Chronic obstructive pulmonary disease: beclometasone/formoterol (Fostair)

Evidence summary
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Key points from the evidence

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

Summary

Fostair is a combination inhaler containing beclometasone and formoterol which has been licensed for asthma since 2007. In April 2014, a licence extension was granted for the use of Fostair in people with severe chronic obstructive pulmonary disease (COPD) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

In a randomised controlled trial (RCT; n=718), beclometasone/formoterol was non-inferior to budesonide/formoterol in improving pre-dose morning lung function in people with severe COPD over 48 weeks. There was no significant difference between the treatments in the rate of COPD exacerbations/patient per year. The incidence of adverse events was similar between the treatments. This study also included a formoterol alone arm.

In a second RCT (n=419), beclometasone/formoterol statistically significantly improved the onset of bronchodilation in people with moderate-to-severe COPD compared with fluticasone/salmeterol, although it is unclear whether the improvement is clinically important. The treatments...
were equivalent in improving dyspnoea over 12 weeks. Serious adverse events were statistically significantly more common with fluticasone/salmeterol.

From the published data, beclometasone/formoterol appears to work as well in COPD as the 2 commonly used ICS/LABA combinations, its constituent ingredients have been available for many years so their safety profile is known, it costs less than most alternatives and it can be used with a spacer, which many people with COPD need.

### Effectiveness

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 1 RCT (<a href="#">Calverley et al. 2010; n=718</a>), compared with budesonide/formoterol, beclometasone/formoterol was:</td>
<td>- In the first RCT, the incidence of adverse events did not differ significantly between beclometasone/formoterol and budesonide/formoterol.</td>
</tr>
<tr>
<td>- non-inferior for improving pre-dose morning forced expired volume in 1 second (FEV₁) over 48 weeks (difference 0.002 L, lower limit of 97.5% confidence interval [CI] −0.052 L).</td>
<td>- In the second RCT, serious adverse events occurred statistically significantly more often in the fluticasone/salmeterol group than the beclometasone/formoterol group (13 people [6.3%] compared with 4 people [1.9%], p=0.024).</td>
</tr>
<tr>
<td>- similar in terms of the rate of COPD exacerbations/patient per year (0.414 compared with 0.423 respectively, not statistically significant).</td>
<td>- According to the summary of product characteristics, adverse effects that have been reported commonly (in between 1 in 10 and 1 in 100 people) with beclometasone/formoterol in combination or as single constituents are pharyngitis, oral candidiasis, headache and dysphonia.</td>
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<td>In a second RCT (<a href="#">Singh et al. 2014; n=419</a>), compared with fluticasone salmeterol, beclometasone/formoterol was</td>
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<tr>
<td>- equivalent in terms of improvement in Transition Dyspnoea Index (TDI) scores over 12 weeks (mean 1.32 compared with 1.15, p=0.56).</td>
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<tr>
<td>- statistically significantly faster for onset of bronchodilation (mean difference in area under the curve from 0–30 minutes [AUC₀-30min] 0.07 L, p&lt;0.001).</td>
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</tbody>
</table>
**Patient factors**

- The NICE clinical guideline on COPD recommends that the choice of treatment should take into account the person's symptomatic response and preference.

- Beclometasone/formoterol is supplied in a metered dose inhaler (which can be used with a spacer), budesonide/formoterol is in a Turbhaler, fluticasone/formoterol is in an Accuhaler and fluticasone/vilanterol is in an Ellipta inhaler.

- Apart from fluticasone/vilanterol, which is administered once daily, these treatments are administered twice daily.

**Resource implications**

A 30-day inhaler costs:

- £29.32 for beclometasone/formoterol.
- £38.00 for budesonide/formoterol.
- £40.92 for fluticasone/salmeterol.
- £27.80 for fluticasone/vilanterol.

(Costs from the Drug Tariff and MIMS, June 2014).

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**Introduction and current guidance**

According to the NICE clinical guideline on Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update) (NICE clinical guideline 101), a combination inhaler containing an inhaled corticosteroid (ICS) and a long-acting beta\(_2\) agonist (LABA) should be offered if FEV\(_1\) is less than 50\% of predicted in people with COPD. An ICS/LABA may also be considered in people with stable COPD and an FEV\(_1\) of 50\% or more of predicted who remain breathless or have exacerbations despite maintenance therapy with a LABA. See the NICE guideline or the NICE pathway on COPD for full details.

This evidence summary considers the best available evidence to support the use of the ICS/LABA (beclometasone/formoterol) combination inhaler, Fostair, for COPD.

Full text of Introduction and current guidance.
Product overview

Fostair (Chiesi) is a pressurised metered dose inhaler containing beclometasone dipropionate (BDP; an ICS) and formoterol fumarate dihydrate (a LABA). Each metered dose contains 100 micrograms of beclometasone and 6 micrograms of formoterol. The summary of product characteristics advises that the particles of BDP in Fostair are extrafine and more potent than in standard formulations of BDP: 100 micrograms of extrafine BDP in Fostair are equivalent to 250 micrograms of standard BDP.

Fostair has been licensed for asthma since 2007 and a licence extension for use in COPD was granted in April 2014. The summary of product characteristics states that Fostair is licensed for the symptomatic treatment of adults with severe COPD (FEV$_1$ less than 50% of the predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

Full text of Product overview.

Evidence review

- This evidence review focuses on 2 RCTs that provide evidence for beclometasone/formoterol (Fostair 100/6 micrograms, 2 puffs twice daily) for managing COPD compared with the established ICS/LABA combinations, budesonide/formoterol (Symbicort 200/6 micrograms, 2 puffs twice daily) and fluticasone/salmeterol (Seretide 500/50 micrograms, 1 puff twice daily).

- Calverley et al. (2010) found that, over 48 weeks, beclometasone/formoterol, budesonide/formoterol and formoterol alone improved pre-dose morning FEV$_1$ (the first primary outcome) by 0.077 L, 0.080 L and 0.026 L respectively in 718 people with severe COPD (FEV$_1$ between 30% and 50% of predicted). These changes in FEV$_1$ are less than the improvement that the full NICE guideline on COPD considers to be clinically important (0.100 L or more). In the intention-to-treat analysis, beclometasone/formoterol was shown to be non-inferior to budesonide/formoterol (the lower limit of the 97.5% CI was −0.052 L, which is within the pre-specified non-inferiority margin of −0.100 L) and statistically significantly better than formoterol alone (p=0.046). Similar results were reportedly obtained in the per-protocol analysis.

- In this study, the mean rate of COPD exacerbations/patient per year (the second primary outcome) was not statistically significantly different between the treatments (beclometasone/formoterol 0.414, budesonide/formoterol 0.423 and formoterol alone 0.431). The number of
patients with exacerbations leading to hospitalisation was statistically significantly higher in the beclometasone/formoterol group compared with the budesonide/formoterol and formoterol alone groups (13 [5.6%] compared with 7 [2.9%, p<0.001] and 8 [3.4%, p=0.008] respectively). However, the numbers of exacerbations were lower than expected and these analyses may have been underpowered.

**Singh et al. (2014)** found that beclometasone/formoterol and fluticasone/salmeterol statistically significantly improved Transition Dyspnoea Index scores (a measure of breathlessness; the first primary outcome) by 1.32 units respectively and 1.15 units over 12 weeks in 419 people with moderate-to-severe COPD. The full NICE guideline on COPD considers an improvement of 1 unit to be clinically important. The combination treatments were found to be equivalent in the intention-to-treat analysis (the 95% CI for the difference [-0.39 to 0.72] was entirely within the pre-specified ±1 equivalence margins). However, both intention-to-treat and per-protocol analyses should be undertaken in equivalence analyses to confirm the findings and it is unclear whether a per-protocol analysis was undertaken in this study.

As assessed by the change in FEV\(_1\) from pre-dose in the first 30 minutes after drug inhalation (the secondary primary outcome), in this study beclometasone/formoterol had a statistically significantly faster onset of action than fluticasone/salmeterol (AUC\(_{0-30\text{min}}\) adjusted means at 12 weeks 0.18 L compared with 0.11 L respectively, p<0.001). It is unclear whether this difference is clinically important.

**Calverley et al. (2010)** found that the incidence of adverse events did not differ significantly between beclometasone/formoterol, budesonide/formoterol and formoterol alone. The most commonly reported adverse event was exacerbation or worsening of COPD, which occurred in 27–28% of participants. Pneumonia was reported by 5 people (2.1%) in the beclometasone/formoterol group, 7 people (2.9%) in the budesonide/formoterol group and 1 person (0.4%) in the formoterol group (statistical significance of differences not reported).

In **Singh et al. (2014)**, serious adverse events occurred statistically significantly more often in the fluticasone/salmeterol group than the beclometasone/formoterol group (13 people [6.3%] compared with 4 people [1.9%), p=0.024). Pneumonia was reported in 3 people (1.4%) treated with fluticasone/salmeterol and none treated with beclometasone/formoterol.

Full text of Evidence review.
Context

The cost of a beclometasone/formoterol inhaler (£29.32; Drug Tariff, June 2014) is less than a budesonide/formoterol or fluticasone/salmeterol inhaler (£38.00 and £40.92 respectively; Drug Tariff, June 2014) and is slightly higher than that of a fluticasone/vilanterol inhaler (£27.80; MIMS, June 2014). All inhalers last for 30 days at usual dosages.

Full text of Context.

Estimated impact for the NHS

The NICE clinical 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.

Beclometasone/formoterol has been compared to the most commonly used ICS/LABA combinations for COPD, budesonide/formoterol and fluticasone/salmeterol. It was found to be similar to budesonide/formoterol in terms of change in pre-dose morning lung function (a disease orientated outcome) over 48 weeks, rate of COPD exacerbations/patient per year and incidence of adverse events, and similar to fluticasone/salmeterol in terms of change in dyspnoea scores over 12 weeks. The onset of bronchodilation was statistically significantly faster with beclometasone/formoterol compared with fluticasone/salmeterol, although it is unclear whether the improvement is clinically important. Serious adverse events were statistically significantly more common with fluticasone/salmeterol, which may be due to the higher BDP equivalent dose of ICS in this combination (see the evidence review section of this evidence summary for more information on the relative ICS doses in the treatments assessed).

The type of inhaler device may affect the choice of treatment for an individual person. A metered dose inhaler is the most appropriate device for people who need to use a spacer. Beclometasone/formoterol is administered using a metered dose inhaler; budesonide/formoterol is administered using a Turbohaler; fluticasone/formoterol is administered using an Accuhaler; and fluticasone/vilanterol is administered using an Ellipta device. Apart from fluticasone/vilanterol, which is administered once daily, these treatments are administered twice daily.

Local decision makers will need to take these factors into account when considering the likely place in therapy of beclometasone/formoterol for COPD.

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

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

The guideline recommends the following inhaled treatments for managing stable COPD. The list is not comprehensive but includes the key recommendations that relate to this evidence summary and the likely place in therapy of beclometasone/formoterol (Fostair: an inhaled corticosteroid [ICS] 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 (FEV₁) is 50% or more of predicted: either a LABA or a long-acting muscarinic antagonist (LAMA)
- if FEV$_1$ is less than 50% of predicted: either a LABA with an ICS in a combination inhaler, or a LAMA. Consider a LAMA in addition to a LABA where an ICS is declined or not tolerated.

- In people with stable COPD and an FEV$_1$ of 50% or more of predicted 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.

**Product overview**

**Drug action**

Fostair (Chiesi) is a pressurised metered dose inhaler containing 100 micrograms beclometasone dipropionate (BDP; an ICS) and 6 micrograms formoterol fumarate dihydrate (a LABA) per dose.

The summary of product characteristics advises that the particles of BDP in Fostair are extrafine and more potent than in standard formulations of BDP: 100 micrograms of extrafine BDP in Fostair are equivalent to 250 micrograms of standard BDP.

**Licensed therapeutic indication**

Fostair was first licensed in the UK in 2007 for treating asthma (see the Evidence summary on Asthma: beclometasone/formoterol (Fostair) for maintenance and reliever treatment for more information).
A licence extension for use in COPD was granted in April 2014. The summary of product characteristics states that Fostair is licensed for the symptomatic treatment of adults with severe COPD (FEV\textsubscript{1} less than 50% of the predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

**Course and cost**

The recommended dose of Fostair for COPD is 2 puffs twice daily (100 micrograms of extrafine BDP and 6 micrograms of formoterol per inhalation: see summary of product characteristics).

The cost of a Fostair inhaler containing 120 doses is £29.32 (Drug Tariff, June 2014).

**Evidence review**

This evidence review focuses on 2 randomised controlled trials (RCTs) that provide published evidence for beclometasone/formoterol (Fostair) for managing COPD compared with the established ICS/LABA combinations, budesonide/formoterol (Symbicort) and fluticasone/salmeterol (Seretide).

Calverley et al. (2010) aimed to show that beclometasone/formoterol was non-inferior to budesonide/formoterol for improving lung function, and superior to formoterol for reducing exacerbations. Singh et al. (2014) investigated whether beclometasone/formoterol was equivalent to fluticasone/salmeterol for improving dyspnoea (breathlessness), and superior to fluticasone/salmeterol for improving the onset of bronchodilation.

A third RCT, the FORWARD study, which compared beclometasone/formoterol with formoterol alone, is also outlined briefly (Wedzicha et al. 2014).

**Beclomethasone/formoterol in the management of COPD: a randomised controlled trial** (Calverley et al. 2010)

- **Design:** this study was a 48-week, double-blind, double-dummy randomised controlled trial undertaken in 76 centres in 8 European countries.

- **Population:** 718 hospital outpatients (mean age 64 years) with severe COPD (post-bronchodilator FEV\textsubscript{1} 30–50% of the predicted normal and at least 0.7 L, and pre-dose FEV\textsubscript{1}/FVC ratio of 0.7, where FEV\textsubscript{1} is forced expired volume in 1 second and FVC is forced vital capacity) which had been clinically stable for the 2 months before study entry. The definition of severe COPD is in agreement with the NICE guideline on COPD. Participants had suffered...
from symptomatic COPD for more than 2 years (mean 10 years) and had a smoking history of 20 pack-years or more (mean 38 pack-years). Also, they had experienced at least 1 exacerbation requiring medical intervention (oral corticosteroid or antibiotic treatment, or the need to visit or be admitted to hospital: mean 1.7) in the 2–12 months before the screening visit. Patients were excluded if they had a history of asthma, symptoms suggestive of asthma, allergic rhinitis or other atopic disease. They were also excluded if they were receiving long term oxygen therapy, were taking certain medications such as corticosteroids and antibiotics, had a lower respiratory tract infection, or had been hospitalised for an acute COPD exacerbation in the 2 months before screening or during the run-in period. In the 4-week run-in period, all non-permitted COPD treatments were discontinued and eligible patients were treated with combination ipratropium/salbutamol 20/100 micrograms. Rescue salbutamol was permitted throughout the study as required.

- Intervention and comparator: patients were randomised in a 1:1:1 ratio to receive treatment with beclometasone/formoterol 100/6 micrograms (2 puffs twice daily: n=237), budesonide/formoterol 200/6 micrograms (2 puffs twice daily: n=242) or formoterol 12 micrograms (1 puff twice daily: n=239). The method of allocation described suggests that this was concealed although it is not explicitly stated in the methods. At baseline, the 3 treatment groups were well-matched. Patients took active medications and matched placebos twice daily to maintain blinding. Clinic visits took place at the start and end of the run-in period, and 4, 12, 24, 36 and 48 weeks after randomisation. Patients recorded symptoms, and use of study and rescue medications in diaries each day.

- Outcomes: the 2 co-primary efficacy outcomes were the change in pre-dose morning FEV₁ from baseline to 48 weeks (non-inferiority analysis, pre-specified non-inferiority margin −0.100 L) and the mean rate of COPD exacerbations per patient per year (defined as need for treatment with oral corticosteroids or antibiotics, or the need to visit or be admitted to hospital: superiority analysis). Secondary outcomes included COPD exacerbations leading to hospitalisation, dyspnoea, health-related quality of life and a 6 minute walking test. Adverse events were also assessed. Efficacy data were analysed for both the intention-to-treat population and the per protocol population. Missing values were accounted for using the last observation carried forward approach.

Table 2 Summary of beclomethasone/formoterol in the management of COPD: a randomised controlled trial (Calverley et al. 2010)
<table>
<thead>
<tr>
<th></th>
<th>Beclometasone/formoterol 100/6 micrograms 2 puffs twice daily</th>
<th>Budesonide/formoterol 200/6 micrograms 2 puffs twice daily</th>
<th>Formoterol 12 micrograms 1 puff twice daily</th>
<th>Analysis</th>
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<tbody>
<tr>
<td>Randomised n=237</td>
<td>n=242</td>
<td>n=239</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy&lt;sup&gt;a&lt;/sup&gt; n=232</td>
<td>n=238</td>
<td>n=233</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome 1: change in pre-dose morning FEV&lt;sub&gt;1&lt;/sub&gt; from baseline to 48 weeks</td>
<td>0.077 L</td>
<td>0.080 L</td>
<td>0.026 L</td>
<td>Both combination treatments statistically significantly improved pre-dose morning FEV&lt;sub&gt;1&lt;/sub&gt; compared with baseline (both p&lt;0.001). Formoterol alone did not. Beclometasone/formoterol was non-inferior&lt;sup&gt;b&lt;/sup&gt; to budesonide/formoterol: Difference −0.002 L 95% CI −0.052 L to 0.048 L Beclometasone/formoterol was statistically significantly superior to formoterol: Difference 0.051 L 95% CI 0.001 L to 0.102 L p=0.046 Similar results were reportedly obtained in the per-protocol population&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
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</table>
Primary outcome 2: mean rate of COPD exacerbations per patient per year

|                | 0.414 | 0.423 | 0.431 | All treatments statistically significantly improved the rate of exacerbations compared with baseline (all p<0.001)
|----------------|-------|-------|-------| No significant differences were found between treatments

Selected secondary outcomes:

| Mean rate of COPD exacerbations needing hospitalisation per patient per year | 0.074 | 0.033 | 0.040 | Both combination treatments were statistically significantly superior to formoterol alone
|-------------------------------------------------------------------------------|-------|-------|-------| Beclometasone/formoterol versus budesonide/formoterol:
|                                                                                | RR 2.222 | 95% CI 1.384 to 3.567 | Beclometasone/formoterol versus formoterol:
|                                                                                | RR 1.844 | 95% CI 1.173 to 2.901 | Both combination treatments statistically significantly improved dyspnoea compared with baseline (both p<0.001). Formoterol alone did not
| Mean change in dyspnoea (MMRC) score from baseline to 48 weeks:               | −0.19 ± 0.74 | −0.18 ± 0.078 | −0.07 ± 0.076 | No significant differences were found between treatments
| Mean change in health-related quality of life (SGRQ) total score from baseline to 48 weeks | −3.75 ± 13.91 | −4.28 ± 11.92 | −2.90 ± 13.28 | All treatments statistically significantly improved the SGRQ total score compared with baseline (all p<0.01) No significant differences were found between treatments |
| Change in 6 minute walking test distance from baseline to 48 weeks | 41 m ± 85 m | 35 m ± 86 m | 35 m ± 79 m | All treatments statistically significantly improved the distance covered in 6 minutes compared with baseline (all p<0.001) No significant differences were found between treatments |
| Safety<sup>d</sup> | n=236 | n=242 | n=238 |
| Patients reporting treatment-related adverse events | 9.3% (22/236) | 5.0% (12/242) | 8.4% (20/238) | No significant difference |
| Patients reporting serious adverse events | 10.2% (24/236) | 7.9% (19/242) | 5.9% (14/238) | No significant difference |
| Withdrawals due to adverse events | 3.8% (9/236) | 2.5% (6/242) | 2.1% (5/238) | No significant difference |
Abbreviations: CI, confidence interval; FEV\textsubscript{1}, forced expired volume in 1 second; ITT, intention-to-treat; MMRC, Modified Medical Research Council questionnaire; PP, per-protocol; RR, relative risk; SGRQ, St George's Respiratory Questionnaire.

\( a \) The ITT population included all randomised patients who received at least 1 puff of study drug and had at least 1 post-baseline efficacy evaluation.

\( b \) The PP population included all patients in the ITT analysis set who did not have any major protocol violations. Both ITT and PP analyses are undertaken in non-inferiority analyses to confirm the findings.

\( c \) Within the pre-specified non-inferiority margin of −0.100 L

\( d \) The safety population included all randomised patients who received at least 1 puff of study medication.

**Extrafine beclometasone/formoterol compared to fluticasone/salmeterol combination therapy in COPD (Singh et al. 2014)**

- **Design:** this study was a 12-week, double-blind, double-dummy randomised controlled trial undertaken in 76 centres in 10 European countries.

- **Population:** 419 hospital outpatients (mean age 64 years) with moderate-to-severe COPD (post-bronchodilator FEV\textsubscript{1} less than 60% of the predicted normal [mean 46.5%] and FEV\textsubscript{1}/FVC ratio less than 0.7). The definition of moderate-to-severe COPD is in agreement with the NICE guideline on COPD. Participants had a smoking history of 10 pack years or more (mean 41 pack years); a Baseline Dyspnoea Index focal score of 10 or less (mean 6) at screening and randomisation, and a history of 1 or no COPD exacerbations treated with antibiotics or systemic corticosteroids in the previous 12 months. Patients were excluded if they had been diagnosed with asthma, other respiratory disorders, or any other clinically relevant condition that could have interfered with the evaluation of results.

- **Intervention and comparator:** following a screening and 2-week run-in period during which they used inhaled ipratropium bromide 4 times daily as maintenance treatment, participants were then randomised 1:1 to receive beclometasone/formoterol 100/6 micrograms (2 puffs twice daily: n=211), fluticasone/salmeterol 500/50 micrograms (1 puff twice daily: n=208) for 12 weeks. The method of allocation described suggests that this was concealed although it is not explicitly stated in the methods. Patients took active medications and matched placebos twice daily to maintain blinding. Baseline characteristics appeared similar at baseline although statistical analyses are not reported. Clinic visits were performed at monthly intervals. Inhaled rescue salbutamol use was permitted throughout the study but no other COPD medications...
were allowed. Patients recorded symptoms, and use of study and rescue medications in diaries each day.

- Outcomes: the 2 co-primary efficacy end points were the change in Transition Dyspnoea Index (TDI) score at the end of the study (week 12: equivalence analysis, pre-specified equivalence margins ±1), and the change in FEV₁ from pre-dose in the first 30 minutes after drug inhalation during the morning of the baseline visit (area under the curve [AUC₀-30min], a measure of onset of bronchodilation: superiority analysis). Secondary end points included COPD exacerbations, health-related quality of life and a 6 minute walking test. Adverse events were also assessed. All analyses were performed on the intention-to-treat population. Missing values were accounted for using the last observation carried forward approach.

Table 3 Summary of extrafine beclometasone/formoterol compared to fluticasone/salmeterol combination therapy in COPD (Singh et al. 2014)

<table>
<thead>
<tr>
<th></th>
<th>Beclometasone/formoterol 100/6 micrograms 2 puffs twice daily</th>
<th>fluticasone/salmeterol 500/50 micrograms 1 puff twice daily</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>n=211</td>
<td>n=208</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>n=211</td>
<td>n=207</td>
<td></td>
</tr>
<tr>
<td>Primary outcome 1: mean change in TDI score from baseline to week 12</td>
<td>1.32 95% CI 0.87 to 1.77</td>
<td>1.15 95% CI 0.70 to 1.60</td>
<td>Beclometasone/formoterol was equivalent to fluticasone/salmeterol: Mean difference 0.17 95% CI −0.39 to 0.72 p=0.56</td>
</tr>
</tbody>
</table>
Primary outcome 2: change in FEV$_1$ from pre-dose in the first 30 minutes after drug inhalation (mean AUC$_{0–30\text{min}}$)

<table>
<thead>
<tr>
<th></th>
<th>0.18 L</th>
<th>0.11 L</th>
<th>Beclometasone/formoterol had a statistically significantly faster onset of action than fluticasone/salmeterol: Mean difference 0.07 L 95% CI 0.05 to 0.10 p&lt;0.001</th>
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<tbody>
<tr>
<td></td>
<td>95% CI 0.16 L to 0.19 L</td>
<td>95% CI 0.09 L to 0.12 L</td>
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</table>

Selected secondary outcomes:

<table>
<thead>
<tr>
<th>Mean rate of COPD exacerbations (not defined)</th>
<th>2.8% (6/211)</th>
<th>1.9% (4/207)</th>
<th>No significant difference between treatments</th>
</tr>
</thead>
</table>

| Mean change in health-related quality of life (SGRQ) total score from baseline to 12 weeks | −5.92 95% CI −7.75 to −4.08 | −3.80 95% CI −5.70 to −1.90 | Both treatments statistically significantly improved the SGRQ total score from baseline (both p<0.001) No significant difference was found between treatments |

| Mean change in 6 minute walking test distance from baseline to 12 weeks | 31.62 m 95% CI 15.18 m to 48.06 m | 22.23 m 95% CI 6.30 m to 38.16 m | Both treatments statistically significantly improved the distance covered in 6 minutes (p=0.001 and p=0.008 respectively) No significant difference was found between treatments |

Safety

<table>
<thead>
<tr>
<th>Patients reporting serious adverse events</th>
<th>1.9% (4/211)</th>
<th>6.3% (13/207)</th>
<th>Statistically significantly more serious adverse events were seen in the fluticasone/salmeterol group (p=0.024)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawals due to adverse events</td>
<td>1.4% (3/211)</td>
<td>2.4% (5/207)</td>
<td>Statistical significance of difference not reported</td>
</tr>
</tbody>
</table>
Clinical effectiveness

**Beclometasone/formoterol compared with budesonide/formoterol and formoterol alone**

Calverley et al. (2010) found that, over 48 weeks, beclometasone/formoterol, budesonide/formoterol and formoterol alone improved pre-dose morning FEV₁ (the first primary outcome) by 0.077 L, 0.080 L and 0.026 L respectively in people with severe COPD. These changes in FEV₁ are less than the improvement that the full NICE guideline on COPD considers to be clinically important (0.100 L or more). In the intention-to-treat analysis, beclometasone/formoterol was shown to be non-inferior to budesonide/formoterol (the lower limit of the 97.5% CI was −0.052 L, which is within the pre-specified non-inferiority margin of −0.100 L) and statistically significantly better than formoterol alone (p=0.046). Similar results were reportedly obtained in the per-protocol population.

In this study, the overall mean rate of COPD exacerbations/patient per year (the second primary outcome) was not statistically significantly different between the treatments (beclometasone/formoterol 0.414, budesonide/formoterol 0.423 and formoterol alone 0.431, an improvement from 1.73, 1.67 and 1.79 respectively in the 2–12 months before screening). The risk of needing hospitalisation for a COPD exacerbation was twice as high in the beclometasone/formoterol group compared with the budesonide/formoterol and formoterol alone groups (RR 2.222, 95% CI 1.384 to 3.567 and RR 1.844, 95% CI 1.173 to 2.901 respectively). However, the rates of COPD exacerbations needing hospitalisation were low (mean/patient per year: beclometasone/formoterol 0.074, budesonide/formoterol 0.033 and formoterol 0.040).

Health-related quality of life, walking distance in 6 minutes and COPD symptom scores generally improved from baseline to 48 weeks in all groups and use of rescue medication decreased, with no statistically significant differences between treatments. At 48 weeks, the improvements in health-related quality of life (SGRQ) scores for beclometasone/formoterol and budesonide/formoterol were around 4 units, the minimum considered to be clinically important. Similarly, the mean
improvements in the 6 minute walking test for all treatments were around the minimum threshold of 37 m that is reported to be clinically important (Calverley et al. 2010: see table 2 for more details).

Another RCT, the FORWARD study (Wedzicha et al. 2014), compared beclometasone/formoterol 100/6 micrograms (2 puffs twice daily) with formoterol 12 micrograms alone (1 puff twice daily) in 1199 people with severe COPD (mean post-bronchodilator FEV₁ at screening 42%) and a history of at least 1 exacerbation (mean 1.5) in the previous year. Compared with formoterol alone, beclometasone/formoterol statistically significantly reduced the exacerbation rate at 48 weeks (exacerbations/patient per year 1.12 compared with 0.80 respectively; RR 0.72, 95% CI 0.62 to 0.84; p<0.001) and improved pre-dose morning FEV₁ at 12 weeks (mean 0.012 L compared with 0.081 L; difference 0.069 L, 95% CI 0.043 L to 0.095 L; p<0.001), the co-primary end points. The difference in FEV₁ is less than the improvement that the full NICE guideline on COPD considers to be clinically important (0.100 L or more).

**Beclometasone/formoterol compared with fluticasone/salmeterol**

Singh et al. (2014) found that beclometasone/formoterol and fluticasone/salmeterol statistically significantly improved TDI scores (a measure of breathlessness; the first primary outcome) by 1.32 units respectively and 1.15 units over 12 weeks in people with moderate-to-severe COPD. The full NICE guideline on COPD considers an improvement of 1 unit to be clinically important. The combination treatments were found to be equivalent in the intention-to-treat analysis (the 95% CI for the difference [−0.39 to 0.72] was entirely within the pre-specified equivalence margins of ±1). However, both intention-to-treat and per-protocol analyses should be undertaken in equivalence analyses to confirm the findings and it is unclear whether a per-protocol analysis was undertaken in this study.

As assessed by the change in FEV₁ from pre-dose in the first 30 minutes after drug inhalation (the secondary primary outcome), in this study beclometasone/formoterol had a statistically significantly faster onset of action than fluticasone/salmeterol (AUC₀⁻³⁰min adjusted means at 12 weeks 0.18 L compared with 0.11 L respectively, p<0.001). It is unclear whether this difference is clinically important.

Health-related quality of life, walking distance in 6 minutes and COPD symptom scores generally improved from baseline to 12 weeks and use of rescue medication decreased, with no statistically significant differences between beclometasone/formoterol and fluticasone/salmeterol. Many of the improvements were not clinically important, although overall beclometasone/formoterol
improved health-related quality of life (SGRQ) scores by more than 4 units (see table 3 for more details).

**Safety and tolerability**

**Beclometasone/formoterol compared with budesonide/formoterol and formoterol alone**

Calverley et al. (2010) found that the incidence of adverse events, treatment-related adverse events, serious adverse events and withdrawals due to adverse events did not differ significantly between beclometasone/formoterol, budesonide/formoterol and formoterol alone (see table 2). The most commonly reported adverse event was exacerbation or worsening of COPD, which occurred in 27–28% of participants. Pneumonia was reported by 5 people (2.1%) in the beclometasone/formoterol group, 7 people (2.9%) in the budesonide/formoterol group and 1 person (0.4%) in the formoterol group (statistical significance of differences not reported).

The most common causes of discontinuations were withdrawn consent and adverse events. A total of 20 participants withdrew from the study due to an adverse event: 9 (3.8%) in the beclometasone/formoterol group, 6 (2.5%) in the budesonide/formoterol group and 5 (2.1%) in the formoterol group (Calverley et al. 2010).

In the FORWARD study the incidence of adverse events, serious adverse events, treatment-related adverse events and withdrawals due to adverse events was similar in the 2 groups. Treatment-related adverse events occurred in 42 people (7.0%) taking beclometasone/formoterol and 26 people (4.4%) taking formoterol alone. Pneumonia was reported by 23 people (3.8%) in the beclometasone/formoterol group and 11 people (1.8%) in the formoterol alone group (statistical significance of differences not reported; Wedzicha et al. 2014).

**Beclometasone/formoterol compared with fluticasone/salmeterol**

Total adverse events and treatment-related adverse events were not reported by Singh et al. (2014). Treatment-emergent serious adverse events occurred statistically significantly more often in the fluticasone/salmeterol group than the beclometasone/formoterol group (13 people [6.3%] compared with 4 people [1.9%], p=0.024). Pneumonia was reported in 3 people (1.4%) treated with fluticasone/salmeterol and none treated with beclometasone/formoterol. Worsening of COPD was reported in 2 people (1.0%) treated with fluticasone/salmeterol and none treated with beclometasone/formoterol. Three people (1.4%) treated with beclometasone/formoterol and 5 people (2.4%) treated with fluticasone/salmeterol discontinued the study due to adverse events (statistical significance of differences not reported).
Summary of product characteristics

Adverse effects that have been reported commonly (in between 1 in 10 and 1 in 100 people) with beclometasone/formoterol in combination or as single constituents are pharyngitis, oral candidiasis, headache and dysphonia. See the summaries of product characteristics for more information.

Evidence strengths and limitations

The 2 main studies discussed in this evidence summary are randomised, double-blind, double-dummy studies and the method of allocation described suggests that this was concealed. The populations studied had moderate-to-severe and severe COPD and were suitable for treatment with an ICS/LABA combination according to the NICE clinical guideline on COPD. Around 39% of participants in Calverley et al. (2010) and 73% of participants in Singh et al. (2014) were taking ICS at baseline suggesting that the populations were representative of those eligible for ICS treatment (in combination with another drug) in clinical practice. Appropriate comparators that reflect current standard treatment were used and 3 of the 4 co-primary outcomes the studies were patient orientated outcomes (COPD exacerbations, dyspnoea and onset of bronchodilation). Analyses for outcomes assessing superiority of beclometasone/formoterol over the comparator treatments were by intention-to-treat.

In the 2 studies discussed in this evidence summary, drop-out rates were 13% and 11% and the last observation carried forward approach was used to take account of missing data. The European Medicines Agency’s guideline on missing data in confirmatory clinical trials notes that this approach can often produce a biased estimate of the treatment effect, which may either be optimistic or conservative depending on the situation and whether the condition being studied would be expected to improve or deteriorate over time. The guideline advises that it will almost always be necessary to investigate the robustness of trial results through appropriate sensitivity analyses that make different assumptions. Sensitivity analyses were not reported in either of the studies.

The study by Calverley et al. (2010) considered whether beclometasone/formoterol was non-inferior to budesonide/formoterol for improving pre-dose morning FEV\textsubscript{1}. Singh et al. (2014) considered whether beclometasone/formoterol was equivalent to fluticasone/salmeterol for improving breathlessness. In contrast to superiority studies, both intention-to-treat and per-protocol analyses should be undertaken in non-inferiority and equivalence studies in order to confirm the findings. Calverley et al. (2010) reported that their findings were confirmed in a per-protocol analysis, but Singh et al. (2014) did not.
In Calverley et al. (2010), beclometasone/formoterol was non-inferior to budesonide/formoterol for improving the disease-orientated outcome, pre-dose morning FEV₁, in people with severe COPD and the authors note that this is despite the lower dose of ICS included in this combination (beclometasone 400 mg daily compared with budesonide 800 mg daily respectively). However, the summary of product characteristics advises that the particles of BDP in Fostair are extrafine and more potent than in standard formulations of BDP: 100 micrograms of extrafine BDP in Fostair are equivalent to 250 micrograms of standard BDP. This suggests that the equivalent dose of standard BDP used in the study was 1000 mg daily with beclometasone/formoterol, compared with 800 mg daily with budesonide/formoterol (BDP equivalence of standard beclometasone:budesonide is 1:1).

Singh et al. (2014) concluded that beclometasone/formoterol was equivalent to fluticasone/salmeterol for improving breathlessness (TDI scores) in people with moderate-to-severe COPD in spite of a lower dose of ICS (400 micrograms beclometasone daily compared with 1000 micrograms fluticasone daily respectively). The equivalent doses of standard BDP are 1000 micrograms daily and 2000 micrograms daily respectively (BDP equivalence of standard beclometasone:fluticasone is 2:1) therefore, the dose of ICS is lower with beclometasone/formoterol in this study.

In Calverley et al. (2010), superiority of beclometasone/formoterol over budesonide/formoterol and formoterol alone was not shown for rate of COPD exacerbations. This may suggest that the addition of beclometasone to formoterol does not reduce exacerbations, an important patient-orientated outcome. However, the authors state that the observed exacerbation rates were less than half of those reported in earlier studies, possibly due to the inclusion criteria, which may have led to the recruitment of people with stable COPD who were less likely to experience exacerbations. Also, participants may have been less likely to have an exacerbation because they were monitored regularly and closely. This may mean that the analyses were underpowered.

According to Singh et al. (2014), beclometasone/formoterol had a statistically significantly faster onset of bronchodilation (change in FEV₁ from pre-dose in the first 30 minutes after drug inhalation) than fluticasone/salmeterol and the authors state that this shows that formoterol has a faster onset of action than salmeterol. However, it is unclear whether the difference is clinically important. A Cochrane review found that formoterol has a more rapid onset of action than salmeterol in people with asthma and Singh et al. reference some studies that suggest that this is also the case in people with COPD.

Both studies were sponsored by the manufacturer of Fostair, Chiesi.
Context

Alternative treatments

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

Apart from the beclometasone/formoterol metered dose inhaler (Fostair 100/6 micrograms), there are 3 combined ICS/LABA inhalers that are currently licensed for treating COPD:

- budesonide/formoterol dry powder inhaler (Symbicort Turbuhaler 200/6 micrograms and Symbicort Turbuhaler 400/12 micrograms)
- fluticasone furoate/vilanterol dry powder inhaler (Reflar 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).

Indacaterol/glycopyrronium (Ultibro Breezhaler 85/43 micrograms) was the first combination inhaler containing a LABA and a LAMA to receive a European marketing authorisation for COPD (see the evidence summary on Chronic obstructive pulmonary disease: indacaterol/glycopyrronium). However, it has not yet been marketed in the UK. Umeclidinium/vilanterol dry powder inhaler (Anoro Ellipta 55/22 micrograms) received a European marketing authorisation for COPD in June 2014 and is the subject of another evidence summary. It has been launched in the UK.

Costs of alternative treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dosagea,b</th>
<th>30-day cost excluding VAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination ICS/LABA inhalers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclometasone/formoterol 100/6 micrograms (Fostair)</td>
<td>2 puffs twice daily</td>
<td>£29.32c</td>
</tr>
<tr>
<td>Budesonide/formoterol 200/6 micrograms (Symbicort Turbuhaler)</td>
<td>2 puffs twice daily</td>
<td>£38.00c</td>
</tr>
</tbody>
</table>
Budesonide/formoterol 400/12 micrograms (Symbicort Turbohaler)  1 puff twice daily  £38.00c

Fluticasone furoate/vilanterol 92/22 micrograms (Relvar Ellipta)  1 puff daily  £27.80d

Fluticasone propionate/salmeterol 500/50 micrograms (Seretide Accuhaler)  1 puff twice daily  £40.92c

Combination LABA/LAMA inhaler

Umeclidinium/vilanterol 55/22 micrograms (Anoro Ellipta)  1 puff daily  £32.50

Abbreviations: ICS, inhaled corticosteroid; 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 the Drug Tariff (June 2014). All costs include the inhaler device.
d Costs taken from MIMS (June 2014). All costs include the inhaler device.

**Estimated impact for the NHS**

**Likely place in therapy**

The NICE clinical 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.

Beclometasone/formoterol has been compared to the most commonly used ICS/LABA combinations for COPD, budesonide/formoterol and fluticasone/salmeterol. Beclometasone/formoterol was non-inferior to budesonide/formoterol in improving pre-dose morning lung function over 48 weeks and there was no significant difference between the treatments in the rate of COPD exacerbations/patient per year. The incidence of adverse events, treatment-related adverse events, serious adverse events and withdrawals due to adverse events were similar between the treatments.

Beclometasone/formoterol statistically significantly improved the onset of bronchodilation compared with fluticasone/salmeterol (although it is unclear whether the improvement is clinically
important), and the treatments were equivalent in improving dyspnoea over 12 weeks. Treatment-emergent serious adverse events were statistically significantly more common with fluticasone/salmeterol (13 people [6.3%] compared with 4 people [1.9%], p=0.024), which may be due to the higher dose of ICS in this combination. Pneumonia was reported in 3 people (1.4%) treated with fluticasone/salmeterol and none treated with beclometasone/formoterol.

It is not known how beclometasone/formoterol compares with the other new ICS/LABA combination, fluticasone/vilanterol, or the LABA/LAMA combinations, indacaterol/glycopyrronium and umeclidinium/vilanterol. However, the safety profiles of beclometasone and formoterol are better established than the safety profiles of the constituents of the other new combination inhalers.

The NICE clinical guideline on COPD advises that an ICS/LABA combination inhaler should be offered if FEV$_1$ is less than 50% of predicted in people with COPD. In addition, an ICS/LABA may be considered in people with stable COPD and an FEV$_1$ of 50% or more of predicted who remain breathless or have exacerbations despite maintenance therapy with a LABA. Beclometasone/formoterol is licensed for the symptomatic treatment of adults with severe COPD (FEV$_1$ less than 50% of the predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators. Use according to NICE guidance in some situations (for example before a long-acting bronchodilator has been tried) would be off-label. However, this is also the case for other ICS/LABA combination inhalers.

The cost of a beclometasone/formoterol inhaler (£29.32; Drug Tariff, June 2014) is less than a budesonide/formoterol or fluticasone/salmeterol inhaler (£38.00 and £40.92 respectively; Drug Tariff, June 2014) and is slightly higher than that of a fluticasone/vilanterol inhaler (£27.80; MIMS, June 2014). All inhalers last for 30 days at usual dosages.

The type of inhaler device may affect the choice of treatment for an individual person. A metered dose inhaler is the most appropriate device for people who need to use spacers, which can improve distribution of drugs within the lungs and reduce some adverse effects such as oral candidiasis. Beclometasone/formoterol is administered using a metered dose inhaler; budesonide/formoterol is administered using a Turbohaler; fluticasone/formoterol is administered using an Accuhaler; and fluticasone/vilanterol is administered using an Ellipta device. Apart from fluticasone/vilanterol, which is administered once daily, these treatments are administered twice daily. A specialist involved in the production of this evidence summary has advised that, although adherence is better when an inhaler is given once daily, some respiratory physicians prefer twice daily administration to avoid larger variations in of peak and trough levels, which may potentially be related to COPD admissions.
Local decision makers will need to take these factors into account when considering the likely place in therapy of beclometasone/formoterol for COPD.

Estimated usage

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

Relevance to NICE guidance programmes

Beclometasone/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 clinical guideline 101), which has been incorporated into a NICE pathway.

References


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Chiesi Limited (2014) Fostair summary of product characteristics [online; accessed 11 August 2014]


National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease. NICE Pathway [online; accessed 9 June 2014]

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

Kevin Gruffydd Jones has acted as a paid consultant and spoken on behalf of GSK, Astra Zeneca, Boehringer Ingelheim, Almirall, Novartis, Chiesi and MSD. He was a member of the NICE 2010 COPD Guidelines Committee and 2011 Quality Standards committee.

John Haughney has received reimbursements for attending symposia, fees for speaking or 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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