

# Chronic obstructive pulmonary disease: indacaterol/glycopyrronium (Ultibro Breezhaler)

## Evidence summary

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[nice.org.uk/guidance/esnm33](https://www.nice.org.uk/guidance/esnm33)

## Key points from the evidence

The content of this evidence summary was up-to-date in February 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

Indacaterol/glycopyrronium (Ultibro Breezhaler 85/43 micrograms) is the first long-acting beta<sub>2</sub> agonist (LABA)/long-acting muscarinic antagonist (LAMA) combination inhaler to be approved for chronic obstructive pulmonary disease (COPD). It is licensed as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD and is expected to be launched in the UK in quarter 2, 2014. Although some small statistically significant improvements in lung function, dyspnoea (breathlessness), health status and use of rescue medication were seen with indacaterol/glycopyrronium compared with active comparators, the clinical importance of these differences is unclear and indacaterol/glycopyrronium's place in therapy is currently difficult to assess.

<p><b>Effectiveness</b></p> <ul style="list-style-type: none"> <li>• Indacaterol/glycopyrronium statistically significantly reduced the rate of moderate or severe exacerbations compared with glycopyrronium alone in people with severe or very severe COPD. However, the <a href="#">European Medicines Agency</a> considered that the reduction was insufficient to support an indication for reducing exacerbations.</li> <li>• Overall, indacaterol/glycopyrronium showed a small but statistically significant improvement in lung function (forced expired volume in 1 second [FEV<sub>1</sub>]) compared with active comparators in people with moderate to very severe COPD.</li> <li>• Indacaterol/glycopyrronium also showed small statistically significant improvements in dyspnoea, health status and use of rescue medication compared with active comparators, which were of uncertain clinical benefit.</li> <li>• The European Medicines Agency noted that, although the differences between treatments were often not large enough to be clinically relevant in the total population, responder analyses have shown that differences can be important to individual patients.</li> </ul>	<p><b>Safety</b></p> <ul style="list-style-type: none"> <li>• The <a href="#">summary of product characteristics</a> reports that up to 15 months' treatment with indacaterol/glycopyrronium showed similar adverse reactions to those observed when people were treated with each drug individually.</li> <li>• In a 52-week safety study, the overall incidence of adverse events was similar between placebo and indacaterol/glycopyrronium (p value not reported).</li> <li>• Compared with established drugs such as formoterol, salmeterol and tiotropium, the long-term safety of indacaterol and glycopyrronium (alone or in combination) is unclear.</li> <li>• A 52-week study that is currently in progress may provide better evidence on the comparative safety and efficacy of LABA/LAMA and inhaled corticosteroid (ICS)/LABA.</li> <li>• Although the combination inhaler delivers the same clinically effective dose of indacaterol as the single-component inhaler, the stated doses are different which may confuse prescribers and patients.</li> </ul>
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Patient factors	Resource implications
<ul style="list-style-type: none"> <li>• People who are prescribed a LABA and a LAMA may find it easier to use a combination inhaler, rather than 2 single-component inhalers.</li> <li>• Indacaterol/glycopyrronium and the single-component inhalers are administered once daily using the Breezhaler dry powder inhalation device. Other LABAs, LAMAs and ICS/LABA inhalers are administered using different devices and many are taken twice daily.</li> <li>• NICE <a href="#">advises</a> that treatment and care should take into account a person's needs and preferences.</li> </ul>	<ul style="list-style-type: none"> <li>• The indacaterol/glycopyrronium combination inhaler is expected to be less expensive than the combined cost of the single-component inhalers (indacaterol £29.26, glycopyrronium £27.50 for 30-days' treatment).</li> </ul>

## Key points

Indacaterol/glycopyrronium (Ultibro Breezhaler 85/43 micrograms) is a once-daily, inhaled LABA/LAMA combination inhaler. It is the first LABA/LAMA combination inhaler to receive marketing authorisation in Europe and is indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD ([summary of product characteristics](#) for Ultibro Breezhaler). The manufacturer (Novartis) declined to share the UK launch date.

This evidence summary focuses on 2 published studies ([SPARK](#) [Wedzicha et al. 2013]) and [BLAZE](#) [Mahler et al. 2013]) that reported exacerbations and dyspnoea respectively, as their primary outcomes. Additional studies that reported lung function outcomes and longer-term assessments of safety are also discussed.

In [SPARK](#) (n=2224), indacaterol/glycopyrronium statistically significantly reduced the annualised rate of moderate to severe exacerbations in people with severe or very severe COPD by 12% compared with glycopyrronium alone ([relative risk](#) [RR] 0.88, 95% [confidence interval](#) [CI] 0.77 to 0.99,  $p=0.038$ ). A non-significant reduction of 10% was seen in this outcome between indacaterol/glycopyrronium and open-label tiotropium (RR 0.90, 95% CI 0.79 to 1.02,  $p=0.096$ ). In the [European public assessment report for indacaterol/glycopyrronium](#), the 12% reduction was considered to be 'very small' and not supportive of the manufacturer's requested indication of 'exacerbation reduction'. The [full NICE guideline on COPD](#) considers a relative reduction in the risk of exacerbations of 20% or more to be [clinically important](#).

BLAZE (n=247) found that indacaterol/glycopyrronium statistically significantly improved dyspnoea scores in people with moderate or severe COPD compared with placebo. The mean difference exceeded the 1 point improvement considered to be clinically important (least squares mean [LSM] difference 1.37, 95% CI 0.95 to 1.79; p<0.001). The dyspnoea score for indacaterol/glycopyrronium was also statistically significantly higher than for tiotropium (LSM difference 0.49, 95% CI 0.07 to 0.91; p=0.021). However, this difference is unlikely to be clinically important.

Two studies have reported lung function measures as primary outcomes: SHINE (Bateman et al. 2013; n=2144) and ILLUMINATE (Vogelmeier et al. 2012; n=523). In SHINE, indacaterol/glycopyrronium statistically significantly improved trough FEV<sub>1</sub> compared with indacaterol, glycopyrronium, open-label tiotropium and placebo (LSM differences 70 ml, 90 ml, 80 ml and 200 ml respectively; p<0.001 in all comparisons). For comparisons with active comparators, these changes in FEV<sub>1</sub> are less than the 100 ml or more that the full NICE guideline on COPD considers to be clinically important. In the other study, ILLUMINATE, FEV<sub>1</sub> standardised area under the curve from 0 to 12 hours (FEV<sub>1</sub> AUC<sub>0-12h</sub>) at week 26 was significantly higher with indacaterol/glycopyrronium compared with salmeterol/fluticasone (LSM difference 138 ml, 95% CI 100 ml to 176 ml; p<0.0001).

A 52-week safety study (ENLIGHTEN; n=339) found that the incidence of adverse events was similar in the indacaterol/glycopyrronium and placebo groups (57.8% and 56.6% respectively; p value not reported). Thirteen people receiving indacaterol/glycopyrronium (5.8%) had an adverse event leading to discontinuation of the study drug compared with 7 people receiving placebo (6.2%; p value not reported).

The summary of product characteristics for Ultibro Breezhaler reports that up to 15 months' treatment with indacaterol/glycopyrronium showed similar adverse reactions to those observed when people were treated with each drug individually. The safety profile of indacaterol/glycopyrronium is characterised by typical anticholinergic and beta-adrenergic symptoms.

Overall, indacaterol/glycopyrronium showed a statistically significant improvement in lung function compared with active comparators (indacaterol, glycopyrronium, tiotropium and fluticasone/salmeterol) in people with moderate to very severe COPD for up to 52 weeks. Indacaterol/glycopyrronium also showed small statistically significant improvements in dyspnoea, health status and use of rescue medication compared with active comparators. These improvements are of uncertain clinical benefit. Nevertheless, the European Medicines Agency states that, although the differences between treatments were often not large enough to be clinically relevant in the total population, responder analyses have shown that differences can be important to individual patients.

The NICE clinical guideline [Chronic obstructive pulmonary disease](#) (NICE clinical guideline 101) 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, side effects and costs. Use of dual therapy with a LAMA and LABA may be considered if an ICS (as part of combination therapy with a LABA) is declined or not tolerated.

The indacaterol/glycopyrronium combination inhaler is expected to be less expensive than the combined cost of the single-component inhalers and may be more convenient for people. However, compared with established drugs such as formoterol, salmeterol and tiotropium, the comparative efficacy and long-term safety of indacaterol and glycopyrronium (alone and in combination) is unclear, particularly in terms of reducing exacerbations. In addition, although the combination inhaler delivers the same clinically effective dose of indacaterol as the single-component inhaler, the stated doses are different which may confuse prescribers and patients.

Patients are currently being recruited for a 52-week study comparing the effects of indacaterol/glycopyrronium and fluticasone/salmeterol on exacerbations in people with moderate to very severe COPD (ClinicalTrials.gov [NCT01782326](#)). In addition to important patient-oriented outcome data, this study is likely to provide better longer-term comparative safety data for the 2 treatments.

#### Key evidence

Mahler DA, Decramer M, D'Urzo A et al. (2013) [Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: BLAZE study](#). *European Respiratory Journal* October 31. doi: 10.1183/09031936.00124013

Wedzicha JA, Decramer M, Ficker JH et al. (2013) [Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium \(SPARK\): a randomised, double-blind, parallel-group study](#). *The Lancet Respiratory Medicine* 1:199–209

## Update

The following information has become available since this ESNM was produced.

**December 2014: Availability of indacaterol/glycopyrronium (Ultibro Breezhaler)**

Indacaterol/glycopyrronium has been launched in the UK as [Ultibro Breezhaler](#). The cost of Ultibro Breezhaler (excluding VAT) is £14.30 for 12 capsules plus an inhaler or £35.75 for 30 capsules plus an inhaler. Costs taken from [MIMS](#), December 2014.

## May 2015: Medicines Evidence Commentary

[Chronic obstructive pulmonary disease \(COPD\): indacaterol/glycopyrronium combination inhaler compared with tiotropium and formoterol in a randomised, non-inferiority study](#)

This article discusses the implications of a 26-week double-blind randomised controlled trial in people with moderate to severe COPD which found that indacaterol/glycopyrronium was non-inferior to tiotropium plus formoterol in terms of health-related quality of life.

Medicines Evidence Commentaries form part of [NICE's Medicines Awareness Service](#) and help to contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. See the article above for more information.

### *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.**

### Relevance to NICE guidance programmes

Indacaterol/glycopyrronium 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 clinical guideline 101), which has been incorporated into a [NICE pathway](#).

### Introduction

The NICE clinical 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 diagnosed 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 clinical guideline on [COPD](#) defines COPD as follows:

- Airflow obstruction is defined as a reduced FEV<sub>1</sub>/FVC ratio (where FEV<sub>1</sub> is forced expired volume in 1 second and FVC is forced vital capacity), such that FEV<sub>1</sub>/FVC is less than 0.7.
- If FEV<sub>1</sub> is 80% predicted normal or more, a diagnosis of COPD should be made only in the presence of respiratory symptoms, for example, breathlessness or cough.

Classification of severity of airflow obstruction in COPD according to the NICE clinical guideline is shown in table 1.

**Table 1 NICE classification of severity of airflow obstruction in COPD**

Severity of airflow obstruction		
Post-bronchodilator FEV <sub>1</sub> /FVC	FEV <sub>1</sub> % predicted	Post-bronchodilator
<0.7	≥80%	Stage 1: Mild <sup>a</sup>
<0.7	50–79%	Stage 2: Moderate
<0.7	30–49%	Stage 3: Severe
<0.7	<30%	Stage 4: Very severe <sup>b</sup>
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV <sub>1</sub> , forced expired volume in 1 second; FVC, forced vital capacity.		
<sup>a</sup> Symptoms should be present to diagnose COPD in people with mild airflow obstruction.		
<sup>b</sup> Or FEV <sub>1</sub> <50% with respiratory failure.		

The NICE clinical 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 guideline recommends the following inhaled treatments for managing stable COPD. The list is not comprehensive but does include the key recommendations that relate to this evidence summary and the likely place in therapy of indacaterol/glycopyrronium.

- 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 FEV<sub>1</sub> is 50% predicted or more: either a long-acting beta<sub>2</sub> agonist (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*

Ultibro Breezhaler is a combination inhaler containing 2 active ingredients: indacaterol (a long-acting beta<sub>2</sub> agonist [LABA]) and glycopyrronium (a long-acting muscarinic antagonist [LAMA]). These are supplied in single-use capsules containing dry powder for inhalation using the Breezhaler. See the [summary of product characteristics](#) for Ultibro Breezhaler for more information.

The active ingredients have previously been licensed as single-component inhalers for maintenance treatment of symptoms of chronic obstructive pulmonary disease (COPD). See the summaries of product characteristics for [Onbrez Breezhaler](#) and [Seebri Breezhaler](#) for more information.

### *New therapeutic indication*

Indacaterol/glycopyrronium ([Ultibro Breezhaler](#); Novartis) received marketing authorisation in Europe in September 2013. It is indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. The manufacturer declined to share information on the expected UK launch date.

### *Course and cost*

According to the [summary of product characteristics](#) for Ultibro Breezhaler, the recommended dose is inhalation of the contents of 1 capsule, once daily using the Breezhaler. Each delivered dose contains 110 micrograms of indacaterol maleate and 50 micrograms of glycopyrronium bromide, which is equivalent to 85 micrograms of indacaterol and 43 micrograms of glycopyrronium.

For comparison, single-component indacaterol ([Onbrez Breezhaler](#)) is licensed at daily delivered doses of 120 and 240 micrograms of indacaterol maleate. The licensed daily dose delivered by the single-component glycopyrronium inhaler ([Seebri Breezhaler](#)) is 44 micrograms.

The manufacturer declined to share the cost of the indacaterol/glycopyrronium combination inhaler. However, it is expected to be less expensive than the combined cost of the single-component inhalers (indacaterol £29.26, glycopyrronium £27.50 for 30-days' treatment).

### **Evidence review**

This evidence review focuses on 2 published [randomised controlled trials](#) (RCTs) that provide published evidence for indacaterol/glycopyrronium in managing patient-oriented symptoms of chronic obstructive pulmonary disease (COPD):

- [SPARK](#) (Wedzicha et al. 2013) investigated whether indacaterol/glycopyrronium prevented more exacerbations than glycopyrronium or another a long-acting muscarinic antagonist (LAMA) (tiotropium) alone in people with severe or very severe COPD.

- **BLAZE** (Mahler et al. 2013) compared the effects of indacaterol/glycopyrronium on dyspnoea (breathlessness) with the effects of placebo and tiotropium in people with moderate to severe COPD.

Two other published 26-week RCTs, which investigated lung function measures as primary outcomes (forced expired volume in 1 second [FEV<sub>1</sub>]) are also discussed:

- **SHINE** (Bateman et al. 2013) compared indacaterol/glycopyrronium with indacaterol, glycopyrronium, tiotropium and placebo in people with moderate to severe COPD.
- **ILLUMINATE** (Vogelmeier et al. 2012) compared indacaterol/glycopyrronium with fluticasone/salmeterol, a combined inhaled corticosteroid/long-acting beta<sub>2</sub>-agonist (ICS/LABA), in people with moderate to severe COPD.

**ENLIGHTEN** (Dahl et al. 2013), a 52-week, placebo-controlled safety study, which also included some efficacy end points as secondary outcomes, is also summarised.

#### **SPARK** (Wedzicha et al. 2013)

- Design: RCT in 362 centres in 27 countries, including the UK, comparing the effects of indacaterol/glycopyrronium with glycopyrronium (the primary objective) and tiotropium (the key secondary objective) on exacerbations in people with severe or very severe COPD. Treatment with indacaterol/glycopyrronium and glycopyrronium was double-blind; tiotropium was used open-label because double-blind treatment was not available. Allocation was concealed. The study included a 14-day run-in period and a 64-week treatment period, extended to 76 weeks after a mid-study reassessment of sample size to ensure the study had sufficient statistical power.
- Population: 2224 adults aged 40 years or over (mean age around 63 years) who were current or ex-smokers with a smoking history of at least 10 pack-years. Patients had severe or very severe airflow limitation (stages III to IV of the 2008 Global Initiative for Chronic Obstructive Lung Disease [GOLD] criteria); post-bronchodilator FEV<sub>1</sub> less than 50% predicted; and FEV<sub>1</sub>/forced vital capacity [FVC] ratio less than 0.70 at screening. Patients were required to have a documented history of at least 1 exacerbation in the previous 12 months that needed treatment with systemic corticosteroids or antibiotics, or both. Long-acting bronchodilators were discontinued before screening but continued use of ICS was permitted during the study, with patients using ICS combination inhalers switched to the same or equivalent dose and regimen of single-component ICS.

- Intervention and comparison: patients were randomised in approximately equal numbers to treatment with:
  - indacaterol/glycopyrronium 110/50 micrograms once daily (using the Breezhaler; delivered doses 85/43 micrograms, as per the approved product)
  - glycopyrronium 50 micrograms once daily (using the Breezhaler)
  - tiotropium 18 micrograms once daily (using the [Spiriva Handihaler](#)).
- Outcome: the primary end point (indacaterol/glycopyrronium compared with glycopyrronium) and the key secondary efficacy end points (indacaterol/glycopyrronium compared with tiotropium) were the annualised rates of moderate or severe COPD exacerbations (number of events per patient per year). Moderate exacerbations were defined as worsening symptoms of COPD needing treatment with systemic corticosteroids and/or antibiotics. Severe exacerbations were defined as worsening symptoms of COPD that needed hospital admission or emergency treatment. Other secondary end points included annualised rates of exacerbations by degree of severity, use of rescue salbutamol and adverse events (summarised in table 2). Measures of lung function, health status scores (as measured by the [St. George's Respiratory Questionnaire](#) [SGRQ]) and adverse events were also assessed.

Table 2 Summary of [SPARK](#): Wedzicha et al. (2013)

	Indacaterol/ glycopyrronium (110/ 50 micrograms once daily)	Glycopyrronium (50 micrograms once daily)	Tiotropium (18 micrograms once daily)	Analysis
Randomised	n=741	n=741	n=742	
Efficacy <sup>a</sup>	n=729	n=739	n=737	
Primary outcome and key secondary outcome				

Annualised rate of moderate or severe exacerbations	0.84 (95% CI 0.75 to 0.94)	0.95 (95% CI 0.85 to 1.06)	0.93 (95% CI 0.83 to 1.04)	Indacaterol/ glycopyrronium versus glycopyrronium: RR 0.88 (95% CI 0.77 to 0.99); p=0.038 (12% reduction; NNT=8 <sup>b</sup> )  Indacaterol/ glycopyrronium versus tiotropium: RR 0.90 (95% CI 0.79 to 1.02); p=0.096 (NS)
Other selected secondary outcomes				
Annualised rate of severe exacerbations	0.09 (95% CI 0.07 to 0.13)	0.12 (95% CI 0.09 to 0.16)	0.08 (95% CI 0.06 to 0.11)	Indacaterol/ glycopyrronium versus glycopyrronium: RR 0.81 (95% CI 0.60 to 1.10); p=0.18 (NS)  Indacaterol/ glycopyrronium versus tiotropium: RR 1.16 (95% CI 0.84 to 1.61); p=0.36 (NS)
Annualised rate of mild exacerbations	2.51 (95% CI 2.25 to 2.80)	2.96 (95% CI 2.66 to 3.29)	2.98 (95% CI 2.68 to 3.32)	Indacaterol/ glycopyrronium versus glycopyrronium: RR 0.85 (95% CI 0.75 to 0.96); p=0.0072  Indacaterol/ glycopyrronium versus tiotropium: RR 0.84 (95% CI 0.75 to 0.95); p=0.0052

Annualised rate of all exacerbations	3.44 (95% CI 3.15 to 3.75)	4.04 (95% CI 3.71 to 4.40)	4.02 (95% CI 3.69 to 4.38)	Indacaterol/ glycopyrronium versus glycopyrronium: RR 0.85 (95% CI 0.77 to 0.94); p=0.0012  Indacaterol/ glycopyrronium versus tiotropium: RR 0.86 (95% CI 0.78 to 0.94); p=0.0017
Rescue salbutamol use (change from mean baseline value puffs/day [SE])	-2.3 (0.13)	-1.5 (1.3)	-1.5 (1.3)	Baseline values ranged from 5.5 to 5.7 puffs/day across groups  LSM differences:  indacaterol/ glycopyrronium versus glycopyrronium: -0.81; p<0.0001;  indacaterol/ glycopyrronium versus tiotropium: -0.76; p<0.0001
Safety <sup>c</sup>	n=729	n=740	n=737	
Patients reporting serious adverse events	22.9% (167/729)	24.2% (179/740)	22.4% (165/737)	Statistical significance not reported
Patients reporting worsening COPD as a serious adverse event	14.7% (107/729)	15.7% (116/740)	11.8% (87/737)	Statistical significance not reported

Patients reporting adverse events leading to discontinuation	8.1% (59/729)	9.1% (67/740)	6.4% (47/737)	Statistical significance not reported
Patients discontinuing treatment because of unsatisfactory therapeutic effect	2.5% (18/729)	4.3% (32/740)	5.2% (38/737)	Statistical significance not reported
<p>Abbreviations: CI, <u>confidence interval</u>; COPD, chronic obstructive pulmonary disease; LSM, least square mean; NNT, <u>number needed to treat</u>; NS, not significant; p, <u>p value</u>; RR, <u>relative risk</u>; SE, standard error.</p> <p><sup>a</sup> All randomised patients who received at least 1 dose of study drug, analysed according to the treatment they were randomly assigned to receive. This definition was later modified to exclude 9 patients from 1 site that did not meet good clinical practice standards.</p> <p><sup>b</sup> NNT quoted from the <u>European public assessment report for indacaterol/glycopyrronium</u>.</p> <p><sup>c</sup> All patients receiving a least 1 dose of study drug whether randomly assigned to a treatment group or not, according to the treatment they received, excluding the 9 patients from 1 site that did not meet good clinical practice standards.</p>				

### BLAZE (Mahler et al. 2013)

- Design: randomised, double-blind, double-dummy, placebo-controlled 3-period crossover study undertaken at 42 centres in Belgium, Canada, Germany, Spain and the UK, comparing the effects of indacaterol/glycopyrronium with placebo (primary objective) and tiotropium (secondary objective) on dyspnoea over 6 weeks.
- Population: 247 adults aged 40 years or over (mean age 62.8 years) who were current or ex-smokers with a smoking history of at least 10 pack-years. Patients had moderate or severe stable COPD (stage II or III according to 2009 GOLD criteria); post-bronchodilator FEV<sub>1</sub> at screening of at least 30% and less than 80% predicted; post-bronchodilator FEV<sub>1</sub>/FVC less than 0.70; and a modified Medical Research Council (mMRC) dyspnoea scale grade of at least 2. Most patients (70%) did not report any exacerbations in the previous year. Use of long-acting bronchodilators or short-acting muscarinic antagonists (SAMAs) was not permitted

during the study, but treatment with ICS was continued, with patients using combined LABA/ICS switched to equivalent ICS monotherapy.

- Intervention and comparison: after a 14-day screening period, patients were randomised to 1 of 6 treatment sequences, to receive each of the following 3 treatments for a block of 6 weeks, with each 6-week treatment separated by a 2-week washout period (it is unclear whether allocation was concealed):
  - indacaterol/glycopyrronium 110/50 micrograms once daily (using the Breezhaler)
  - tiotropium 18 micrograms once daily (using Spiriva Handihaler)
  - placebo (matching double-dummy placebos were used for both active treatments to maintain study blinding).
- Outcome: the primary (indacaterol/glycopyrronium compared with placebo) and key secondary efficacy end points (indacaterol/glycopyrronium compared with tiotropium) were the improvements in patient-reported dyspnoea scores after 6 weeks' treatment, as assessed using a computerised version of the Baseline and Transition Dyspnoea Indices (BDI/TDI). These results are presented in table 3, as are selected safety outcomes. Other secondary outcomes included measures of lung function, use of rescue medications, night-time awakenings due to symptoms, and symptom scores.

Table 3 Summary of BLAZE: Mahler et al. (2013)

	Indacaterol/ glycopyrronium (110/ 50 micrograms, once daily)	Tiotropium (18 micrograms, once daily)	Placebo	Analysis
Randomised	247 patients were randomised to 1 of the 6 crossover treatment sequences with overall exposure to treatment as shown below			
Efficacy <sup>a</sup>	n=223	n=220	n=218	
Primary outcome and key secondary outcome				

Dyspnoea (TDI total score after 6 weeks' treatment <sup>b</sup> )	0.88	0.39	-0.49	LSM differences: indacaterol/glycopyrronium versus placebo: 1.37 (95% CI 0.95 to 1.79); p<0.001 Indacaterol/glycopyrronium versus tiotropium: 0.49 (95% CI 0.07 to 0.91); p=0.021
Safety <sup>c</sup>	n=223	n=220	n=218	
Patients reporting adverse events <sup>d</sup>	35.0% (78/223)	35.5% (78/220)	39.4% (86/218)	Statistical significance not reported
Patients reporting serious adverse events <sup>d</sup>	2.7% (6/223)	2.7% (6/220)	2.3% (5/218)	Statistical significance not reported
Discontinuations due to adverse events <sup>d</sup>	4.9% (11/223)	5.5% (12/220)	4.1% (9/218)	Statistical significance not reported

Abbreviations: CI, confidence interval; LSM, least squares mean; p, p value; TDI, Transition Dyspnoea Index.

<sup>a</sup> All randomised patients who received at least 1 dose of study drug.

<sup>b</sup> Change in dyspnoea is measured by the TDI total score, which assesses change from the baseline dyspnoea index score for 3 domains. A score of -3 indicates major deterioration in a domain, a score of +3 indicates major improvement. Domain scores are then added together to give the total score. **A total score of 1 unit on the TDI is considered to be the minimal clinically important difference.**

<sup>c</sup> All patients who received at least 1 dose of study drug, whether or not they were randomised.

<sup>d</sup> Adverse events, serious adverse events and discontinuations occurring in the corresponding 6-week drug treatment period.

## Additional studies

The results of these studies are briefly summarised in the clinical effectiveness section of this evidence summary.

### SHINE (Bateman et al. 2013)

- Design: 26-week, multicentre, placebo-controlled RCT, comparing the effects of indacaterol/glycopyrronium with indacaterol, glycopyrronium and placebo (all administered double-blind) and tiotropium (administered open-label) on trough FEV<sub>1</sub>.
- Population: 2144 adults recruited from centres in Europe, North and South America, Asia, Australia and South Africa who were aged 40 years or over (mean age about 64 years) and were current or ex-smokers with a smoking history of at least 10 pack-years. Patients had moderate or severe stable COPD (stage II or III according to GOLD 2008 criteria); post-bronchodilator FEV<sub>1</sub> at screening of at least 30% and less than 80% predicted; and post-bronchodilator FEV<sub>1</sub>/FVC less than 0.70. Patients using fixed-dose ICS/LABA at study entry were switched to an equivalent dose of ICS monotherapy. Most patients (75%) did not report any exacerbations in the previous year.
- Intervention and comparison: participants were randomised 2:2:2:2:1 to the following 5 treatments (all delivered using the Breezhaler except tiotropium, which was delivered using the Spiriva Handihaler), taken once daily in the morning:
  - indacaterol/glycopyrronium 110/50 micrograms (n=475)
  - indacaterol 150 micrograms (the lower of the 2 licensed doses for single-component indacaterol; n=477)
  - glycopyrronium 50 micrograms (n=475)
  - tiotropium 18 micrograms (n=483)
  - placebo (n=234).
- Outcomes: the primary outcome was trough FEV<sub>1</sub> (measured at 23.25 and 23.75 hours post-dose) at week 26 for indacaterol/glycopyrronium compared with its individual components. Secondary outcomes included trough FEV<sub>1</sub> compared with placebo and tiotropium, changes in dyspnoea and health status scores, use of rescue medication, other lung function end points, patient-reported symptoms and adverse events.

### ILLUMINATE (Vogelmeier et al. 2012)

- Design: 26-week, multicentre, double-blind, double-dummy RCT, comparing the effects of indacaterol/glycopyrronium and fluticasone/salmeterol on lung function.

- Population: 523 adults from 93 centres in 10 countries who were aged 40 years or over (mean age 63.3 years) and were current or ex-smokers with a smoking history of at least 10 pack-years. Patients had moderate or severe stable COPD (stage II or III according to GOLD 2009 criteria); post-bronchodilator FEV<sub>1</sub> between 40% and 80% predicted; and post-bronchodilator FEV<sub>1</sub>/FVC less than 0.70 at screening. Patients with a history of a COPD exacerbation needing treatment with antibiotics, systemic corticosteroids or hospitalisation in the previous 12 months were excluded. Long-acting COPD maintenance therapy (LAMAs, LABAs, ICS and LABA/ICS) was withdrawn in a washout period.
- Intervention and comparison: participants were randomised in a 1:1 ratio to:
  - indacaterol/glycopyrronium 110/50 micrograms once daily (using the Breezhaler; n=258)
  - fluticasone/salmeterol 500/50 micrograms twice daily (using the Seretide 500 Accuhaler; n=264)
- Outcomes: the primary outcome was the standardised area under the curve from 0 to 12 hours post-dose for FEV<sub>1</sub> (FEV<sub>1</sub> AUC<sub>0-12h</sub>) at week 26. Secondary outcomes included other measures of lung function, changes in dyspnoea and health status scores, use of rescue medication and adverse events.

#### ENLIGHTEN (Dahl et al. 2013)

- Design: 52-week, multicentre, double-blind, placebo-controlled RCT, comparing the safety and efficacy of indacaterol/glycopyrronium with placebo.
- Population: 339 adults from centres in Europe, Canada, Asia and South Africa who were aged 40 years or over (mean age 62.6 years) and were current or ex-smokers with a smoking history of at least 10 pack-years. Patients had moderate or severe stable COPD (stage II or III according to GOLD 2008 criteria); post-bronchodilator FEV<sub>1</sub> at least 30% and less than 80% predicted; and post-bronchodilator FEV<sub>1</sub>/FVC less than 0.70 at screening). Use of LABAs, LAMAs and SAMAs was not permitted during the study but ICS use was maintained.
- Intervention and comparison: participants were randomised in a 2:1 ratio to once-daily treatment with :
  - indacaterol/glycopyrronium 110/50 micrograms (n=226)
  - placebo (n=113).

- Outcomes: the primary outcome was the frequency of treatment-emergent adverse events. Secondary outcomes included lung function, use of rescue medication and symptom scores.

## Clinical effectiveness

### Exacerbations

In [SPARK](#), indacaterol/glycopyrronium statistically significantly reduced the annualised rate of moderate to severe exacerbations (the primary outcome) in people with severe or very severe chronic obstructive pulmonary disease (COPD) by 12% compared with glycopyrronium ([relative risk \[RR\]](#) 0.88, 95% [confidence interval \[CI\]](#) 0.77 to 0.99,  $p=0.038$ ). A non-significant reduction of 10% was seen in this outcome between indacaterol/glycopyrronium and open-label tiotropium (RR 0.90, 95% CI 0.79 to 1.02,  $p=0.096$ ).

In the [European public assessment report for indacaterol/glycopyrronium](#), the 12% reduction was considered to be 'very small' and not supportive of the manufacturer's requested indication of 'exacerbation reduction'. The [full NICE guideline on COPD](#) considers a relative reduction in the risk of exacerbations of 20% or more to be [clinically important](#).

The annualised rate of severe exacerbations (defined as worsening symptoms needing admission to hospital or emergency treatment) was not statistically significantly reduced with indacaterol/glycopyrronium compared with either glycopyrronium or tiotropium (see table 2 for details).

### Dyspnoea

In [BLAZE](#), after 6 weeks' treatment, indacaterol/glycopyrronium statistically significantly improved dyspnoea scores (the primary outcome) in people with moderate or severe COPD compared with placebo ([Transition Dyspnoea Index \[TDI\]](#) total score +0.88 compared with -0.49,  $p<0.001$ ). The mean difference (but not the lower limit of the 95% CI value) exceeded the 1 point improvement considered to be clinically important (least squares mean [LSM] difference 1.37, 95% CI 0.95 to 1.79;  $p<0.001$ ). The dyspnoea score for indacaterol/glycopyrronium was also statistically significantly higher than for tiotropium (TDI score +0.88 compared with +0.39; LSM difference 0.49, 95% CI 0.07 to 0.91;  $p=0.021$ ). However, this difference is unlikely to be clinically important.

In [SHINE](#), dyspnoea (TDI total) scores were statistically significantly improved with indacaterol/glycopyrronium at week 26 compared with placebo (LSM difference 1.09,  $p<0.001$ ) and open-label tiotropium (LSM difference 0.51,  $p=0.007$ ), but not compared with single-component indacaterol or glycopyrronium. Improvements in dyspnoea scores were seen with indacaterol/glycopyrronium

in the [ILLUMINATE](#) study, compared with fluticasone/salmeterol (LSM difference at week 26 0.76,  $p=0.0031$ ).

## Health status

In [SPARK](#), health status ([St. George's Respiratory Questionnaire](#) [SGRQ] total) scores were statistically significantly lower (improved) with indacaterol/glycopyrronium at all time points assessed (12, 24, 38, 52 and 64 weeks). LSM differences ranged from  $-1.7$  to  $-3.1$  compared with glycopyrronium and open-label tiotropium ( $p<0.05$  in all comparisons). According to the [full NICE guideline on COPD](#), a difference of 4 units is considered to be the minimum clinically important difference in the SGRQ total score.

In [SHINE](#), SGRQ total scores at week 26 were statistically significantly lower (improved) with indacaterol/glycopyrronium compared with placebo (LSM difference  $-3.01$ ;  $p=0.002$ ) and open-label tiotropium (LSM difference  $-2.13$ ;  $p=0.009$ ). There were no significant improvements with the other treatments compared with placebo. In [ILLUMINATE](#), there was no significant difference in health status scores between indacaterol/glycopyrronium and fluticasone/salmeterol.

## Use of rescue salbutamol

In [SPARK](#), use of rescue salbutamol was significantly reduced by 2.3 puffs/day in people receiving indacaterol/glycopyrronium compared with 1.5 puffs/day in people receiving glycopyrronium or open-label tiotropium, a difference of approximately 0.8 puffs/day ( $p<0.0001$ ).

In [BLAZE](#), people taking indacaterol/glycopyrronium used significantly less rescue medication and had a significantly higher percentage of days with no rescue medication use compared with those taking placebo ( $p<0.001$  for both) or tiotropium ( $p=0.002$  and  $p<0.001$  respectively).

In the [SHINE](#), [ILLUMINATE](#) and [ENLIGHTEN](#) studies, treatment with indacaterol/glycopyrronium was associated with small but statistically significant reductions in the use of rescue salbutamol compared with placebo and active comparators.

## Night-time awakenings and daytime symptoms

In [BLAZE](#), the percentage of nights with no awakenings over 6 weeks was significantly higher for indacaterol/glycopyrronium compared with placebo ( $p<0.001$ ). The percentage of days with no daytime symptoms was also significantly higher with indacaterol/glycopyrronium compared with placebo ( $p=0.001$ ). However, for both assessments, indacaterol/glycopyrronium was not statistically significantly better than tiotropium.

In [ENLIGHTEN](#), compared with placebo, people receiving indacaterol/glycopyrronium reported an increased percentage of days with no daytime symptoms ( $p=0.012$ ), and days able to perform usual daily activities ( $p=0.028$ ). The number of nights with no night-time awakenings did not differ between the groups.

## Lung function

In [SPARK](#), trough forced expired volume in 1 second ( $FEV_1$ ) was statistically significantly higher with indacaterol/glycopyrronium at all assessments (continued to 64 weeks) compared with glycopyrronium (differences 70 to 80 ml;  $p<0.0001$ ) and open-label tiotropium (differences 60 to 80 ml;  $p<0.0001$ ). The [full NICE guideline on COPD](#) considers a change in  $FEV_1$  of 100 ml or more to be clinically important.

In [BLAZE](#), indacaterol/glycopyrronium provided statistically significant improvements in lung function, with higher post-dose  $FEV_1$ , standardised area under the curve from 0 to 4 hours ( $FEV_1 AUC_{0-4h}$ ) compared with placebo and tiotropium at day 1 and week 6 (all  $p<0.001$ )

In [SHINE](#) (1 of the 2 studies investigating lung function as a primary outcome), indacaterol/glycopyrronium statistically significantly improved trough  $FEV_1$  compared with indacaterol, glycopyrronium, open-label tiotropium and placebo at week 26 (LSM differences 70 ml, 90 ml, 80 ml and 200 ml respectively;  $p<0.001$  in all comparisons). In the other study, [ILLUMINATE](#),  $FEV_1 AUC_{0-12h}$  at week 26 was significantly higher with indacaterol/glycopyrronium compared with salmeterol/fluticasone (LSM difference 138 ml, 95% CI 100 ml to 176 ml;  $p<0.0001$ ).

In [ENLIGHTEN](#), pre-dose  $FEV_1$  at week 52 was increased by 189 ml with indacaterol/glycopyrronium compared with placebo ( $p<0.001$ ).

## Safety

The [summary of product characteristics](#) for Ultibro Breezhaler reports that up to 15 months' treatment with indacaterol/glycopyrronium showed similar adverse reactions to those observed when people were treated with each drug individually. The safety profile of indacaterol/glycopyrronium is characterised by typical anticholinergic and beta-adrenergic symptoms. Other most common adverse reactions (reported in at least 3% of people and also greater than placebo) are cough and oropharyngeal pain (including throat irritation).

In the 52-week safety study, [ENLIGHTEN](#), statistical analyses of the primary outcome (incidence of all adverse events) in the indacaterol/glycopyrronium and placebo groups were not presented,

although the overall incidence does appear to be similar (130/225 [57.8%] and 64/113 [56.6%] respectively). Thirteen people receiving indacaterol/glycopyrronium (5.8%) had an adverse event leading to discontinuation of the study drug compared with 7 people receiving placebo (6.2%; p value not reported).

In ENLIGHTEN, some respiratory-related adverse events occurred in greater numbers of people in the indacaterol/glycopyrronium treatment group compared with the placebo group, including cough (8.0% compared with 6.2%) and lower respiratory tract infections (6.7% compared with 3.5%; p values not reported). Significantly more people in the indacaterol/glycopyrronium group experienced pneumonia (8 compared with 0; p=0.074). In additional post-hoc analyses to investigate these differences, rates of pneumonia and respiratory-related serious adverse events were found not to be statistically significantly different. The authors suggest that the numerical difference for some adverse events may, in part, be explained by demographic imbalances at baseline, with greater numbers of people in the indacaterol/glycopyrronium group with severe COPD and using ICS. The European public assessment report for indacaterol/glycopyrronium indicates this imbalance relates to stratification of people based only on their smoking status, in accordance with regulatory guidance on clinical trials for COPD treatments. Also, a higher discontinuation rate was seen in the placebo group leading to a healthier population in that group.

In ILLUMINATE, the overall incidences of adverse events and serious adverse events were similar for indacaterol/glycopyrronium and fluticasone/salmeterol treatment groups (55.4% compared with 60.2%, and 5.0% compared with 5.3%, respectively; p values not reported). Reports of pneumonia, an adverse event associated with long-term ICS, were numerically higher in the fluticasone/salmeterol treatment group (4/159 compared with 0/143), although no statistical comparisons were provided.

## *Evidence strengths and limitations*

SPARK demonstrated that indacaterol/glycopyrronium statistically significantly reduced the annualised rate of all exacerbations compared with glycopyrronium and open-label tiotropium alone, and of moderate to severe exacerbations compared with glycopyrronium. However, the relative reductions were all below the 20% considered in the full NICE guideline on COPD to be clinically important. In addition, the rate of severe exacerbations was not reduced compared with either active comparator. The European Medicines Agency concluded that the benefits of indacaterol/glycopyrronium in terms of reducing exacerbations were not sufficiently proven to grant a license for this indication.

Although there is evidence of a statistically significant improvement compared with placebo in the [SHINE](#) study, the clinical significance of improvements in trough FEV<sub>1</sub> for indacaterol/glycopyrronium compared with glycopyrronium alone, open-label tiotropium or the lower licensed dose of indacaterol (150 micrograms) is unclear because the differences did not meet the 100 ml difference considered in the [full NICE guideline on COPD](#) to be clinically important. Similar results were seen in [SPARK](#).

Interpretation of both [SPARK](#) and [SHINE](#), within the context of the NICE pathway on [COPD](#), is complicated because many participants (75% in SPARK and 57% in SHINE) used ICS. This meant that many people in the indacaterol/glycopyrronium group received triple therapy (LAMA/LABA plus ICS), and were compared with a LAMA treatment arm in which a substantial number of people received dual therapy with a LAMA and an ICS. LAMA/ICS is not recommended in the NICE clinical guideline on [COPD](#) because of the paucity of evidence. Furthermore, no single-component ICS inhalers are licensed for treating COPD in the UK.

According to the [European public assessment report for indacaterol/glycopyrronium](#), the improvement in FEV<sub>1</sub> AUC<sub>0-12h</sub> of approximately 140 ml seen in [ILLUMINATE](#) is not unexpected because indacaterol/glycopyrronium contains 2 bronchodilators compared with 1 in fluticasone/salmeterol. In addition, the eligibility criteria for [ILLUMINATE](#) permitted enrolment of people with less severe COPD (post-bronchodilator FEV<sub>1</sub> between 40% and 80% predicted) than that for which fluticasone/salmeterol is currently licensed in the UK (pre-bronchodilator FEV<sub>1</sub> less than 60% predicted).

Although statistically significant improvements in several other outcomes have been reported for indacaterol/glycopyrronium (for example, dyspnoea scores, health status scores and use of rescue salbutamol) compared with some active comparators, the differences appear small and are of uncertain clinical importance. Nevertheless, the [European Medicines Agency](#) considered that, taking the overall results and the safety profile of glycopyrronium/indacaterol into account, a first-line indication for relieving symptoms in people with COPD is justified.

Patients are currently being recruited for a 52-week study comparing the effects of indacaterol/glycopyrronium and fluticasone/salmeterol on exacerbations in people with moderate to very severe COPD (ClinicalTrials.gov [NCT01782326](#)). In addition to important patient-oriented outcome data, this study is likely to provide better longer-term comparative safety data for the 2 treatments.

## Context

### *Treatment alternatives*

NICE recommendations for using inhaled treatments for chronic obstructive pulmonary disease (COPD) are outlined in the [introduction](#) to this evidence summary.

Three single-component long-acting beta<sub>2</sub> agonists (LABAs) are currently licensed for treating COPD in the UK: formoterol, indacaterol and salmeterol. Single-component long-acting muscarinic antagonists (LAMAs) licensed for treating COPD are aclidinium, glycopyrronium and tiotropium.

There are also 2 combined inhaled corticosteroid (ICS) and LABA inhalers that are currently licensed for treating COPD in the UK:

- fluticasone propionate/salmeterol 500/50 micrograms dry powder inhaler (Seretide 500 Accuhaler)
- budesonide/formoterol dry powder inhaler (Symbicort 200/6 Turbohaler and Symbicort 400/12 Turbohaler).

### *Costs of treatment alternatives*

The indacaterol/glycopyrronium combination inhaler is expected to be less expensive than the combined cost of the single-component inhalers (indacaterol £29.26, glycopyrronium £27.50 for 30-days' treatment).

Drug	Usual dosage <sup>a,b</sup>	30-day cost excluding VAT <sup>c</sup>
<b>Single-component LABAs</b>		
Formoterol fumarate 12 micrograms (Foradil) <sup>d</sup>	1 puff twice daily	£23.38
Indacaterol maleate 150 and 300 micrograms (Onbrez Breezhaler)	1 puff daily	£29.26
Salmeterol xinafoate 50 micrograms (Serevent Accuhaler) <sup>d</sup>	1 puff twice daily	£29.26
<b>Single-component LAMAs</b>		

Aclidinium bromide 322 micrograms (Eklira Genuair)	1 puff twice daily	£28.60
Glycopyrronium bromide 50 micrograms (Seebri Breezhaler)	1 puff daily	£27.50
Tiotropium bromide 18 micrograms, dry powder (Spiriva Handihaler)	1 puff daily	£34.87
Tiotropium bromide 2.5 micrograms, aerosol (Spiriva Respimat)	2 puffs daily	£35.50
<b>Combination ICS/LABA inhalers</b>		
Fluticasone propionate/salmeterol xinafoate 500/50 micrograms (Seretide 500 Accuhaler)	1 puff twice daily	£40.92
Budesonide/formoterol fumarate 200/6 micrograms (Symbicort Turbohaler 200/6)	2 puffs twice daily	£38.00
Budesonide/formoterol fumarate 400/12 micrograms (Symbicort Turbohaler 400/12)	1 puff twice daily	£38.00
<p>Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta<sub>2</sub> agonist; LAMA, long-acting muscarinic antagonist.</p> <p><sup>a</sup> Doses taken from the relevant <a href="#">summary of product characteristics</a>.</p> <p><sup>b</sup> The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.</p> <p><sup>c</sup> Costs taken from the <a href="#">Drug Tariff</a> (January 2013) except aclidinium, glycopyrronium and tiotropium Respimat (<a href="#">MIMS</a>, December 2013). All costs include the inhaler device.</p> <p><sup>d</sup> Lowest cost dry powder formulations selected; other brands and formulations are available.</p>		

## Estimated impact for the NHS

### *Likely place in therapy*

Overall, indacaterol/glycopyrronium showed a small but statistically significant improvement in lung function (forced expired volume in 1 second [FEV<sub>1</sub>]) compared with active comparators (indacaterol, glycopyrronium, tiotropium and fluticasone/salmeterol) in people with moderate to very severe chronic obstructive pulmonary disease (COPD) for up to 52 weeks. Indacaterol/glycopyrronium also showed small statistically significant improvements in dyspnoea, health status and use of rescue medication compared with active comparators. These improvements are of

uncertain clinical benefit. Nevertheless, the [European Medicines Agency](#) states that, although the differences between treatments were often not large enough to be clinically relevant in the total population, responder analyses have shown that differences can be important to individual patients.

The NICE clinical guideline on [COPD](#) 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 costs. The use of dual therapy with a component long-acting muscarinic antagonist (LAMA) and long-acting beta<sub>2</sub> agonist (LABA) may be considered if an inhaled corticosteroid (ICS; as part of combination therapy with a LABA) is declined or not tolerated. It is noted that NICE developed these recommendations in 2010, which predates the publication of the key clinical evidence for indacaterol, glycopyrronium and aclidinium.

The indacaterol/glycopyrronium combination inhaler is expected to be less expensive than the combined cost of the single-component inhalers and may be more convenient for people. However, compared with established drugs such as formoterol, salmeterol and tiotropium, the comparative efficacy and long-term safety of indacaterol and glycopyrronium (alone or in combination) is unclear, particularly in terms of reducing exacerbations. In addition, although the combination inhaler delivers the same clinically effective dose of indacaterol as the single-component inhaler, the stated doses are different which may confuse prescribers and patients.

In [SPARK](#), indacaterol/glycopyrronium statistically significantly reduced the risk of moderate to severe exacerbations in people with severe or very severe COPD by 12%. However, the [European Medicines Agency](#) concluded that the 12% reduction was considered to be 'very small' and not supportive of the manufacturer's requested indication of 'exacerbation reduction'. Similarly, the [full NICE guideline on COPD](#) considers a relative reduction in the risk of exacerbations of 20% or more to be [clinically important](#).

Specialists involved in producing this evidence summary consider that indacaterol/glycopyrronium may be used to relieve symptoms in people with COPD who remain symptomatic on a LABA or LAMA. However, current evidence does not support the use of indacaterol/glycopyrronium to reduce exacerbations in people with COPD, either as an intermediate step between LAMA monotherapy and LAMA plus LABA/ICS triple therapy, or as an alternative to LABA/ICS.

### *Estimated usage*

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

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## Changes after publication

March 2014:

The following changes have been made after publication of this evidence summary:

- The figure for improvement in trough FEV<sub>1</sub> seen with indacaterol compared with placebo in the SHINE study has been corrected to read 200 ml, instead of 20 ml. The text has also been amended to clarify that only comparisons with active comparators, not placebo, were less than the 100 ml that NICE considers to be clinically important for this outcome.
- The discussion around dyspnoea, health status and use of rescue medication has been focused on comparisons with active comparators; references to placebo have been removed.
- The text has been altered to make it clear that, although the combination inhaler appears to contain a different dose of indacaterol from the single-component inhaler, the delivered doses are equivalent.
- All references to personal communication with Novartis, including the estimated cost and launch date, have been removed at the manufacturer's request.

None of the changes alter the key messages of the evidence summary.

## 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.**

For information about the process used to develop this evidence summary, see [Evidence summaries: new medicines – integrated process statement](#).

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