/1033) of the tiotropium group and 3.5% (36/1038) of the olodaterol group. No statistical analysis was provided for these safety outcomes.

As highlighted in the PAR for Spiolto Respimat inhalation solution both tiotropium and olodaterol may have cardiovascular side effects. The Medicines and Healthcare products Regulatory Agency (MHRA) has previously issued safety warnings on cardiovascular side effects with tiotropium. The [February 2015 Drug Safety Update](#) issued the following advice when prescribing tiotropium delivered via the Respimat or Handihaler for COPD:

- take the risk of cardiovascular side effects into account for people with conditions that may be affected by the anticholinergic action of tiotropium, including: myocardial infarction in the last 6 months, unstable or life threatening cardiac arrhythmia, cardiac arrhythmia requiring

intervention or a change in drug therapy in the past year and hospitalisation for heart failure (NYHA Class III or IV) within the past year

- tell people with these conditions to report any worsening of cardiac symptoms after starting tiotropium; people with these conditions were excluded from clinical trials of tiotropium
- review the treatment of all people already taking tiotropium as part of the comprehensive management plan to ensure that it remains appropriate for them; regularly review treatment of people at high risk of cardiovascular events
- remind people not to exceed the recommended once daily dose.

Buhl et al. (2015) excluded people with myocardial infarction within the previous year, unstable or life-threatening cardiac arrhythmia, hospitalisation for heart failure within the previous year and people with paroxysmal tachycardia. For the combined studies rate ratios for any cardiac event and major adverse cardiac events were similar between the groups. For any cardiac event the rate ratio for tiotropium/olodaterol compared with tiotropium was 0.81 (95% confidence interval [CI] 0.55 to 1.20) and compared with olodaterol it was 0.75 (95% CI 0.51 to 1.10). For major adverse cardiac events the rate ratio for tiotropium/olodaterol compared with tiotropium was 1.11 (95% CI 0.68 to 1.80) and compared with olodaterol it was 1.07 (95% CI 0.66 to 1.73). The PAR for Spiolto Respimat inhalation solution commented that in a subgroup of people with a history of cardiac disorders, a higher incidence of cardiac arrhythmias was seen with tiotropium/olodaterol compared with the mono-components. However, the exposure adjusted risk ratio did not show an increased risk.

The SPC for Spiolto Respimat inhalation solution includes a warning on cardiovascular effects. It highlights that experience of use is limited in people with a history of myocardial infarction during the previous year, unstable or life-threatening cardiac arrhythmia, hospitalisation for heart failure during the previous year or with a diagnosis of paroxysmal tachycardia (greater than 100 beats per minute) because people with these conditions were excluded from the clinical trials. It further adds that like other beta-2 agonists, olodaterol may produce clinically significant cardiovascular effects in some people such as increases in pulse rate, blood pressure or symptoms; and LABAs should be used with caution in people with cardiovascular disorders.

A number of other special warnings and precautions for use are listed in the SPC, including: a warning that tiotropium/olodaterol should not be used in asthma and that it should not be used as a rescue therapy for acute episodes of bronchospasm. Warnings on the anticholinergic effects related to tiotropium and precautions on use in people with renal impairment are also given. The SPC recommends that in people with moderate to severe renal impairment (creatinine clearance ≤ 50 ml/min) tiotropium/olodaterol should be used only if the expected benefit outweighs the potential risk. There is no long term experience in people with severe renal impairment. See the

[SPC](#) for further information on contraindications, warnings and precautions for use, potential interactions and adverse effects of tiotropium/olodaterol.

Evidence strengths and limitations

Tiotropium/olodaterol has been compared with its individual mono-components tiotropium and olodaterol. There are no published studies which directly compare the efficacy and safety of tiotropium/olodaterol with other combination LAMA/LABA inhalers or with combination treatment with tiotropium (Spiriva Handihaler or Respimat) plus an individual component LABA inhaler.

The Dutch [PAR](#) for Spiolto Respimat inhalation solution states that the clinical study programme for tiotropium/olodaterol was designed according to the [regulatory authority COPD guidelines](#). These regulatory guidelines require at least 2 co-primary outcome measures: a lung function improvement and a symptomatic improvement. Both [Buhl et al. 2015](#) and [Singh et al. 2015](#) had 3 primary outcomes; 2 lung-function outcomes and a health-related quality of life outcome ([SGRQ total score](#)). Buhl et al. (2015) had a secondary outcome which assessed breathlessness ([TDI focal score](#)). However, due to the hierarchical design of the studies which were used to avoid spurious statistically significant findings arising through chance (given the number of possible comparisons), although statistical analysis is provided for the TDI focal score outcome, it is not strictly inferential. Singh et al. (2015) also included TDI focal score as a secondary outcome for comparison with tiotropium. Buhl et al. (2015) provided some limited data on exacerbation rates; however the studies were not designed to assess this outcome. In addition, the PAR reported that for tiotropium/olodaterol the risk of having a severe exacerbation was inconsistent between the 2 trials. A 52 week RCT comparing tiotropium/olodaterol with tiotropium for a primary outcome of moderate to severe COPD exacerbation rates is currently ongoing ([NCT02296138](#)).

In Buhl et al. (2015) for trough FEV₁, SGRQ total score and TDI focal score the treatment difference between tiotropium/olodaterol and the individual mono-components was less than what is generally considered to be the minimum clinically important difference for these outcomes (see the [clinical effectiveness](#) section). However, it is unclear if these minimum clinically important differences are appropriate as a benchmark for clinical significance for comparisons between a combination of 2 bronchodilators (LAMA/LABA) with 1 bronchodilator (either a LAMA or a LABA). The PAR commented that the lung function improvements seen with tiotropium/olodaterol were in-line with other currently available LAMA/LABA combination inhalers.

Buhl et al. (2015) included participants with moderate to very severe COPD ([GOLD](#) stage 2 to 4) and Singh et al. (2015) included participants with moderate to severe COPD ([GOLD](#) stage 2 to 3). In

Buhl et al. (2015), 11% of participants had an FEV₁ less than 30% predicted (GOLD stage 4), 39% had an FEV₁ between 30 and 50% predicted (GOLD stage 3) and 50% had an FEV₁ between 50 and 80% predicted (GOLD stage 2). In Singh et al. (2015) only 0.5% of participants had GOLD stage 4 COPD, 35% had GOLD stage 3 COPD and 64% had GOLD stage 2 COPD. In Buhl et al. (2015) the groups appeared balanced for age, sex, current smoking status and COPD severity. In Singh et al. (2015) groups did not appear as well balanced for some parameters for example, current smoking status.

For all of the studies discussed in this evidence summary which compared tiotropium/olodaterol with the individual mono-components ([Buhl et al. 2015](#) and [Singh et al. 2015](#)) participants were allowed to continue treatment with ICS. Pre-treatment use varied across the allocated groups by between 45.1% and 49.2% in Buhl et al. (2015) and between 34.8% and 41.9% in Singh et al. (2015).

Although Buhl et al. (2015) was a 52-week study, the primary outcomes were evaluated after 24 weeks' treatment. Secondary outcomes included lung function outcomes after 52 weeks' treatment, however limited data are provided on this. Singh et al. (2015) was a 12-week study. There is therefore limited efficacy and safety data for longer term use.

Context

Alternative treatments

Tiotropium/olodaterol is the fourth LAMA/LABA combination inhaler to be launched in the UK for treating COPD, following umeclidinium/vilanterol ([Anoro Ellipta](#): see the evidence summary on [chronic obstructive pulmonary disease: umeclidinium/vilanterol](#)), indacaterol/glycopyrronium ([Ultibro Breezhaler](#): see the evidence summary on [chronic obstructive pulmonary disease: indacaterol/glycopyrronium](#)) and aclidinium/formoterol ([Duaklir Genuair](#): see the evidence summary on [chronic obstructive pulmonary disease: aclidinium/formoterol](#)).

Combination ICS/LABA inhalers currently licensed for treating COPD include:

- beclometasone/formoterol metered dose inhaler: [Fostair 100/6 micrograms](#): see the [evidence summary on chronic obstructive pulmonary disease – beclometasone/formoterol](#)
- beclomethasone/formoterol dry powder inhaler: [Fostair NEXThaler 100/6 micrograms](#)
- budesonide/formoterol dry powder inhalers: [Symbicort Turbohaler 400/12 micrograms](#) and [DuoResp Spiromax 320/9 micrograms](#)

- fluticasone furoate/vilanterol dry powder inhaler: [Relvar Ellipta 92/22 micrograms](#): see the evidence summary on [chronic obstructive pulmonary disease – fluticasone furoate plus vilanterol](#)
- fluticasone propionate/salmeterol dry powder inhalers: [Seretide Accuhaler 500/50 micrograms](#) and [AirFluSal Forspiro 500/50 micrograms](#).

Four single-component LABAs are currently licensed for treating COPD, formoterol, indacaterol, olodaterol and salmeterol (see the evidence summary on [chronic obstructive pulmonary disease: olodaterol](#)).

Single-component LAMAs licensed for treating COPD are aclidinium, glycopyrronium, tiotropium and umeclidinium (see the evidence summary on [chronic obstructive pulmonary disease: umeclidinium](#)).

Costs of alternative treatments

Drug	Usual dosage ^{a,b}	30-day cost excluding VAT
Single-component LABAs		
Formoterol 12 micrograms (Formoterol Easyhaler)	1 puff twice daily	£11.88 ^{c,d}
Indacaterol 150 micrograms and 300 micrograms (Onbrez Breezhaler)	1 puff daily	£29.26 ^c
Olodaterol 2.5 micrograms (Striverdi Respimat)	2 puffs once daily	£26.35 ^c
Salmeterol 50 micrograms (Serevent Accuhaler)	1 puff twice daily	£29.26 ^{c,d}
Single-component LAMAs		
Aclidinium 322 micrograms (Eklira Genuair)	1 puff twice daily	£28.60 ^e

Glycopyrronium 44 micrograms (Seebri Breezhaler)	1 puff daily	£27.50 ^e
Tiotropium 18 micrograms, dry powder (Spiriva Handihaler)	1 puff daily	£34.87 ^c
Tiotropium 2.5 micrograms, aerosol (Spiriva Respimat)	2 puffs once daily	£33.50 ^c
Umeclidinium 55 micrograms (Incruse Ellipta)	1 puff daily	£27.50 ^e
Combination LAMA/LABA inhalers		
Tiotropium/olodaterol 2.5/2.5 micrograms (Spiolto Respimat)	2 puffs once daily	£32.50 ^e
Aclidinium/formoterol 340/12 micrograms (Duaklir Genuair)	1 puff twice daily	£32.50 ^e
Indacaterol/glycopyrronium 85/43 micrograms (Ultibro Breezhaler)	1 puff daily	£32.50 ^e
Umeclidinium/vilanterol 55/22 micrograms (Anoro Ellipta)	1 puff daily	£32.50 ^e
Combination ICS/LABA inhalers		
Beclometasone/formoterol 100/6 micrograms, aerosol (Fostair)	2 puffs twice daily	£29.32 ^c
Beclometasone/formoterol 100/6 micrograms, dry powder (Fostair NEXThaler)	2 puffs twice daily	£29.32 ^e
Budesonide/formoterol 320/9 micrograms [equivalent to a metered dose of 400/12 micrograms] (DuoResp Spiromax)	1 puff twice daily	£29.97 ^e

Budesonide/formoterol 400/12 micrograms (Symbicort Turbohaler)	1 puff twice daily	£38.00 ^c
Fluticasone furoate/vilanterol 92/22 micrograms (Relvar Ellipta)	1 puff daily	£27.80 ^e
Fluticasone propionate/salmeterol 500/50 micrograms (AirFluSal Forspiro)	1 puff twice daily	£32.74 ^e
Fluticasone propionate/salmeterol 500/50 micrograms (Seretide Accuhaler)	1 puff twice daily	£40.92 ^c
<p>Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist.</p> <p>^a Doses taken from the relevant summary of product characteristics.</p> <p>^b The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.</p> <p>^c Costs taken from the Drug Tariff (March 2016). All costs include the inhaler device.</p> <p>^d Lowest cost dry powder formulations selected; other brands and formulations are available.</p> <p>^e Costs taken from MIMS (March 2016). All costs include the inhaler device.</p>		

Estimated impact for the NHS

Likely place in therapy

There are no published studies which directly compare the efficacy and safety of tiotropium/olodaterol (Spiolto Respimat) with other combination LAMA/LABA inhalers or with combination treatment with tiotropium plus an individual component LABA inhaler. In addition for all of the studies discussed in this evidence summary which compared tiotropium/olodaterol with the individual mono-components ([Buhl et al. 2015](#) and [Singh et al. 2015](#)) participants were allowed to continue treatment with inhaled corticosteroids. The Dutch [PAR](#) for Spiolto Respimat inhalation solution states that the lung function improvements seen with tiotropium/olodaterol were in-line with other currently available LAMA/LABA combination inhalers. There is limited evidence on exacerbation rates.

The [NICE guideline on COPD](#) (which is currently being [updated](#), publication date to be confirmed) recommends that the choice of drug treatment should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and its costs.

Tiotropium/olodaterol is an inhalation solution delivered by the Respimat soft mist inhaler. Acclidinium/formoterol and umeclidinium/vilanterol are both multi-dose breath-activated dry powder inhalers (Genuair and Ellipta devices respectively). Indacaterol/glycopyrronium is a single-dose breath-activated dry powder inhaler (Breezhaler device). Some people may prefer a particular device or be able to use one device better than another. Tiotropium/olodaterol is used once daily. Two out of the 3 other currently available LAMA/LABA combination inhalers are also used once daily.

Spiolto Respimat costs less than combination treatment with tiotropium plus a currently available LABA individual component inhaler. The 30-day cost is the same as the 3 other available LAMA/LABA combination inhalers.

Local decision makers will need to take safety, efficacy, patient factors and cost into account when considering the likely place in therapy of tiotropium/olodaterol. Costs for the 4 currently available LAMA/LABA inhalers are the same; however there are no published RCTs which directly compare their efficacy and safety.

Estimated usage

The manufacturer estimates that 38% of people eligible for tiotropium/olodaterol currently receive tiotropium monotherapy. They estimate that the proportion of eligible people who will receive tiotropium/olodaterol will be 1% in year 1, rising to 32% in year 5.

Relevance to NICE guidance programmes

Tiotropium/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 clinical guideline on [chronic obstructive pulmonary disease](#) (NICE guideline 101), which has been incorporated into a [NICE pathway](#). Following a recent review, it has been decided that the NICE guideline on COPD should be [updated](#) (publication date to be confirmed).

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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

Toby Capstick: in the past 2 years has received sponsorship from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer and Teva for educational events and conferences.

Anastasios Lekkas: no relevant interests to declare.

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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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