Chronic obstructive pulmonary disease: aclidinium/formoterol

Evidence summary
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Key points from the evidence

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

Summary

Aclidinium/formoterol (Duaklir Genuair) is a combination inhaler containing a long-acting muscarinic antagonist (LAMA) and long-acting beta-2 agonist (LABA). It is licensed for treating chronic obstructive pulmonary disease (COPD).

Two randomised controlled trials (RCTs) found that aclidinium/formoterol statistically significantly improved lung function and breathlessness over 24 weeks compared with placebo and aclidinium and formoterol monotherapies. Not all of the improvements compared with aclidinium or formoterol monotherapy were considered to be clinically important using conventional criteria. Improvements in lung function and breathlessness were similar to those seen with the other recently licenced LAMA/LABA combinations, umeclidinium/vilanterol and indacaterol/glycopyrronium.

Regulatory status: Duaklir Genuair (aclidinium/formoterol) received a European marketing authorisation for maintenance bronchodilator treatment to relieve symptoms in adults with COPD in December 2014.
### Effectiveness

In a pooled analysis of 2 RCTs (n=1729 and n=1692) aclidinium/formoterol statistically significantly improved:

- 1 hour post-dose FEV₁ more than aclidinium monotherapy (difference 118 ml, p<0.0001) and placebo (difference 293 ml, p<0.0001)

- trough FEV₁ more than formoterol monotherapy (difference 68 ml, p<0.0001: not clinically important) and placebo (difference 138 ml, p<0.0001)

- breathlessness compared with placebo (difference 1.43 units, p<0.0001) and aclidinium (difference 0.44 units, p=0.016: not clinically important) and formoterol monotherapy (difference 0.47 units, p=0.009: not clinically important)

- exacerbations of any severity compared with placebo (difference 0.33 exacerbations per patient/year, p=0.01: clinical importance unclear).

There are no published studies comparing the efficacy and safety of aclidinium/formoterol with other single or combination treatments for COPD.

### Safety

- According to the European Public Assessment Report for aclidinium/formoterol, the number of drug-related adverse events was generally low in the studies and did not give rise to any major safety concerns.

- According to the summary of product characteristics, adverse effects associated with aclidinium/formoterol are similar to those of the individual components. The adverse effects most frequently reported with the combination are nasopharyngitis (7.9%) and headache (6.8%).

- As for other LABA/LAMA combination inhalers, warnings about cardiovascular risk are included in the summary of product characteristics.
**Patient factors**

- Aclidinium/formoterol is used twice daily. Other LAMA/LABA combination inhalers are available which are used once daily.

- Aclidinium/formoterol and umeclidinium/vilanterol are both multi-dose breath-activated dry powder inhalers (Genuair and Ellipta respectively). Indacaterol/glycopyrronium is a single dose breath-activated dry powder inhaler (Breezhaler). Some people may prefer a particular device.

- Some people with COPD like to use a spacer. None of the LAMA/LABA combination inhalers can be used with a spacer.

**Resource implications**

- The aclidinium/formoterol combination inhaler costs less than the combined cost of the single-component inhalers.


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**Introduction and current guidance**

The NICE clinical guideline on chronic obstructive pulmonary disease (COPD) makes several recommendations about inhaled treatments for managing stable COPD that are relevant to the likely place in therapy of aclidinium/formoterol. The use of dual therapy with a LAMA and LABA may be considered if an inhaled corticosteroid (ICS; as part of combination therapy with a LABA) is declined or not tolerated. See the NICE guideline or the NICE pathway on COPD for full details.

Full text of introduction and current guidance.

**Product overview**

Duaklir Genuair (aclidinium/formoterol) is a breath-activated dry powder inhaler containing aclidinium bromide (a LAMA) and formoterol fumarate dihydrate (a LABA). It received a European marketing authorisation for maintenance bronchodilator treatment to relieve symptoms in adults with COPD in December 2014.

Full text of product overview.
Evidence review

- This evidence summary is based on 2 RCTs (ACLIFORM-COPD and AUGMENT-COPD), which evaluated the efficacy of aclidinium/formoterol compared with placebo and aclidinium and formoterol monotherapies in people with moderate or severe stable COPD over 24 weeks. It includes pooled analyses of data from ACLIFORM and AUGMENT, taken from the European Public Assessment Report for aclidinium/formoterol.

- In the pooled population at week 24, aclidinium/formoterol improved 1 hour post-dose forced expired volume in 1 second (FEV\textsubscript{1}) statistically significantly more than aclidinium monotherapy (primary outcome 1: difference 118 ml, p<0.0001) and placebo (difference 293 ml, p<0.0001). These results are clinically important because they are above the 100 ml level generally considered to be a minimum clinically important difference in FEV\textsubscript{1} (see the full NICE guideline on COPD).

- Aclidinium/formoterol also improved trough FEV\textsubscript{1} statistically significantly more than formoterol monotherapy (primary outcome 2: difference 68 ml, p<0.0001) and placebo (difference 138 ml, p<0.0001). The difference between the combination and formoterol is below the 100 ml level generally thought to be clinically important (see the full NICE guideline on COPD). According to the European Public Assessment Report for aclidinium/formoterol, this difference is similar to that seen with other recently licensed LAMA/LABA combinations. The European Public Assessment Report also notes that it has been argued that an additional improvement in FEV\textsubscript{1} of 100 ml cannot be achieved by adding a second bronchodilator to the first because people with moderate to severe COPD generally have limited airways reversibility.

- In the pooled population, aclidinium/formoterol improved breathlessness (Transition Dyspnoea Index [TDI] focal scores) statistically significantly more than placebo (difference 1.43 units, p<0.0001), aclidinium monotherapy (difference 0.44 units, p=0.016) and formoterol monotherapy (difference 0.47 units, p=0.009). Only the comparison with placebo is above the 1 unit improvement generally considered to be clinically important for this outcome (see the full NICE guideline on COPD).

- Aclidinium/formoterol improved health-related quality of life (St. George’s Respiratory Questionnaire [SGRQ]) total scores statistically significantly more than placebo in AUGMENT (difference 4.36 units, p≤0.01: 4 units is generally considered to be clinically important; see the full NICE guideline on COPD). No statistically significant differences were found when the combination was compared with aclidinium or formoterol monotherapy. In ACLIFORM, a high and clinically important placebo response was seen (6.51 units compared with 2.21 units in
Post-hoc analyses failed to identify a single reason for this unexpected result and suggest that the cause is likely to have been multi-factorial.

- The percentages of people in the pooled aclidinium/formoterol group who achieved 1 unit for TDI focal score (62%) and 4 units for SGRQ total score (57%) were similar to those achieved by the 2 other recently approved LAMA/LABA combinations (umeclidinium/vilanterol, 58% and 49% respectively; and indacaterol/glycopyrronium, 68% and 64% respectively; European Public Assessment Report for aclidinium/formoterol).

- In the pooled population, rates of moderate or severe exacerbations using the Healthcare Resource Utilisation definition (an increase of COPD symptoms for 2 days or more that needed a change in COPD treatment), but not exacerbations of any severity, were statistically significantly lower with aclidinium/formoterol compared with placebo (difference 0.13 per patient/year, p=0.036). A statistically significant difference was seen in the rate of exacerbations of any severity using the EXAcerbations of Chronic pulmonary disease Tool (EXACT) definition (a persistent increase from baseline in total EXACT score of at least 9 points for at 3 days or more, or at least 12 points for 2 days or more; difference between aclidinium/formoterol and placebo 0.33 per patient/year, p=0.01). The European Public Assessment Report for aclidinium/formoterol notes that a reduction of at least 1 exacerbation/year is currently the best estimate of a minimum clinically important difference in exacerbations and it is debatable whether a reduction of 0.33 exacerbations per year is clinically meaningful. However, the RCTs were too short to assess exacerbations satisfactorily.

- The incidences of adverse events that led to discontinuation in AUGMENT were the same between aclidinium/formoterol (6.3%) and placebo (6.3%), and slightly lower in the aclidinium (4.7%) and formoterol (4.2%) groups (p values not reported). In ACLIFORM, the number of adverse events that led to discontinuation was similar across the groups (placebo 4.1%, aclidinium/formoterol 4.2%, aclidinium 4.4% and formoterol 3.6%; p values not reported).

- The most commonly reported treatment-emergent adverse events were cough, nasopharyngitis and headache in AUGMENT and exacerbations of COPD, headache and nasopharyngitis in ACLIFORM. According to the European Public Assessment Report for aclidinium/formoterol, the number of drug-related adverse events seen with the combination was generally low and the reported events did not give rise to any major safety concerns. Many people with COPD have significant cardiovascular risk or cardiovascular co-morbidities and warnings about the potential cardiovascular risks of aclidinium/formoterol were included in the summary of product characteristics. This is consistent with the warnings for other LABA/LAMA combination inhalers.
• The study participants had moderate to severe COPD and it is unclear how effective aclidinium/formoterol is in people with mild or very severe COPD. The length of follow up in ACLIFORM and AUGMENT was 24 weeks only; therefore, the long-term effects of aclidinium/formoterol are currently uncertain. An extension study to AUGMENT (NCT01572792) and another long-term safety study (NCT01437540) have been undertaken but not yet published.

Full text of evidence review.

Context

The aclidinium/formoterol combination inhaler costs less than the combined cost of the single-component inhalers. The cost of an aclidinium/formoterol inhaler is the same as an umeclidinium/vilanterol inhaler (£32.50) and less than an indacaterol/glycopyrronium inhaler (£36.88) (MIMS, January 2015).

Full text of context.

Estimated impact for the NHS

The NICE guideline on COPD recommends that the choice of drug treatment for COPD should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and its costs. Dual therapy with a LAMA and a LABA may be considered if an ICS/LABA is declined or not tolerated.

According to the European Public Assessment Report for aclidinium/formoterol, improvements in lung function and breathlessness were similar to those seen with the other recently licenced LAMA/LABA combinations, umeclidinium/vilanterol and indacaterol/glycopyrronium. However, it is unclear whether the combination has clinically important benefits over aclidinium or formoterol monotherapy, or whether it reduces exacerbations by a clinically important amount. Also, there are no published studies which directly compare the efficacy and safety of aclidinium/formoterol with other combination LAMA/LABAs or other single or combination treatments for COPD. A study comparing aclidinium/formoterol with salmeterol/fluticasone has been completed but not yet published (NCT01908140).

Aclidinium/formoterol is administered twice daily, whereas umeclidinium/vilanterol and indacaterol/glycopyrronium, the other LAMA/LABA combination inhalers available, are administered once daily.
Aclidinium/formoterol and umeclidinium/vilanterol are both multi-dose breath-activated dry powder inhalers (Genuair and Ellipta devices respectively). Indacaterol/glycopyrronium is a single dose breath-activated dry powder inhaler (Breezhaler device). Some people may prefer a particular device or be able to use one device better than another. Some people with COPD are unable to use a spacer, others are; none of these combination inhalers can be used with a spacer.

Local decision makers will need to take safety, efficacy, cost and patient factors into account when considering the likely place in therapy of aclidinium/formoterol.

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 measurable impact on the airflow obstruction. Exacerbations often occur, during which there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations.

The NICE guideline includes the following key recommendations for stable COPD that are relevant to this evidence summary and the likely place in therapy of aclidinium/formoterol (Duaklir Genuair: a long-acting muscarinic antagonist [LAMA] and long-acting beta-2 agonist [LABA] combination 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\textsubscript{1}) is 50% predicted or more: either a LABA or a LAMA

- if FEV\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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 its cost.

See the NICE pathway on COPD for more information.

**Product overview**

**Drug action**

**Duaklir Genuair** is a breath-activated dry powder inhaler containing aclidinium bromide (a LAMA) and formoterol fumarate dihydrate (a LABA).

**Licensed therapeutic indication**

**Duaklir Genuair** received a European marketing authorisation in November 2014. It is licensed as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD.
Course and cost

The recommended dose of Duaklir Genuair is 1 puff twice daily. Each delivered dose (the dose leaving the mouthpiece) contains 396 micrograms of aclidinium bromide (equivalent to 340 micrograms of aclidinium) and 11.8 micrograms of formoterol fumarate dihydrate. This corresponds to a metered dose of 400 micrograms of aclidinium bromide (equivalent to 343 micrograms of aclidinium) and a metered dose of 12 micrograms of formoterol fumarate dihydrate.

The cost of a Duaklir Genuair inhaler containing 60 doses is £32.50 (MIMS, March 2015).

Evidence review

This evidence summary is based on 2 randomised controlled trials (RCTs: ACLIFORM-COPD and AUGMENT-COPD), which evaluated the efficacy of aclidinium/formoterol compared with placebo and aclidinium and formoterol monotherapies in people with moderate or severe stable COPD. Additional data, including pooled analyses of ACLIFORM and AUGMENT, is taken from the European Public Assessment Report for aclidinium/formoterol.

An extension study to AUGMENT (NCT01572792) and another long-term safety study (NCT01437540) have been undertaken but not yet published.

ACLIFORM (Singh et al. 2014) and AUGMENT (D’Urzo et al. 2014)

- **Design:** 2 multicentre, randomised, double-blind, parallel-group studies with similar designs compared the efficacy and safety of aclidinium/formoterol with the individual constituents and placebo over 24 weeks.

- **Population:** ACLIFORM included 1729 people from 193 centres in Europe, South Africa and South Korea. AUGMENT included 1692 people from 222 centres in North America, Australia and New Zealand. Participants in both RCTs:
  - were aged 40 years or older (mean age 63 years and 64 years in the RCTs respectively)
  - had a diagnosis of stable moderate to severe COPD (about 60% of people in both RCTs had moderate COPD and about 40% had severe COPD)
  - were current or ex-smokers with a smoking history of 10 pack-years or more (around half were current smokers across the RCTs).
Exclusion criteria included respiratory tract infections or exacerbations of COPD within 6 weeks (3 months if hospitalisation was required), clinically relevant respiratory conditions other than COPD (including asthma), and clinically significant cardiovascular conditions. ICS could be continued provided treatment was stable for at least 4 weeks before screening, and inhaled salbutamol was permitted as rescue medication. Baseline characteristics and demographics were broadly similar across the treatment groups in both RCTs.

- **Intervention and comparator:** following screening and a 2- to 3-week run-in period, participants were randomised to 24 weeks of double-blind treatment with twice daily aclidinium/formoterol 400/12 micrograms or 400/6 micrograms, aclidinium 400 micrograms, formoterol 12 micrograms or placebo via the breath-actuated, multiple-dose dry powder Genuair inhaler (Pressair in the US). Randomisation was 2:2:2:2:1 in ACLIFORM and 1:1:1:1:1 in AUGMENT. The manufacturer of aclidinium/formoterol has confirmed that allocation was concealed in both studies. Efficacy results for the 400/6 microgram dose of aclidinium/formoterol are not discussed in this evidence summary because this dose is not licensed in the UK.

- **Outcomes:** the 2 co-primary endpoints were change from baseline to week 24 in:
  - 1-hour morning post-dose FEV$_1$ compared with aclidinium 400 micrograms (chosen to test rapid-onset bronchodilation with formoterol)
  - morning pre-dose (trough) FEV$_1$ compared with formoterol 12 micrograms (chosen to test long-term bronchodilation with aclidinium).

These endpoints were specified based on regulatory authority guidelines, which state that each drug in a fixed-dose combination must make a documented contribution within the combination to the claimed effects. Secondary endpoints were change in Transition Dyspnoea Index (TDI; a measure of breathlessness) focal score and change in St. George's Respiratory Questionnaire (SGRQ; a measure of health-related quality of life) total score at week 24 (both compared with placebo). Other efficacy endpoints included further lung function outcomes, TDI and SGRQ responders (percentage of people achieving the minimum clinically important difference in TDI [at least 1 unit] and SGRQ [at least 4 units]), change in COPD symptoms and use of rescue medication. COPD exacerbations were assessed using Healthcare Resource Utilisation (HCRU; an increase of COPD symptoms for 2 days or more that needed a change in COPD treatment) and the EXAcerbations of Chronic pulmonary disease Tool (EXACT: a persistent increase from baseline in total EXACT score of at least 9 points for at 3 days
or more, or at least 12 points for 2 days or more). Key outcomes only are discussed in this evidence summary. Adverse events were also assessed.

- **Analyses:** Efficacy analyses (with the exception of exacerbation rate in ACLIFORM and EXACT-respiratory symptom scores [ER-S] in AUGMENT) were assessed in the intention to treat (ITT) population, which included people who took at least 1 dose of study medication and had a baseline and at least 1 post-baseline FEV₁ assessment. Safety outcomes (and the excepted efficacy outcomes) were assessed in the safety population, which included people who took at least 1 dose of study medication.

The full NICE guideline on COPD includes details on what it considers the minimum clinically important difference to be for a number of outcome measures used in COPD clinical studies (see table 1). These values are appropriate for comparisons of active treatment with placebo. However, it is unclear if they are appropriate as a benchmark for clinical significance for comparisons between a combination of 2 bronchodilators (LAMA/LABA) with 1 bronchodilator (either a LAMA or a LABA).

**Table 1: Minimum clinically important differences in outcomes in COPD studies (active treatment compared with placebo)**

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Minimum clinically important difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in FEV₁</td>
<td>100 ml</td>
</tr>
<tr>
<td>Change in transition dyspnoea index (TDI) score</td>
<td>1 unit</td>
</tr>
<tr>
<td>Change in St Georges Respiratory Questionnaire (SGRQ) score</td>
<td>−4 points</td>
</tr>
<tr>
<td>Relative risk reduction for exacerbations</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Table 2: Summary of ACLIFORM (Singh et al. 2014) and AUGMENT (D'Urzo et al. 2014)**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Placebo</th>
<th>Aclidinium/formoterol</th>
<th>Aclidinium 400 mcg twice daily</th>
<th>Formoterol 12 mcg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>400/400 mcg twice daily</td>
<td></td>
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<tr>
<td>Randomised</td>
<td>ACLIFORM</td>
<td>n=194</td>
<td>n=385</td>
<td>n=385</td>
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<tr>
<td>------------</td>
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<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>AUGMENT</td>
<td>n=337</td>
<td>n=338</td>
<td>n=340</td>
<td>n=339</td>
</tr>
<tr>
<td><strong>Efficacy</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ACLIFORM</td>
<td>n=194&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n=385&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n=383&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>AUGMENT</td>
<td>n=331</td>
<td>n=335</td>
<td>n=337</td>
<td>n=332</td>
</tr>
<tr>
<td><strong>Primary outcome 1:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-hour morning post-dose FEV&lt;sub&gt;1&lt;/sub&gt; at week 24 compared with aclidinium (least squares mean)</td>
<td>ACLIFORM</td>
<td>−30 ml&lt;sup&gt;b&lt;/sup&gt;</td>
<td>269 ml&lt;sup&gt;b&lt;/sup&gt;</td>
<td>144 ml&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>AUGMENT</td>
<td>−37 ml</td>
<td>247 ml</td>
<td>139 ml</td>
<td>165 ml</td>
</tr>
<tr>
<td><strong>Acclidinium/formoterol difference:</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>vs aclidinium 125 ml, p&lt;0.001</td>
<td>vs placebo 299 ml, p&lt;0.001</td>
<td>vs formoterol 139 ml&lt;sup&gt;c&lt;/sup&gt;, p&lt;0.001</td>
<td></td>
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<tr>
<td>vs placebo 284 ml, p&lt;0.01</td>
<td>vs formoterol 82 ml, p&lt;0.01</td>
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</tbody>
</table>

<sup>a</sup>Efficacy results compared with placebo and formoterol are secondary outcomes.
Primary outcome 2: trough FEV\textsubscript{1} at week 24 compared with formoterol (least squares mean)
Results compared with placebo and aclidinium are secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>ACLIFORM</th>
<th></th>
<th></th>
<th></th>
<th>Aclidinium/formoterol difference:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>−61 ml\textsuperscript{b}</td>
<td>83 ml\textsuperscript{b}</td>
<td>56 ml\textsuperscript{b}</td>
<td>vs formoterol 85 ml, p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vs placebo 143 ml\textsuperscript{c}, p&lt;0.001</td>
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<tr>
<td></td>
<td></td>
<td>vs aclidinium 27 ml, NS</td>
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<table>
<thead>
<tr>
<th></th>
<th>AUGMENT</th>
<th></th>
<th></th>
<th></th>
<th>Aclidinium/formoterol difference:</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>−35 ml</td>
<td>94 ml</td>
<td>66 ml</td>
<td>vs formoterol 45 ml\textsuperscript{c}, p=0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vs placebo 129 ml, p&lt;0.0001</td>
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<tr>
<td></td>
<td></td>
<td>vs aclidinium 28 ml, NS</td>
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Selected secondary outcomes:
<table>
<thead>
<tr>
<th>Improvement in TDI focal score at week 24</th>
<th>ACLIFORM</th>
<th>AUGMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.22</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>2.51</td>
<td>2.02</td>
</tr>
<tr>
<td></td>
<td>2.11</td>
<td>1.56</td>
</tr>
<tr>
<td></td>
<td>2.06</td>
<td>1.52</td>
</tr>
</tbody>
</table>

Aclidinium/formoterol difference:
- vs placebo 1.29, p<0.001
- vs aclidinium 0.40, NS
- vs formoterol 0.45, NS

Aclidinium/formoterol difference:
- vs placebo 1.44, p<0.0001
- vs aclidinium 0.46, NS
- vs formoterol 0.50, NS
<table>
<thead>
<tr>
<th>TDI % responders (≥1 unit improvement)</th>
<th>ACLIFORM</th>
<th>ACLIFORM</th>
<th>ACLIFORM</th>
<th>ACLIFORM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45.5%</td>
<td>64.8%</td>
<td>56.5%</td>
<td>61.3%</td>
</tr>
<tr>
<td>Augment</td>
<td>36.6%</td>
<td>58.1%</td>
<td>54.8%</td>
<td>51.7%</td>
</tr>
</tbody>
</table>

Aclidinium/formoterol: vs placebo
OR 2.54, 95% CI 1.57 to 4.10, p<0.001
vs aclidinium
OR 1.42, 95% CI 0.97 to 2.07, NS
vs formoterol
OR 1.19, 95% CI 0.81 to 1.74, NS

Aclidinium/formoterol:
vs placebo
OR 2.8, 95% CI not reported, p<0.0001
vs aclidinium
NS
vs formoterol
NS
<table>
<thead>
<tr>
<th>Improvement in SGRQ total score at week 24</th>
<th>ACLIFORM</th>
<th>AUGMENT</th>
<th>ACLIFORM</th>
<th>ACLIFORM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−6.51</td>
<td>−2.21</td>
<td>−7.16</td>
<td>−6.57</td>
</tr>
<tr>
<td></td>
<td>−5.80</td>
<td>−6.44</td>
<td>−5.58</td>
<td>−4.70</td>
</tr>
</tbody>
</table>

Acclidinium/formoterol difference:

- vs placebo: −0.65, OR −3.08 to 1.78, NS
- vs aclidinium: −1.36, −3.30 to 0.58, NS
- vs formoterol: −1.59, −3.52 to 0.35, NS

SQRQ % responders (≥4 unit improvement) | ACLIFORM | Not reported |
|--------------------------------------|----------|--------------|

Acclidinium/formoterol difference:

- vs placebo: −4.36, p≤0.001
- vs aclidinium: 0.13, NS
- vs formoterol: 1.87, NS
<table>
<thead>
<tr>
<th>Rate of COPD exacerbations per patient/year based on HCRU definition</th>
<th>AUGMENT</th>
<th>ACLIFORM</th>
<th>aclidinium/formoterol vs placebo</th>
<th>aclidinium vs formoterol</th>
<th>formoterol vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUGMENT</td>
<td>38.7%</td>
<td>58.2%</td>
<td>54.5%</td>
<td>52.4%</td>
<td>38.7%</td>
</tr>
<tr>
<td>ACLIFORM</td>
<td>0.36</td>
<td>0.26</td>
<td>0.29</td>
<td>0.41</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Aclidinium/formoterol: vs placebo OR 2.3, 95% CI not reported, p≤0.001 vs aclidinium NS vs formoterol NS

Rate of COPD exacerbations per patient/year based on HCRU definition: Not reported.
<table>
<thead>
<tr>
<th>Rate of COPD exacerbations per patient/year based on EXACT definition</th>
<th>ACLIFORM</th>
<th>1.54</th>
<th>1.09</th>
<th>1.40</th>
<th>1.26</th>
<th>Aclidinium/formoterol: vs placebo RR 0.71, 95% CI 0.5 to 0.9, p&lt;0.05 vs aclidinium RR 0.78, 95% CI 0.6 to 1.0, NS vs formoterol RR 0.86, 95% CI 0.7 to 1.1, NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUGMENT</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safetya</td>
<td>ACLIFORM</td>
<td>n=194</td>
<td>n=385</td>
<td>n=385</td>
<td>n=384</td>
<td></td>
</tr>
<tr>
<td>AUGMENT</td>
<td>n=332</td>
<td>n=335</td>
<td>n=337</td>
<td>n=332</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients reporting treatment-emergent adverse eventsd</td>
<td>ACLIFORM</td>
<td>53.1% (103/194)</td>
<td>50.4% (194/385)</td>
<td>49.4% (190/385)</td>
<td>56.5% (217/384)</td>
<td>Statistical significance of differences not reported</td>
</tr>
<tr>
<td>AUGMENT</td>
<td>54.5% (181/332)</td>
<td>64.2% (215/335)</td>
<td>62.3% (210/333)</td>
<td>56.9% (189/332)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients reporting treatment-emergent serious adverse events</td>
<td>ACLIFORM</td>
<td>6.2% (12/194)</td>
<td>6.0% (23/385)</td>
<td>4.2% (16/385)</td>
<td>3.6% (14/384)</td>
<td></td>
</tr>
<tr>
<td>AUGMENT</td>
<td>3.6%</td>
<td>5.7%</td>
<td>5.0%</td>
<td>4.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Numbers of patients not reported
Clinical effectiveness

Results for ACLIFORM and AUGMENT are shown individually in table 2. In this section, they are supplemented by pooled analyses taken from the European Public Assessment Report for aclidinium/formoterol, which were undertaken to:

- increase the precision of treatment effect estimates for selected clinically relevant efficacy endpoints
- assess the effect of aclidinium/formoterol on COPD exacerbations (for which the individual studies were not powered to detect a difference) and
- assess the consistency of the treatment effect in subpopulations.

Lung function

In both RCTs, aclidinium/formoterol statistically significantly improved 1-hour morning post-dose FEV₁ at week 24 compared with aclidinium monotherapy (primary outcome 1), formoterol monotherapy and placebo (all p<0.01). Also, aclidinium/formoterol statistically significantly

<table>
<thead>
<tr>
<th>Patients reporting treatment-emergent adverse events resulting in stopping treatment</th>
<th>ACLIFORM</th>
<th>AUGMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.1% (8/194)</td>
<td>4.2% (16/381)</td>
</tr>
<tr>
<td></td>
<td>6.3% (21/332)</td>
<td>6.3% (21/335)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EXACT, EXAcerbations of Chronic pulmonary disease Tool; FEV₁, forced expired volume in 1 second; HCRU, Healthcare Resource Utilisation; mcg, micrograms; ml, millilitre; NS, not significant; OR, odds ratio; p, p value; RR, relative risk; SGRQ, St. George's Respiratory Questionnaire; TDI, Transition Dyspnoea Index; vs, versus

a Apart from exacerbation rate in ACLIFORM, the efficacy analyses shown in this table were assessed in the intention to treat population, which included people who took at least 1 dose of study medication and had a baseline and at least 1 post-baseline FEV₁ assessment. The exacerbation rate in ACLIFORM and the safety outcomes were assessed in the safety population, which included people who took at least 1 dose of study medication.

b Data obtained from the European Public Assessment Report for aclidinium/formoterol.

c Figures may vary if calculated due to rounding.

d Events emerging during treatment having been absent pre-treatment or worsening relative to pre-treatment.
improved trough FEV\textsubscript{1} compared with formoterol (primary outcome 2) and placebo (both p<0.01), but not aclidinium, at week 24 (see table 2).

In the pooled population, aclidinium/formoterol improved 1 hour post-dose FEV\textsubscript{1} statistically significantly more than aclidinium monotherapy (difference 118 ml, 95\% confidence interval [CI] 93 ml to 143 ml, p<0.0001) and placebo (difference 293 ml, 95\% CI 265 ml to 321 ml, p<0.0001). These results are also critically important because they are above the 100 ml level generally considered to be a minimum clinically important difference. The combination also improved trough FEV\textsubscript{1} statistically significantly more than formoterol monotherapy (difference 68 ml, 95\% CI 44 ml to 92 ml, p<0.0001) and placebo (difference 138 ml, 95\% CI 111 ml to 165 ml, p<0.0001). However, the difference between the aclidinium/formoterol and formoterol monotherapy is below the 100 ml level generally thought to be critically important.

**Breathlessness**

At week 24, aclidinium/formoterol improved breathlessness (TDI focal scores) statistically significantly more than placebo (p<0.001 in both RCTs), whereas aclidinium or formoterol monotherapy did not (see table 2). In the pooled analysis, the difference was statistically significant for all comparisons (difference compared with placebo 1.43 units, 95\% CI 1.03 units to 1.83 units, p<0.0001; aclidinium monotherapy 0.44 units, 95\% CI 0.08 units to 0.79 units, p=0.016; and formoterol monotherapy 0.47 units, 95\% CI 0.12 units to 0.83 units, p=0.009). However, only the comparison with placebo is above the 1 unit improvement generally considered to be critically important.

In the pooled population, 62\% of people taking aclidinium/formoterol, 56\% taking aclidinium and 57\% taking formoterol achieved a clinically important improvement in breathlessness at week 24 compared with 40\% of people taking placebo. In the 2 RCTs, the improvement with aclidinium/formoterol was statistically significantly better than placebo (both p<0.001), but not aclidinium or formoterol monotherapy (see table 2). Similar results were obtained in the pooled analysis (combination compared with placebo odds ratio [OR] 2.76, 95\% CI 1.99 to 3.83, p<0.0001; aclidinium monotherapy OR 1.32, 95\% CI 0.99 to 1.76, p=0.056; and formoterol monotherapy OR 1.27, 95\% CI 0.95 to 1.69, p=0.100).

**Health-related quality of life**

At week 24, aclidinium/formoterol improved SGRQ total scores statistically and clinically significantly more than placebo in AUGMENT (difference 4.36 units, p≤0.001) but not ACLIFORM, in which a high and critically important placebo response was seen (6.51 units compared with 2.21 units placebo response in AUGMENT). Clinically important improvements of more than
4 units from baseline were seen with all active treatments and no statistically significant differences were found when the combination was compared with aclidinium or formoterol monotherapy.

For this outcome, the pooled analysis in the European Public Assessment Report for aclidinium/formoterol does not add any helpful information on aclidinium/formoterol because of the large, unexpected placebo response in ACLIFORM.

In AUGMENT, 58% of people using aclidinium/formoterol, 54% using aclidinium and 52% using formoterol achieved a clinically important improvement in SGRQ total score from baseline at week 24 compared with 39% with placebo. The difference between the combination and placebo, but not the combination and the active treatments, was statistically significant (p≤0.001).

Exacerbations

Exacerbations were reported in ACLIFORM but not AUGMENT. The European Public Assessment Report for aclidinium/formoterol states that rates (per patient/year) of moderate or severe exacerbations and of exacerbations of any severity (mild, moderate or severe) were generally higher in AUGMENT than in ACLIFORM. According to the European Public Assessment Report for aclidinium/formoterol, in the 2 RCTs, numerical reductions in exacerbation rate reached statistical significance only for the comparison between aclidinium/formoterol and placebo in the rate of EXACT exacerbations in ACLIFORM (p<0.05).

In the pooled population, rates of moderate or severe exacerbations (but not exacerbations of any severity) using the HCRU definition were statistically significantly lower with aclidinium/formoterol compared with placebo (0.29 per patient/year compared with 0.42 per patient/year, relative risk [RR] 0.71, 95% CI 0.51 to 0.98, p=0.036). A statistically significant difference was seen in the rate exacerbations of any severity using the EXACT definition (1.18 per patient/year with aclidinium/formoterol compared with 1.51 per patient/year with placebo, RR 0.78, 95% CI 0.65 to 0.94, p=0.01). Comparisons between the combination and aclidinium and formoterol monotherapies are not reported.

Safety and tolerability

Over 24 weeks, in AUGMENT, the overall incidence of treatment-emergent adverse events (events emerging during treatment having been absent pre-treatment or worsening relative to pre-treatment) with aclidinium/formoterol was similar to those of aclidinium and placebo and numerically greater than formoterol (64.2%, 62.3%, 64.5% and 56.9% respectively; p values not reported). In ACLIFORM, the incidence of treatment-emergent adverse events was slightly higher.
in the formoterol and placebo groups than in the other active treatment groups (aclidinium/formoterol 50.4%, aclidinium 49.4%, formoterol 56.5% and placebo 53.1%; p values not reported).

The majority of treatment-emergent adverse events reported in AUGMENT, were mild or moderate in severity and were considered unrelated to treatment by trial investigators. The most commonly reported were cough, nasopharyngitis and headache. The most commonly reported treatment-emergent adverse events in ACLIFORM were exacerbations of COPD, headache and nasopharyngitis.

The incidences of adverse events that led to discontinuation in AUGMENT were the same between aclidinium/formoterol (6.3%) and placebo (6.3%), and slightly lower in the aclidinium (4.7%) and formoterol (4.2%) groups (p values not reported). The adverse event most commonly associated with discontinuation was dyspnoea, reported most often in the placebo group. In ACLIFORM, the number of adverse events that led to discontinuation was similar across the groups (placebo 4.1%, aclidinium/formoterol 4.2%, aclidinium 4.4% and formoterol 3.6%; p values not reported).

In both RCTs, over 24 weeks, the overall incidence of serious adverse events was low. In AUGMENT, the proportion of serious adverse events was higher in all active treatment groups compared with placebo (aclidinium/formoterol 5.7%, aclidinium 5.0%, formoterol 4.5% and placebo 3.6%; p values not reported). In ACLIFORM, the proportion of people experiencing a serious adverse event was similar in the placebo and aclidinium/formoterol groups (6.2% and 6.0% respectively) and higher than in the 2 monotherapy groups (aclidinium 4.2% and formoterol 3.6%; p values not reported).

According to the European Public Assessment Report for aclidinium/formoterol, the number of drug-related adverse events was generally low and the reported events did not give rise to any major safety concerns. From the safety data presented there were no particular safety signals that suggested an additive effect of aclidinium and formoterol compared with the monotherapies. Common adverse effects of formoterol (occurring in more than 1 in 10 people) include headache, tremor and palpitations. Common adverse effects of aclidinium include sinusitis, nasopharyngitis, headache, cough and diarrhoea.

The European Public Assessment Report for aclidinium/formoterol states that cardiac safety was a concern because both aclidinium and formoterol can cause cardiac adverse effects (via different pathways), which can lead to cardiac arrhythmias. Although there was no evidence of an additive effect on conduction defects, more deaths were reported in the aclidinium/formoterol group than in the other groups (9 compared with 2 with placebo, 4 with aclidinium and 3 with formoterol in the RCTs and unpublished extension studies). Analysis found that 4 of the 9 deaths in the aclidinium/
formoterol group were considered to be of cardiac origin and 2 deaths were of unknown origin. The majority of people who died (and all whose deaths were considered of cardiovascular origin) had pre-existing cardiac conditions that would have contributed to their death. The sudden cardiac deaths seen in the clinical development programme were generally not considered by the investigators to be related to the study medication. However, many people with COPD have significant cardiovascular risk or cardiovascular co-morbidities and, in common with other LABA/LAMA combinations (umeclidinium/vilanterol and indacaterol/glycopyrronium), warnings about the potential cardiovascular risks of aclidinium/formoterol were included in the summary of product characteristics. According to the European Public Assessment Report for aclidinium/formoterol, a post-authorisation safety study is planned to evaluate the risk of cardiovascular events with aclidinium/formoterol.

Evidence strengths and limitations

The European Public Assessment Report for aclidinium/formoterol states that the chosen co-primary endpoints of the RCTs, 1 hour post-dose and trough FEV$_1$, are appropriate for exploring the contributions of formoterol and aclidinium respectively. In addition, the key secondary symptomatic endpoints of TDI and SGRQ scores are in line with the CHMP guideline on the investigation of medicinal products for the treatment of COPD.

In ACLIFORM and AUGMENT, aclidinium/formoterol statistically significantly improved lung function compared with placebo. However, the results compared with aclidinium or formoterol monotherapy are less clear. In both RCTs, a clinically significant improvement in 1-hour post-dose FEV$_1$ was seen in the aclidinium/formoterol group compared with aclidinium monotherapy, suggesting that formoterol contributes to the efficacy of the combination. A clinically significant improvement in trough FEV$_1$ was not seen with aclidinium/formoterol compared with formoterol, raising questions over the contribution aclidinium makes to the efficacy of the combination. In the pooled analysis, aclidinium/formoterol statistically significantly improved trough FEV$_1$ by 68 ml compared with formoterol monotherapy, which is less than the 100 ml improvement threshold generally considered to be clinically relevant. According to the European Public Assessment Report for aclidinium/formoterol, this difference is similar to that seen with other recently licensed LAMA/LABA combinations, and post hoc responder analyses provided by the manufacturer supported the conclusion that aclidinium contributes to a clinically significant extent to the overall positive effect of the combination. The European Public Assessment Report also notes that it has been argued that a clinically meaningful improvement in FEV$_1$ cannot be achieved by adding a second bronchodilator to the first because people with moderate to severe COPD generally have limited airways reversibility.
Aclidinium/formoterol statistically significantly improved breathlessness (TDI focal scores) compared with aclidinium or formoterol monotherapy. However, the treatment differences of less than half a unit are below the minimum 1 unit improvement in TDI score which is generally considered to be clinically relevant. The results for health-related quality of life (SGRQ scores) are difficult to interpret because a large placebo effect was seen in ACLIFORM. Post-hoc analyses failed to identify a single reason for this unexpected result and suggest that the cause is likely to have been multi-factorial. In both RCTs, a clinically significant improvement in SGRQ total score of more than 4 units was seen in all active treatment groups. In AUGMENT, a clinically significant improvement was seen with aclidinium/formoterol compared with placebo but not the active treatments. To support their license application, the manufacturer supplied post-hoc responder analyses. These showed that the proportions of people in the pooled aclidinium/formoterol group who achieved a 1 unit improvement in TDI focal score (62%) and a 4 unit improvement in SGRQ total score (57%) were similar to the proportions seen in studies of the recently approved LAMA/LABA combinations (umeclidinium/vilanterol, 58% and 49% respectively; and indacaterol/glycopyrronium, 68% and 64% respectively; European Public Assessment Report for aclidinium/formoterol).

In a pooled analysis of the 2 RCTs, improvement in all severities of exacerbation with aclidinium/formoterol compared with placebo was found to be 0.33 exacerbations per patient/year based on the EXACT definition. This means that a patient would need to be treated with the combination for about 3 years to prevent 1 exacerbation (p=0.01). The European Public Assessment Report for aclidinium/formoterol notes that a reduction of at least 1 event per year is currently the best estimate of the minimum clinically important difference in exacerbations and it is debatable whether a reduction of 0.33 exacerbations per year is clinically meaningful. However, the RCTs were too short to assess exacerbations satisfactorily.

The study participants had moderate to severe COPD and it is unclear how effective aclidinium/formoterol is in people with mild or very severe COPD. The length of follow up in ACLIFORM and AUGMENT was 24 weeks only; therefore, the long-term effects of aclidinium/formoterol are uncertain. An extension study to AUGMENT (NCT01572792) and another long-term safety study (NCT01437540) have been undertaken but not yet published. Some information on these studies is available in the European Public Assessment Report for aclidinium/formoterol but the results are affected by high dropout rates.

It is not known how aclidinium/formoterol compares with other combination treatments for COPD. A study comparing aclidinium/formoterol with salmeterol/fluticasone has been completed but not yet published (NCT01908140).
Context

Alternative treatments

NICE recommendations for using inhaled treatments for COPD are outlined in the introduction to this evidence summary.

Aclidinium/formoterol is the third LAMA/LABA combination inhaler to be launched in the UK for treating COPD, following umeclidinium/vilanterol (Anoro Ellipta: see the evidence summary on Chronic obstructive pulmonary disease: umeclidinium/vilanterol) and indacaterol/glycopyrronium (Ultibro Breezhaler: see the evidence summary on Chronic obstructive pulmonary disease: indacaterol/glycopyrronium).

Four combination ICS/LABA inhalers are currently licensed for treating COPD:

- beclometasone/formoterol metered dose inhaler (Fostair 100/6 micrograms: see the evidence summary on Chronic obstructive pulmonary disease – beclometasone/formoterol)
- budesonide/formoterol dry powder inhaler (Symbicort Turbohaler 200/6 micrograms and Symbicort Turbohaler 400/12 micrograms)
- fluticasone furoate/vilanterol dry powder inhaler (Relvar Ellipta 92/22 micrograms: see the evidence summary on Chronic obstructive pulmonary disease – fluticasone furoate plus vilanterol)
- fluticasone propionate/salmeterol dry powder inhaler (Seretide Accuhaler 500/50 micrograms).

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

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

Table 3: Costs of alternative treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dosage</th>
<th>30-day cost excluding VAT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a,b</td>
<td></td>
</tr>
</tbody>
</table>

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### Single-component LABAs

<table>
<thead>
<tr>
<th>Drug Description</th>
<th>Dosage</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol 12 micrograms (Formoterol Easyhaler)</td>
<td>1 puff twice daily</td>
<td>£11.88&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Indacaterol 150 micrograms and 300 micrograms (Onbrez Breezhaler)</td>
<td>1 puff daily</td>
<td>£29.26&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Olodaterol 2.5 micrograms (Striverdi Respimat)</td>
<td>2 puffs daily</td>
<td>£26.35&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Salmeterol 50 micrograms (Serevent Accuhaler)</td>
<td>1 puff twice daily</td>
<td>£29.26&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Single-component LAMAs

<table>
<thead>
<tr>
<th>Drug Description</th>
<th>Dosage</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aclidinium 322 micrograms (Eklira Genuair)</td>
<td>1 puff twice daily</td>
<td>£28.60&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glycopyrronium 50 micrograms (Seebri Breezhaler)</td>
<td>1 puff daily</td>
<td>£27.50&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tiotropium 18 micrograms, dry powder (Spiriva Handihaler)</td>
<td>1 puff daily</td>
<td>£34.87&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tiotropium 2.5 micrograms, aerosol (Spiriva Respimat)</td>
<td>2 puffs daily</td>
<td>£33.50&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Umeclidinium 55 micrograms (Incruse Ellipta)</td>
<td>1 puff daily</td>
<td>£27.50&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Combination LAMA/LABA inhalers

<table>
<thead>
<tr>
<th>Drug Description</th>
<th>Dosage</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aclidinium/formoterol 340/12 micrograms (Duaklir Genuair)</td>
<td>1 puff twice daily</td>
<td>£32.50&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Indacaterol/glycopyrronium 110/50 micrograms (Ultibro Breezhaler)</td>
<td>1 puff daily</td>
<td>£36.88&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Umeclidinium/vilanterol 55/22 micrograms (Anoro Ellipta)</td>
<td>1 puff daily</td>
<td>£32.50&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Combination ICS/LABA inhalers

<table>
<thead>
<tr>
<th>Drug Description</th>
<th>Dosage</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclometasone/formoterol 100/6 micrograms (Fostair)</td>
<td>2 puffs twice daily</td>
<td>£29.32&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Budesonide/formoterol 200/6 micrograms (Symbicort Turbohaler)</td>
<td>2 puffs twice daily</td>
<td>£38.00&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Budesonide/formoterol 400/12 micrograms (Symbicort Turbohaler)</td>
<td>1 puff twice daily</td>
<td>£38.00&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dose Formulation</td>
<td>Dose</td>
<td>Cost</td>
</tr>
<tr>
<td>------------------------------------------------------</td>
<td>-------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Fluticasone furoate/vilanterol 92/22 micrograms (Relvar Ellipta)</td>
<td>1 puff daily</td>
<td>£27.80</td>
</tr>
<tr>
<td>Fluticasone propionate/salmeterol 500/50 micrograms (Seretide Accuhaler)</td>
<td>1 puff twice daily</td>
<td>£40.92</td>
</tr>
</tbody>
</table>

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

*Doses taken from the relevant summary of product characteristics.*

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

*Costs taken from the Drug Tariff (March 2015). All costs include the inhaler device.*

*Lowest cost dry powder formulations selected; other brands and formulations are available.*

*Costs taken from MIMS (March 2015). All costs include the inhaler device.*

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**Estimated impact for the NHS**

**Likely place in therapy**

The NICE guideline on COPD recommends that dual therapy with a LAMA and a LABA may be considered if an ICS/LABA is declined or not tolerated. There are no published studies which directly compare the efficacy and safety of aclidinium/formoterol with other combination LAMA/LABAs or other single or combination treatments for COPD.

NICE recommends that the choice of drug treatment for COPD should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and its costs.

Aclidinium/formoterol has been shown to statistically significantly improve lung function and breathlessness over 24 weeks compared with placebo and aclidinium and formoterol monotherapies. Not all of the comparisons with aclidinium or formoterol monotherapy were considered to be clinically important using conventional criteria but, according to the European Public Assessment Report for aclidinium/formoterol, improvements in lung function and breathlessness were similar to those seen with the other recently licenced LAMA/LABA combinations, umeclidinium/vilanterol and indacaterol/glycopyrronium. ACLIFORM and AUGMENT were too short to assess exacerbations, and results for health-related quality of life were difficult to interpret because of a high, unexplained placebo response in ACLIFORM.
According to the European Public Assessment Report for aclidinium/formoterol, the number of drug-related adverse events seen with aclidinium/formoterol was generally low and the reported events did not give rise to any major safety concerns. As for other LABA/LAMA combination treatments for COPD, warnings about the potential cardiovascular risks of aclidinium/formoterol are included in the summary of product characteristics. Little information is available on its long-term safety.

Aclidinium/formoterol is administered twice daily, whereas umeclidinium/vilanterol and indacaterol/glycopyrronium, the other LAMA/LABA combination inhalers available, are administered once daily.

Aclidinium/formoterol and umeclidinium/vilanterol are both multi-dose breath-activated dry powder inhalers (Genuair and Ellipta devices respectively). Indacaterol/glycopyrronium is a single dose breath-activated dry powder inhaler (Breezhaler device). Some people may prefer a particular device or be able to use one device better than another. Some people with COPD are unable to use a spacer, others are; none of these combination inhalers can be used with a spacer.

The aclidinium/formoterol combination inhaler costs less than the combined cost of the single-component inhalers. The 30-day cost of an aclidinium/formoterol inhaler is the same as an umeclidinium/vilanterol inhaler (£32.50) and less than an indacaterol/glycopyrronium inhaler (£36.88) (costs taken from MIMS, February 2015).

Local decision makers will need to take safety, efficacy, cost and patient factors into account when considering the likely place in therapy of aclidinium/formoterol.

Estimated usage

Of people with COPD in England and Wales who are eligible for treatment according to the product license, AstraZeneca estimates that 2% (about 21,500) will be treated with aclidinium/formoterol at a cost of £8.5 million in 2015, rising to 13.5% (about 164,000) at a cost of £65 million in 2019. The manufacturer estimates that this will lead to budget impact savings of £6.8 million and £52 million in those years because aclidinium/formoterol will be used in preference to more costly medicines. However, this assumes effective rationalisation of use of medicines for COPD in line with recommendations in guidelines, which may not be straightforward (Franssen et al. 2011).
Relevance to NICE guidance programmes

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

In 2010, NICE published a clinical guideline on chronic obstructive pulmonary disease (NICE guideline 101), which has been incorporated into a NICE pathway. 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.

References


National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease, NICE pathway [online; accessed 20 March 2015]

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.

Expert advisers

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Declarations of interest

John Haughney has received reimbursements for attending symposia, fees for speaking, organising educational events, funds for research or fees for consulting from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Merck Sharp & Dohme, Mundipharma, Novartis, and Teva. The University of Aberdeen and NHS Greater Glasgow and Clyde Research and Development have received funding from most pharmaceutical companies and numerous other organisations. John Haughney will have indirectly benefitted from these.

Anastasios Lekkas had no relevant interests to declare.

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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