NICE advice

Chronic obstructive pulmonary disease: umeclidinium inhaler (Incruse)

Evidence summary
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Key points from the evidence

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

Summary

Umeclidinium bromide is a new long-acting muscarinic antagonist (LAMA) for chronic obstructive pulmonary disease (COPD). Studies have shown improvements in forced expired volume in 1 second (FEV_1) compared with placebo. Patient-orientated outcomes such as dyspnoea have had varying results with some showing an improvement and others showing no difference compared with placebo. There are no published studies which directly compare the licensed dose with a currently available LAMA or long-acting beta2 agonist (LABA).

Regulatory status: Umeclidinium (Incruse) received a European marketing authorisation in April 2014 and was launched in the UK in October 2014.

Effectiveness • Statistically significant improvement from baseline in trough FEV_1 with umeclidinium 55 micrograms compared with placebo of 0.127 litres (1 RCT; n=206; 12 weeks) and 0.115 litres (1 RCT; n=1536; 24 weeks). • Statistically significant improvement in transition dyspnoea index (TDI) score of 1.0 unit with umeclidinium compared with placebo (1 RCT; n=1536; 24 weeks). No statistically significant difference between umeclidinium and placebo for TDI score in the 12-week RCT (1 RCT; n=206; 12 weeks).	**Safety** • The summary of product characteristics (SPC) lists nasopharyngitis, upper respiratory tract infection and headache as common adverse reactions (frequency 1 in 10 to 1 in 100 people). • The SPC states that cardiovascular effects, such as cardiac arrhythmias, atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists, including umeclidinium. • The SPC states that umeclidinium should be used with caution in people with severe cardiovascular disease, particularly cardiac arrhythmias. In addition, it states that consistent with its antimuscarinic activity, umeclidinium should be used with caution in people with urinary retention or with narrow-angle glaucoma.
Patient factors • Once daily dosage. Other LAMAs such as tiotropium and glycopyrronium are also used once a day. • Umeclidinium is delivered via the dry powder Ellipta inhaler. Individual patient assessment is needed when choosing an inhaler device.	**Resource implications** • The cost of umeclidinium (Incruse) is £27.50 for 30 days' supply. • The cost of 30 days' supply of an alternative currently available LAMA ranges from approximately £27.50 to £34.87. • Umeclidinium offers a modest cost saving over tiotropium but not over newer LAMAs such as glycopyrronium or aclidinium.

Introduction and current guidance

The NICE guideline on chronic obstructive pulmonary disease (COPD) states that COPD is characterised by airflow obstruction that is usually progressive and not fully reversible; it is

predominantly caused by smoking. The guideline makes several recommendations about inhaled treatments for managing stable COPD, which are relevant to the likely place in therapy of umeclidinium (Incruse, a LAMA inhaler). See the NICE guideline or the NICE pathway on COPD for full details.

Full text of Introduction and current guidance.

Product overview

Incruse is a multi-dose, dry powder inhaler containing umeclidinium bromide (a LAMA). The recommended dose is 1 inhalation once a day. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 55 micrograms umeclidinium which is equivalent to 65 micrograms of umeclidinium bromide. This corresponds to a pre-dispensed dose of 62.5 micrograms umeclidinium equivalent to 74.2 micrograms umeclidinium bromide (Incruse summary of product characteristics).Throughout this evidence summary the licensed umeclidinium dose is referred to as umeclidinium 55 micrograms.

Full text of Product overview.

Evidence review

- This evidence summary is based on the best available published evidence. This is 2 randomised controlled trials (RCTs): Trivedi et al. 2014 and Donohue et al. 2013. Both studies had trough FEV_1 as primary outcomes.
- Trivedi et al. 2014 found that there was a statistically significant improvement in trough FEV_1 of 0.127 litres (95% confidence interval [CI] 0.052 to 0.202; p<0.001) with umeclidinium 55 micrograms compared with placebo after 12 weeks' treatment. Donohue et al. 2013 found a statistically significant improvement in trough FEV_1 of 0.115 litres (95% CI 0.076 to 0.155; p≤0.001) with umeclidinium 55 micrograms compared with placebo after 24 weeks' treatment. The full NICE guideline on COPD considers 0.100 litres to be the minimum clinically important difference for change in FEV_1.
- Trivedi et al. 2014 and Donohue et al. 2013 both included patient-orientated secondary and additional outcomes. Donohue et al. 2013 reported a statistically significant improvement in the transition dyspnoea index (TDI) score with umeclidinium 55 micrograms compared with placebo (1.0 unit; 95% CI 0.5 to 1.5; p≤0.001) at 24 weeks. The full NICE guideline considers 1.0 unit to be the minimum clinically important difference for TDI score. However, in the study

by Trivedi et al. 2014 there was no statistically significant difference between umeclidinium 55 micrograms and placebo for this outcome at 12 weeks.

- Trivedi et al. 2014 found a statistically significant improvement in the St George's Respiratory Questionnaire (SGRQ) score of −7.90 points (95% CI −12.20 to −3.60; p<0.001) with umeclidinium 55 micrograms compared with placebo; which is greater than the −4 points that the full NICE guideline considers to be the minimum clinically important difference. There was also a statistically significant reduction in rescue salbutamol use with umeclidinium compared with placebo in this study. However, the clinical significance of this reduction (0.7 puffs per day) is unclear. Donohue et al. 2013 found no difference between umeclidinium and placebo for rescue salbutamol use. An improvement in the SGRQ score was seen with umeclidinium compared with placebo in this study; statistical analysis is described for this outcome but it is not strictly inferential due to the statistical testing procedure used in the study.

- The European public assessment report for umeclidinium concluded that the overall safety profile was generally consistent with the known class effects of LAMAs.

- There are limited long-term efficacy and safety data for the licensed dose. A long-term 52-week safety study (Donohue et al. 2014) has been published. However this study evaluates umeclidinium 113 micrograms and does not include the licensed umeclidinium dose.

Full text of Evidence review.

Context

Three other single-component LAMAs are currently licensed for use in COPD in the UK: aclidinium, glycopyrronium and tiotropium. Four single-component LABAs are currently licensed for use in COPD in the UK: formoterol, indacaterol, olodaterol and salmeterol.

Full text of Context.

Estimated impact for the NHS

The NICE guideline on COPD recommends that for people with stable COPD and an FEV_1 of 50% predicted or more who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, a LABA or a LAMA should be offered as maintenance therapy. For people with an FEV_1 of less than 50% predicted either a LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or a LAMA should be offered. There are only limited data to support the use of umeclidinium alone as ICS were also permitted in the studies. In both Trivedi et al. 2014 and Donohue et al. 2013, ICS at a stable dose of up to 1000 micrograms per day fluticasone propionate

or equivalent was allowed throughout the study period; at baseline around 24% of the study population in Trivedi et al. 2014 and around 51% in Donohue et al. 2013 were using ICS.

NICE also recommends that for people who remain breathless or have exacerbations despite taking a LABA with an ICS, a LAMA should be offered in addition to a LABA with an ICS irrespective of the FEV_1. Four studies (NCT01772134, NCT01772147, NCT01957163 and NCT02119286) have compared umeclidinium with placebo in a population of people also taking ICS/LABA combination inhalers. However, none of these studies has been published in full. All 4 of these studies had FEV_1 primary outcomes.

Both Trivedi et al. 2014 and Donohue et al. 2013 compared umeclidinium with placebo for FEV_1 primary outcomes. There are no published studies which directly compare umeclidinium 55 micrograms with a currently available LAMA or LABA.

Umeclidinium is an alternative to the other currently available LAMAs. There are no data to show that it is safer. It offers a modest cost saving over tiotropium but not over newer LAMAs such as glycopyrronium or aclidinium. There are no studies comparing umeclidinium with other available LAMAs, so comparisons cannot be made. It is most likely to make an impact by offering people with COPD another choice of inhaler device.

Full text of Estimated impact for the NHS.

About this evidence summary

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

Full evidence summary

Introduction and current guidance

The NICE guideline on chronic obstructive pulmonary disease (COPD) states that COPD is characterised by airflow obstruction that is usually progressive and not fully reversible; it is predominantly caused by smoking. About 900,000 people in the UK have 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 guideline includes the following key recommendations for stable COPD that are relevant to this evidence summary and the likely place in therapy of umeclidinium (Incruse: a long-acting muscarinic antagonist [LAMA] inhaler).

- Short-acting bronchodilators, as necessary, should be the initial empirical treatment for the relief of breathlessness and exercise limitation.
- In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, offer the following as maintenance therapy:
    - if forced expired volume in 1 second (FEV_1) is 50% predicted or more: either a long-acting beta2 agonist (LABA) or a LAMA
    - if FEV_1 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_1 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_1.
- 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_1.
- 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.

The full NICE guideline on COPD includes details on what it considers the minimum clinically important difference for a number of outcome measures used in COPD clinical studies to be.

Outcome measure	Minimum clinically important difference
Relative risk reduction for mortality	15%
Relative risk reduction for exacerbations	20%
Relative risk reduction for hospitalisation	20%
Change in St Georges Respiratory Questionnaire score	−4 points
Change in FEV_1	0.100 litres
Change in transition dyspnoea index score	1 unit

Product overview

Drug action

Incruse is a multi-dose, dry powder inhaler containing umeclidinium bromide (a long-acting muscarinic antagonist [LAMA]).

Licensed therapeutic indication

Umeclidinium is licensed as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD (Incruse summary of product characteristics). Incruse was launched in the UK in October 2014.

Course and cost

The recommended dose is 1 inhalation once a day. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 55 micrograms umeclidinium which is equivalent to 65 micrograms of umeclidinium bromide. This corresponds to a pre-dispensed dose of 62.5 micrograms umeclidinium equivalent to 74.2 micrograms umeclidinium bromide (Incruse summary of product characteristics). Throughout this evidence summary the licensed umeclidinium dose is referred to as umeclidinium 55 micrograms.

Incruse is available as a 30-dose inhaler, the cost of which is £27.50 (1 month of treatment; excluding VAT; costs taken from MIMS; December 2014). Based on this, the cost per patient per year is approximately £330.

Evidence review

This evidence summary is based on the best available published evidence. This is 2 randomised controlled trials (RCTs): Trivedi et al. 2014 and Donohue et al. 2013. Triveldi et al. 2014 compared two different doses of umeclidinium with placebo over 12 weeks. Donohue et al. 2013 compared umeclidinium/vilanterol 55/22 micrograms, umeclidinium 55 micrograms alone and vilanterol 22 micrograms alone with placebo over 24 weeks. Both of these studies had trough forced expired volume in 1 second (FEV_1) as primary outcomes.

Trivedi et al. 2014

- Design: 12-week, multicentre, randomised, blinded, parallel group study. The study was conducted in 27 centres in three countries (USA, Germany and Japan). The method of allocation described suggests that this was concealed.
- Population: 206 participants aged 40 years and over (mean age 63 years) with a clinical history of COPD (GOLD stage II to IV). Participants were current or former smokers with a smoking history of at least 10 pack-years (mean 48.3 pack-years). They had a post-salbutamol FEV_1 of 70% or less predicted normal (mean FEV_1 46.5%), an FEV_1 to FVC (forced vital capacity) ratio of less than 0.7 and a score of 2 or higher on the modified Medical Research Council dyspnoea scale. Exclusion criteria included hospital admission due to COPD or pneumonia within the previous 12 weeks or a diagnosis of asthma or other known respiratory disorder. Participants were also excluded if they had used oral or parenteral corticosteroids within the previous 6 weeks or inhaled corticosteroids (ICS) at a dosage greater than 1000 micrograms fluticasone propionate or equivalent within the last 30 days.
- Intervention and comparison: participants were randomised to umeclidinium 55 micrograms, umeclidinium 113 micrograms or placebo. All doses were taken once daily. Participants who were receiving ICS at baseline (24% of participants) were permitted to continue with this treatment at a stable dose. Use of salbutamol for symptom relief was allowed throughout the study.
- Outcomes: the primary outcome was trough FEV_1 (the mean of FEV_1 values obtained at 23 hours and 24 hours after the previous days dosing) on day 85. Secondary and additional outcomes included St George's Respiratory Questionnaire (SGRQ) score (a measure of health-related quality of life), rescue salbutamol use and transition dyspnoea index (TDI) focal score (a measure of dyspnoea).

Trivedi et al. 2014 included a comparator arm investigating umeclidinium 113 micrograms. However, results are presented here only for the umeclidinium 55 micrograms arm because that is the dose and strength that has been licensed.

Table 1 Summary of Trivedi et al. 2014

	Umeclidinium 55 micrograms once daily	**Placebo**	**Analysis**
Randomised	n=69	n=68	
Efficacy (ITT population[a])	n=69	n=68	
Primary outcome: trough FEV_1 LS mean change from baseline on day 85 (litres) [SE][b]	0.120 (0.0257)	−0.007 (0.028)	Statistically significant increase compared with placebo 0.127 (95% CI 0.052 to 0.202; p<0.001)
Selected secondary and additional outcomes:			
LS mean TDI[c] focal score on day 84	0.7	−0.3	No statistically significant difference with umeclidinium compared with placebo 1.0 (95% CI 0.0 to 2.0, p=0.05)
LS mean change in SGRQ[d] total score from baseline on day 84	−3.14	4.75	Statistically significant improvement compared with placebo −7.90 (95% CI −12.20 to −3.60; p<0.001)
Safety	n=69	n=68	
Patients reporting on treatment adverse events	39%	35%	No statistical analysis presented
Adverse events that led to withdrawal from study	1% (1/69)	0	No statistical analysis presented
Upper respiratory tract infection	3% (2/69)	0	No statistical analysis presented

Abbreviations: CI, confidence interval; ITT, intention-to-treat; LS, least-squares; TDI, transition dyspnoea index; SE, standard error; SGRQ, St George's Respiratory Questionnaire.

[a] ITT population: all randomised participants who received at least 1 dose of study medication.

[b] It was reported that the primary outcome was based on the ITT population. However, analysable data at day 85 were only available for 50 participants in the placebo group and 61 participants in the umeclidinium 55 microgram group.

[c] TDI: transition dyspnoea index – a measure of dyspnoea which ranges from −9 to +9. The lower the score, the more deterioration in severity of dyspnoea.

[d] SGRQ: 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.

Donohue et al. 2013

- Design: 24-week, multicentre, randomised, blinded, parallel group study. The study was conducted in 163 centres in 13 countries. The method of allocation described suggests that this was concealed.

- Population: 1536 participants aged 40 years and over (mean age 63 years) with a clinical history of COPD (GOLD stage II to IV). Participants were current or former smokers with a smoking history of at least 10 pack-years (mean approximately 46 pack-years). They had a post-salbutamol FEV_1 of 70% or less predicted normal (mean FEV_1 around 47%), an FEV_1 to FVC (forced vital capacity) ratio of less than 0.7 and a score of 2 or higher on the modified Medical Research Council dyspnoea scale. Exclusion criteria included hospital admission due to COPD or pneumonia within the previous 12 weeks or a diagnosis of asthma or other known respiratory disorder.

- Intervention and comparison: participants were randomised 3:3:3:2 to umeclidinium/ vilanterol 55/22 micrograms, umeclidinium 55 micrograms, vilanterol 22 micrograms and placebo. All doses were taken once a day. Use of inhaled salbutamol for symptom relief was allowed throughout the study as were inhaled corticosteroids at a stable dose of up to 1000 micrograms per day fluticasone propionate or equivalent.

- Outcomes: the primary outcome was the trough FEV_1 (the mean of FEV_1 values obtained at 23 hours and 24 hours after the previous days dosing) on day 169. The study was powered to detect a 0.100 litre difference between treatments for trough FEV_1. Additional efficacy outcomes included transition dyspnoea index (TDI) focal score (the study was powered to detect a 1 unit difference between treatments for this outcome measure), rescue salbutamol use, time to first COPD exacerbation and St George's Respiratory Questionnaire (SGRQ) score

(a measure of health-related quality of life). A step down statistical testing procedure was used in this study to avoid spurious statistically significant findings arising through chance, given the number of possible comparisons. Inference for a test in the pre-defined hierarchy was dependent upon statistical significance having been achieved for previous tests in the hierarchy. If at any point in the hierarchy a comparison did not demonstrate statistical significance, all further statistical analyses pre-specified in the hierarchy were fully described but are not strictly inferential.

Donohue et al. 2013 compared the umeclidinium/vilanterol combination inhaler with its individual components and placebo. However, results for the combination inhaler are not discussed in this evidence summary. An evidence summary on chronic obstructive pulmonary disease: umeclidinium/vilanterol combination inhaler has been published. The vilanterol (a long-acting beta2 agonist) comparator arm is presented. However, no direct comparison between umeclidinium and vilanterol was made and in addition, vilanterol as a single-component inhaler is not currently available.

Table 2 Summary of Donohue et al. 2013

	Umeclidinium 55 micrograms	Vilanterol 22 micrograms	Placebo	Analysis
Efficacy (ITT population[a])	n=418	n=421	n=280	
Primary outcome: trough FEV_1 LS mean change from baseline on day 169 (litres) [SE]	0.119 (0.0126)	0.076 (0.0127)	0.004 (0.0158)	Statistically significant increase in trough FEV_1 for umeclidinium versus placebo: 0.115 (95% CI 0.076 to 0.155; p≤0.001)
Selected secondary and additional outcomes:				
LS mean TDI focal score on day 168[b] (SE)	2.2 (0.16)	2.1 (0.16)	1.2 (2.0)	Statistically significant improvement with umeclidinium versus placebo: 1.0 (95% CI 0.5 to 1.5; p≤0.001)

LS mean change in SGRQ total score from baseline on day 168[c] (SE)	−7.25 (0.753)	−7.75 (0.760)	−2.56 (0.950)	Treatment difference with umeclidinium versus placebo: −4.69 (95% CI −7.07 to −2.31; p≤0.001[d]) statistical significance cannot be inferred due to statistical hierarchy
Salbutamol use (puffs per day) LS mean change from baseline over weeks 1 to 24 (SE)	−1.7 (0.16)	−2.4 (0.16)	−1.4 (0.2)	No difference with umeclidinium versus placebo −0.3 (95% CI −0.8 to 0.2)
Time to first COPD exacerbation	_	_	_	Treatment difference with umeclidinium versus placebo (HR 0.6; 95% CI 0.4 to 1.0; p<0.05[d]) statistical significance cannot be inferred due to statistical hierarchy
Safety	n=418	n=421	n=280	
Participants reporting on-treatment adverse events	52% (216/418)	48% (204/421)	46% (130/280)	No statistical analysis presented
Participants reporting on-treatment serious adverse events	6% (27/418)	6% (24/421)	3% (9/280)	No statistical analysis presented
Adverse events leading to withdrawal of study medication	8% (34/418)	6% (24/421)	3% (9/280)	No statistical analysis presented

Fatal adverse events[e]	<1% (3/418)	<1% (3/421)	0	No statistical analysis presented

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; LS, least-squares; TDI, transition dyspnoea index; SE, standard error; SGRQ, St George's Respiratory Questionnaire.

[a] ITT population: all randomised participants who received at least 1 dose of study medication.

[b] TDI: transition dyspnoea index – a measure of dyspnoea which ranges from −9 to +9. The lower the score, the more deterioration in severity of dyspnoea.

[c] SGRQ: 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] p value nominal only because of restrictions of the predefined statistical testing hierarchy.

[e] The 3 fatal adverse events in the umeclidinium group were COPD/acute respiratory failure, sudden death, cholecystitis and peritonitis and the 3 fatal adverse events in the vilanterol group were sudden death, COPD exacerbation and COPD exacerbation/renal failure.

Clinical effectiveness

There are no published studies which directly compare umeclidinium 55 micrograms with a currently available LAMA or LABA.

Triveldi et al. 2014 compared umeclidinium with placebo only. Donohue et al. 2013 compared the umeclidinium/vilanterol combination inhaler with its individual components and placebo. Comparisons were also made between umeclidinium and vilanterol alone and placebo.

Trivedi et al. 2014 compared umeclidinium with placebo for a FEV_1 primary outcome. Compared with placebo, there was a statistically significant improvement from baseline in trough FEV_1 of 0.127 litres with umeclidinium 55 micrograms, which is greater than the improvement that the full NICE guideline on COPD considers to be clinically important (0.100 litres or more). However, the lower 95% CI was less than 0.100 litres (see table 1).

In Donohue et al. 2013 there was also a statistically significant improvement from baseline in trough FEV_1 of 0.115 litres with umeclidinium 55 micrograms compared with placebo, although again the lower 95% CI was less than the 0.100 litres or more considered to be clinically important (see table 2). This study also included vilanterol 22 micrograms (a long-acting beta2 agonist) as a comparator arm (see table 2). However, no direct comparison between umeclidinium and vilanterol was made and in addition, vilanterol as a single-component inhaler is not currently available. Comparisons between the umeclidinium/vilanterol combination inhaler and umeclidinium are not

discussed in this evidence summary. An evidence summary on chronic obstructive pulmonary disease: umeclidinium/vilanterol combination inhaler has been published.

Trivedi et al. 2014 and Donohue et al. 2013 both included patient-orientated secondary and additional outcomes. Donohue et al. 2013 found a statistically significant improvement in the TDI score of 1.0 unit with umeclidinium 55 micrograms compared with placebo. The full NICE guideline on COPD considers 1.0 unit to be the minimum clinically important difference for TDI score. However, in Trivedi et al. 2014 there was no statistically significant difference between umeclidinium 55 micrograms and placebo for this outcome. Trivedi et al. 2014 found an improvement in the SGRQ score of −7.90 points with umeclidinium compared with placebo. This is greater than the improvement that the full NICE guideline considers to be clinically important (−4 points or more). There was also a statistically significant reduction in the mean number of salbutamol puffs per day with umeclidinium 55 micrograms compared with placebo. However the clinical significance of this reduction: −0.7 puffs per day (95% CI −1.3 to −0.1; p=0.025) is unclear.

Donohue et al. 2013 also included SGRQ score, rescue salbutamol use and COPD exacerbations as additional patient-orientated outcomes. However, a step-down statistical testing procedure was used in this study and comparisons for these outcomes were below a comparison that did not achieve statistical significance. Therefore comparisons between umeclidinium and placebo for these outcomes are described, but they are not strictly inferential and the p values are nominal only. In addition the study was not designed or powered to evaluate treatment effects on COPD exacerbations. In Donohue et al. 2013, an improvement in the SGRQ score of −4.69 points was seen with umeclidinium 55 micrograms compared with placebo. However, there was no difference between umeclidinium and placebo for rescue salbutamol use. On treatment COPD exacerbations were reported in 13% of participants in the placebo group and 7% to 9% of participants in the active treatment groups.

Trivedi et al. 2014 also included umeclidinium 113 micrograms as a comparator arm. However, results are presented here only for the umeclidinium 55 micrograms arm because that is the dose and strength that has been licensed. The European public assessment report for umeclidinium concluded that although greater differences in efficacy outcomes versus placebo for umeclidinium 113 micrograms compared to umeclidinium 55 micrograms were noted in some studies, these differences were not consistent and tended to be modest. In addition, a dose-trend could be seen for some adverse events such as cardiovascular adverse events and respiratory infections. No marketing authorisation for umeclidinium 113 micrograms was sought by the manufacturers.

Safety and tolerability

The summary of product characteristics (SPC:Incruse) lists nasopharyngitis, upper respiratory tract infection and headache as common (between 1 in 10 and 1 in 100) adverse reactions.

The SPC states that cardiovascular effects, such as cardiac arrhythmias, atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists, including umeclidinium. People with clinically significant uncontrolled cardiovascular disease were excluded from clinical studies. Therefore, the SPC states that umeclidinium should be used with caution in people with severe cardiovascular disease, particularly cardiac arrhythmia's. In addition, it states that consistent with its antimuscarinic activity, umeclidinium should be used with caution in people with urinary retention or with narrow-angle glaucoma.

The SPC states that umeclidinium should not be used in people with asthma as it has not been studied in people with this condition. In addition, the SPC states that umeclidinium is intended for the maintenance treatment of COPD and that it should not be used for the relief of acute symptoms. The SPC also states that administration of umeclidinium may produce paradoxical bronchospasm that may be life-threatening. Treatment should be discontinued immediately if paradoxical bronchospasm occurs and alternative therapy started if necessary.

In Trivedi et al. 2014 results were presented for 'on-treatment' adverse events and adverse events that led to withdrawal from the study (see table 1 for more information). The authors state that overall incidence of adverse events was similar across treatments. However, no statistical analysis was presented. Serious adverse events occurred in 4 participants (2 in the umeclidinium 113 microgram group, 1 in the umeclidinium 55 microgram group and 1 in the placebo group); none of which were considered to be drug-related. Seven participants reported a cardiovascular adverse event including 2 participants in the umeclidinium 55 microgram group (supraventricular tachycardia and ventricular extrasystoles) and 1 participant in the placebo group (atrioventricular block first degree). No notable differences for blood pressure, heart rate or ECG changes were reported.

In Donohue et al. 2013 results were also presented for 'on-treatment' adverse events, serious 'on-treatment' adverse events, adverse events that led to discontinuation of the study drug and fatal adverse events (see table 2 for more information). However no statistical analysis was presented. No clinical relevant changes were reported for vital signs, ECG or clinical laboratory tests for umeclidinium compared with placebo.

The European public assessment report for umeclidinium concluded that the overall safety profile was generally consistent with the known class effects of LAMAs. However, it did state that although umeclidinium belongs to a well-established and known drug class, it is a new active substance and safety data from this class may not necessarily be applicable. A post-authorisation observational safety study is planned which will compare umeclidinium and tiotropium for the incidence and comparative safety of selected cardiovascular and cerebrovascular events and lower respiratory tract infections including pneumonia in people with COPD.

Long-term safety data for the licensed dose are limited. A long-term 52-week safety study (Donohue et al. 2014) has been published. However this study evaluates umeclidinium 113 micrograms and does not include the licensed umeclidinium dose.

Evidence strengths and limitations

There are no published studies which directly compare umeclidinium 55 micrograms with a currently available LAMA or LABA. There are some limited comparative data with tiotropium: a seven day cross-over study (Church et al. 2014) which included an open-label tiotropium arm and a 14-day crossover study (Donohue et al. 2012) which included an open-label tiotropium arm. Both studies had FEV_1 primary outcomes, however no direct comparisons between umeclidinium 55 micrograms and tiotropium are made.

A 24-week study (Decramer et al. 2014) which evaluated the umeclidinium/vilanterol combination inhaler included umeclidinium 113 micrograms and tiotropium 18 micrograms as comparator arms. However, this study did not include umeclidinium 55 micrograms and in addition no direct comparisons between umeclidinium and tiotropium were made. Although, the European public assessment report for umeclidinium has stated that this study showed that the efficacy of umeclidinium 113 micrograms was similar to tiotropium 18 micrograms and that this may provide an indirect estimation of the effect size of umeclidinium 55 micrograms in relation to tiotropium.

Triveldi et al. 2014 compared umeclidinium with placebo. Donohue et al. 2013 included vilanterol (a LABA) as a comparator arm, however no direct comparisons between umeclidinium and vilanterol are made and in addition, vilanterol alone is not currently available.

Baseline characteristics' of participants in the studies were generally well-balanced. However, in Triveldi et al. 2014 there were differences between the umeclidinium 55 microgram and placebo group in the proportion of participants who had severe or very severe COPD (63% and 51% in the umeclidinium and placebo groups respectively) although the statistical significance of any differences was not reported. All participants recruited to the studies had to have a

post-salbutamol FEV_1 of 70% or less predicted normal; no participants had mild COPD. The majority of participants had moderate (46%) or severe (41%) COPD and around 66% were male, limiting applicability to female patients and those with mild or very severe COPD.

The NICE guideline on COPD recommends that the choice of treatment should take into account the person's symptomatic response and preference, and the medicine's potential to reduce exacerbations, side effects and costs. Both Triveldi et al. 2014 and Donohue et al. 2013 had disease-orientated FEV_1 primary outcomes. However, patient-orientated secondary and additional outcomes were included in the 2 studies including TDI score, rescue salbutamol use and SGRQ score. Donohue et al. 2013 included an additional outcome on time to first on-treatment COPD exacerbation. However, it was not designed or powered to evaluate treatment effects on COPD exacerbations. In addition, for the majority of the patient-orientated outcomes in Donohue et al. 2013 statistical analyses are described but they are not strictly inferential due to the step down statistical testing procedure that was used in this study.

There are only limited data to support the use of umeclidinium alone as ICS were also permitted in the studies. In both Trivedi et al. 2014 and Donohue et al. 2013, ICS at a stable dose of up to 1000 micrograms per day fluticasone propionate or equivalent was allowed throughout the study period; at baseline around 24% of the study population in Trivedi et al. 2014 and around 51% in Donohue et al. 2013 were using ICS.

There are limited long-term efficacy and safety data for the licensed dose. Triveldi et al. 2014 was conducted over 12 weeks only and Donohue et al. 2013 was conducted over 24 weeks. A long-term 52-week safety study (Donohue et al. 2014) has been published. However this study evaluates umeclidinium 113 micrograms and does not include the licensed umeclidinium dose.

Context

Alternative treatments

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

Three other single-component LAMAs are currently licensed for use in COPD in the UK: aclidinium, glycopyrronium and tiotropium. Four single-component LABAs are currently licensed for use in COPD in the UK: formoterol, indacaterol, olodaterol and salmeterol. An evidence summary on the use of olodaterol for the treatment of COPD is in development with an anticipated publication date of February 2015.

Costs of alternative treatments

Drug and formulation			Usual dosage[a,b]	30-day cost excluding VAT
LAMA inhalers				
Umeclidinium 55 micrograms/inhalation		Dry powder inhaler (Incruse)	1 puff daily	£27.50[c]
Aclidinium 322 micrograms/inhalation		Dry powder inhaler (Eklira Genuair)	1 puff twice daily	£28.60[c]
Glycopyrronium 44 micrograms/inhalation		Dry powder capsules (Seebri Breezhaler)	1 puff daily	£27.50[c]
Tiotropium	18 micrograms/inhalation	Dry powder capsules (Spiriva Handihaler)	1 puff daily	£34.87[d,e]
	2.5 micrograms/dose	Inhalation solution (Spiriva Respimat)	2 puffs daily	£33.50[c]
LABA inhalers				
Indacaterol 150 microgram/inhalation and 300 microgram/inhalation		Inhalation powder (Onbrez Breezhaler)	1 puff daily	£29.26[d]

Formoterol 12 micrograms/inhalation		Dry powder inhaler (Formoterol Easyhaler)	1 puff twice daily	£11.88[d]
		Inhalation solution (Atimos Modulite)	1 puff twice daily	£18.04[d]
		Dry powder capsules (Foradil)	1 puff twice daily	£23.38[d]
		Dry powder inhaler (Oxis Turbohaler)	1 puff twice daily	£24.80[d]
Olodaterol 2.5 micrograms/inhalation		Inhalation solution (Striverdi Respimat)	2 puffs daily	£26.35[c]
Salmeterol	25 micrograms/inhalation	Metered dose inhaler (Serevent Evohaler)	2 puffs twice daily	£29.26[d]
	50 micrograms/inhalation	Dry powder inhaler (Serevent Accuhaler)	1 puff twice daily	£29.26[d]

Abbreviations: LABA, long-acting beta2 agonist; LAMA, long-acting muscarinic antagonist.

[a] Doses taken from the relevant summary of product characteristics.

[b] The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

[c] Costs taken from MIMS (October 2014). All costs include the inhaler device.

[d] Costs taken from the Drug Tariff (October 2014). All costs include the inhaler device.

[e] Refills are available and cost £33.50.

Estimated impact for the NHS

Likely place in therapy

NICE recommends that for people with stable COPD and an FEV_1 of 50% predicted or more who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, a LABA or a LAMA should be offered as maintenance therapy. For people with an FEV_1 of less than 50% predicted either a LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or a LAMA should be offered. There are only limited data to support the use of umeclidinium alone as ICS were also permitted in the studies. In both Trivedi et al. 2014 and Donohue et al. 2013, ICS at a stable dose of up to 1000 micrograms per day fluticasone propionate or equivalent was allowed throughout the study period. In Donohue et al. 2013 approximately 51% of the study population were using an ICS at baseline. In Trivedi et al. 2014, 24% of the population were reported to be using an ICS at baseline.

NICE also recommends that for people who remain breathless or have exacerbations despite taking a LABA with an ICS, a LAMA should be offered in addition to a LABA with an ICS irrespective of the FEV_1. Two studies (NCT01772134 and NCT01772147) have compared umeclidinium with placebo in people also taking fluticasone propionate/salmeterol 250/50 micrograms twice daily. In addition, 2 other studies (NCT01957163 and NCT02119286) have compared umeclidinium with placebo in people taking open-label fluticasone furoate/vilanterol. All 4 studies had trough FEV_1 primary outcomes. However, none of these studies has been published in full.

The NICE guideline on COPD recommends that the choice of treatment should take into account the person's symptomatic response and preference, and the medicine's potential to reduce exacerbations, side effects and costs. Both Trivedi et al. 2014 and Donohue et al. 2013 had FEV_1 primary outcomes. However, both studies did include patient-orientated secondary and additional outcomes looking at dyspnoea and health-related quality of life. Improvements compared with placebo were seen with some but not all outcomes. Donohue et al. 2013 also included an additional

outcome on time to first on-treatment COPD exacerbation. However, it was not designed or powered to evaluate treatment effects on COPD exacerbations.

Both Trivedi et al. 2014 and Donohue et al. 2013 compared umeclidinium with placebo. There are no published studies which directly compare umeclidinium 55 micrograms with a currently available LAMA or LABA.

Umeclidinium is an alternative to the other currently available LAMAs. There are no data to show that it is safer. It offers a modest cost saving over tiotropium but not over newer LAMAs such as glycopyrronium. There are no studies comparing umeclidinium with other available LAMAs, so comparisons cannot be made. It is most likely to make an impact by offering people with COPD another choice of inhaler device.

Estimated usage

Using data from the quality and outcomes framework the manufacturers estimate that 819,524 people in England have a diagnosis of COPD. They estimate that approximately 62.56% of people with a diagnosis of COPD (which is approximately 516,694 people in England) are prescribed a LAMA.

Relevance to NICE guidance programmes

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

In 2010, NICE published a guideline on chronic obstructive pulmonary disease (NICE guideline CG101), which has been incorporated into a NICE pathway. A review decision was made on this guideline in July 2014 and it was decided that this guideline should not be updated at this time.

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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

No relevant interests declared.

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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