Asthma: fluticasone/formoterol (Flutiform) combination inhaler

Evidence summary
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nice.org.uk/guidance/esnm3

Overview

Key points from the evidence

The content of this evidence summary was up-to-date in October 2012. See summaries of product characteristics (SPCs), British national formulary (BNF), BNF for children (BNFc) or the MHRA or NICE websites for up-to-date information.

Fluticasone/formoterol (Flutiform) is a combination inhaler containing an inhaled corticosteroid (ICS) and a long-acting beta-2 agonist (LABA). It was launched in the UK in September 2012 and is indicated for regular treatment of asthma when a combination inhaler is appropriate:

- for people whose asthma is not adequately controlled on an ICS and an 'as required' inhaled short-acting beta-2 agonist, or
- for people whose asthma is adequately controlled on both an ICS and a LABA.

Fluticasone/formoterol is available in 3 strengths: 50/5 micrograms, 125/5 micrograms and 250/10 micrograms. The low and medium strengths are licensed for people aged 12 years and over; the high strength for people aged 18 years and over.

Evidence from 2 published non-inferiority studies indicates that fluticasone/formoterol is non-inferior to a comparable dose of fluticasone plus formoterol in separate inhalers, and non-inferior to a fluticasone/salmeterol combination inhaler in terms of effect on lung function, as measured by
FEV₁ (forced expiratory volume in 1 second). Side-effect profiles were similar and no significant differences were observed in asthma exacerbations and serious adverse events, although the 2 studies were not sufficiently powered to measure these outcomes. There are currently no published studies in people with asthma who are under 18 years.

When considering using the fluticasone/formoterol combination inhaler, local decision makers will need to consider its use alongside other treatment options when an ICS plus a LABA is appropriate, in accordance with the British guideline on the management of asthma. Although the limited published data appear to suggest that the efficacy and safety of fluticasone/formoterol is similar to other ICS/LABA combination inhalers, choice of inhaler device may be important to individual patients and may need to be taken into account by decision makers.

The cost of treatment options will also be a factor for local decision-making. If a combination inhaler is chosen, NICE guidance on Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over (NICE technology appraisal guidance 138) recommends the least costly device that is suitable for the individual.

### Key evidence

- Bodzenta-Lukaszyk A, Dymek A, McAulay K et al. (2011) Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: an open-label, randomised study. BMC Pulmonary Medicine 11: 28

### About this evidence summary

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

### Relevance to NICE guidance programmes

The fluticasone/formoterol combination inhaler is not currently being considered for a NICE technology appraisal or other work programme.
Introduction

The British guideline on the management of asthma, published jointly by the Scottish Intercollegiate Guidelines Network and British Thoracic Society, advocates the following stepwise approach for the treatment of asthma. Inhaled corticosteroids (ICS) are the first-choice regular preventer therapy for children and adults. If asthma is not adequately controlled on an ICS alone (at step 2), add-on therapy may be needed (step 3). For children aged 5 years and over and adults, an ICS and a LABA should be considered. However, before starting a new drug or stepping up treatment, adherence with existing therapies, inhaler technique, and appropriate elimination of trigger factors should be confirmed.

Adding a LABA to an ICS can improve lung function and symptoms, and reduce exacerbations. However, an increase in the risk of serious adverse events has been observed with LABAs (both formoterol and salmeterol), which does not appear to be completely abolished when an ICS is used concurrently\(^1\)\(^2\).

After an assessment of the risks and benefits in asthma, the Medicines and Healthcare products Regulatory Agency concluded that the benefits of using a LABA with an ICS outweigh any apparent risks. The Commission on Human Medicines has issued advice\(^3\) for prescribers to ensure safe use of LABAs for chronic asthma.

If treatment with an ICS and LABA is considered appropriate, NICE guidance on ICS for asthma recommends that the decision to use a combination device or the 2 agents in separate devices should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence. If a combination device is chosen, then the least costly device that is suitable for the individual is recommended.

\(^1\) Cates CJ, Cates MJ (2012) Regular treatment with formoterol for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews issue 4: CD006923

\(^2\) Cates CJ, Cates MJ (2011) Regular treatment with salmeterol for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews issue 4: CD006363

Product overview

Drug action

Flutiform\(^\text{[4]}\) is a CFC-free aerosol combination of fluticasone propionate (an ICS) and formoterol fumarate (a LABA) in a pressurised metered dose inhaler. The potency of fluticasone is approximately double that of beclometasone (except Qvar and Fostair devices) or budesonide\(^\text{[5]}\). Formoterol has a more rapid onset of action than salmeterol\(^\text{[6]}\).

Licensed therapeutic indication

Flutiform was given a UK marketing authorisation in August 2012 and launched in September 2012 for the regular treatment of asthma when a combination inhaler (ICS/LABA) is appropriate:

- for people whose asthma is not adequately controlled on an ICS and an 'as required' inhaled short-acting beta-2 agonist, or
- for people whose asthma is adequately controlled on both an ICS and a LABA.

Flutiform 50/5 micrograms and 125/5 micrograms are licensed for people aged 12 years and over; Flutiform 250/10 micrograms is licensed for people aged 18 years and over.

Course and cost

Flutiform is available in 3 strengths (50/5, 125/5 and 250/10 micrograms) for the maintenance treatment of asthma, using a regimen of 2 puffs twice daily. The lowest dose at which effective control of asthma is maintained should be used\(^\text{[5]}\). The costs are shown in table 1.

Table 1 Cost of Flutiform

<table>
<thead>
<tr>
<th>Strength</th>
<th>Cost of 120-dose units</th>
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<tbody>
<tr>
<td>Low strength</td>
<td>50/5 micrograms</td>
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<tr>
<td>Medium strength</td>
<td>125/5 micrograms</td>
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<tr>
<td>High strength</td>
<td>250/10 micrograms</td>
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</table>

Costing information from MIMS October 2012.
For the purpose of this evidence summary, the name 'Flutiform' is used when referring specifically to the Flutiform metered dose inhaler; ‘fluticasone/formoterol’ is used when referring to the evidence on the use of this combination.

SIGN/BTS (2012) British guideline on the management of asthma

Cates CJ, Lasserson TJ (2010) Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews issue 1: CD007694

Evidence review

Summary of the studies

This evidence review is based on 2 published randomised, non-inferiority studies (see tables 2 and 3).

Study 1: Bodzenta-Lukaszyk et al.

- Design: double-blind, randomised, non-inferiority trial.
- Population: 620 people aged 18 years and over with severe persistent asthma for at least 6 months (ICS treatment of at least 500 micrograms/day of fluticasone or equivalent ICS dose[7]).
- Intervention and comparison: fluticasone/formoterol compared with separate inhalers of the individual components administered concurrently (fluticasone plus formoterol) and fluticasone alone. There were 4 study arms:
  - fluticasone/formoterol 250/10 micrograms 2 puffs twice daily
  - fluticasone/formoterol 50/5 micrograms 2 puffs twice daily
  - fluticasone 250 micrograms plus formoterol 12 micrograms, both 2 puffs twice daily
  - fluticasone 250 micrograms 2 puffs twice daily.

Only results for fluticasone/formoterol 250/10 micrograms 2 puffs twice daily and the fluticasone plus formoterol regimen are reported in table 2 because they were the only comparable dose regimens. Follow-up was 8 weeks.
<p>| Table 2 Summary of study 1: Bodzenta-Lukaszyk et al. II (fluticasone/formoterol compared with fluticasone plus formoterol) |
|---|---|---|---|
| <strong>ITT group</strong>(^a) | Fluticasone/formoterol 250/10 micrograms 2 puffs twice daily | Fluticasone 250 micrograms 2 puffs twice daily plus formoterol 12 micrograms 2 puffs twice daily | <strong>Analysis</strong> |
| n=154 | n=156 | <strong>LS mean difference</strong> 0.079 litres 95% CI −0.032 to 0.190 (p&lt;0.001) |
| <strong>Primary outcome: mean change in pre-morning dose FEV(_1) from baseline to week 8</strong> | 0.346 litres | 0.267 litres | <strong>LS mean difference</strong> 0.040 litres 95% CI −0.069 to 0.149 (p&lt;0.001) |
| <strong>Co-primary outcome: mean change in FEV(_1) from baseline pre-morning dose to 2 hours post-morning dose at week 8</strong> | 0.517 litres | 0.477 litres | <strong>LS mean difference</strong> 0.079 litres 95% CI −0.032 to 0.190 (p&lt;0.001) |
| <strong>Selected patient-oriented secondary outcomes:</strong> | | | |
| At least 1 mild to moderate asthma exacerbation(^b) | 35.1% | 35.3% | (p=1.0) |
| Mean AQLQ score at week 8 | 5.34±1.07 | 5.30±1.00 | (p) value not stated |
| Patients reporting 1 or more adverse events(^c) | 19.5% (30/154) | 19.9% (31/156) | (p) value not stated |
| Per protocol group(^d) | n=133 | n=140 | |</p>
<table>
<thead>
<tr>
<th>Study 2: Bodzenta-Lukaszyk et al.</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary outcome:</strong> mean change in pre-morning dose FEV$_1$ from baseline to week 8</td>
</tr>
<tr>
<td><strong>Co-primary outcome:</strong> mean change in FEV$_1$ from baseline pre-morning dose to 2 hours post-morning dose at week 8</td>
</tr>
</tbody>
</table>

**Abbreviations:** AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FEV$_1$, forced expiratory volume in 1 second; ITT, intention to treat; LS, least-squares; n, number of patients.

- All patients randomised who received at least 1 dose of study treatment and had at least 1 post-dose primary efficacy (FEV$_1$) measurement.
- Pre-dose morning peak expiratory flow rate (PEFR) more than 30% below baseline (visit 3 value) on 2 or more consecutive days, or awakening at night due to asthma for 2 or more consecutive days (that is, sleep disturbance score due to asthma more than 0), or use of salbutamol rescue medication more than 4 times a day for 2 or more consecutive days (information supplied by Napp Pharmaceuticals).
- All patients randomised to receive study treatment and had at least 1 post-dose safety assessment. Adverse events were defined as: mild (awareness of sign, symptom, or event, but easily tolerated); moderate (discomfort enough to interfere with usual activity and may warrant intervention; and severe (incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention).
- All ITT patients who completed the study without major protocol violations affecting the primary efficacy outcome.
• Population: 202 people aged 18 years and over with mild-to-moderate to severe persistent asthma for at least 6 months. More than 90% were taking an ICS at baseline and 77% were taking a LABA.

• Intervention and comparison: fluticasone/formoterol (50/5 or 125/5 micrograms, 2 puffs twice daily) compared with fluticasone/salmeterol (Seretide: 50/25 or 125/25 micrograms, 2 puffs twice daily). The starting dose depended on the person’s asthma history and pre-study medication. Follow-up was 12 weeks.

Table 3 Summary of study 2: Bodzenta-Lukaszyk et al. (fluticasone/formoterol compared with fluticasone/salmeterol)

<table>
<thead>
<tr>
<th></th>
<th>Fluticasone/formoterol 50/5 or 125/5 micrograms 2 puffs twice daily</th>
<th>Fluticasone/salmeterol 50/25 or 125/25 micrograms 2 puffs twice daily</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full analysis set group</td>
<td>n=101</td>
<td>n=101</td>
<td></td>
</tr>
<tr>
<td>Primary outcome: mean pre-dose FEV₁ at week 12</td>
<td>Not reported in paper</td>
<td>Not reported in paper</td>
<td>LS mean difference: -0.074 litres</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI: -0.174 to 0.027</td>
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<td></td>
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<td>p=0.014</td>
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</tbody>
</table>

Selected patient-oriented secondary outcomes:

- Asthma exacerbations: mild/moderate: 10.9% (11/101) vs 11.9% (12/101), p<0.999
- Asthma exacerbations: severe: 3.0% (3/101) vs 1.0% (1/101), p=0.621
- Mean AQLQ score at week 12: 5.4 (SD 1.1) vs 5.5 (SD 0.9), p=0.051

Per protocol group: n=96 vs n=95
<table>
<thead>
<tr>
<th>Primary outcome: mean pre-dose FEV\textsubscript{1} at week 12</th>
<th>2.402 L\textsuperscript{b}</th>
<th>2.463 L\textsuperscript{b}</th>
<th>LS mean difference −0.061 L 95% CI −0.161 to 0.040 p=0.007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected patient-oriented secondary outcomes</td>
<td>Not reported in paper</td>
<td>Not reported in paper</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FEV\textsubscript{1}, forced expiratory volume in 1 second; LS, least-squares; n, number of patients; SD, standard deviation.

\textsuperscript{a} All randomised patients who received study treatment and had at least 1 post-dose primary efficacy (FEV\textsubscript{1}) measurement.

\textsuperscript{b} Not reported in paper. Information supplied by Napp Pharmaceuticals.

\textsuperscript{c} Pre-dose morning peak expiratory flow rate (PEFR) more than 30% below baseline on at least 2 consecutive days; night awakening due to asthma on at least 2 consecutive days; or use of salbutamol rescue medication more than 4 times a day for at least 2 consecutive days.

\textsuperscript{d} Deterioration in asthma needing additional therapy, or emergency visit or hospitalisation due to asthma.

\textsuperscript{e} All full analysis group patients who completed the study without major protocol violations affecting the primary efficacy (FEV\textsubscript{1}) outcome.

**Clinical effectiveness**

The primary outcomes in both studies used FEV\textsubscript{1} as a measure of lung function. In study 1, fluticasone/formoterol was non-inferior to a comparable dose of fluticasone plus formoterol for the primary outcome, based on both the intention-to-treat and per protocol analysis. In addition, fluticasone/formoterol was as effective as fluticasone plus formoterol for all secondary outcomes, including measures of lung function, mild to moderate exacerbations and quality of life (measured by Asthma Quality of Life Questionnaire score).

In study 2, fluticasone/formoterol was found to be non-inferior to fluticasone/salmeterol for the primary outcome, based on the per protocol analysis. The intention-to-treat analysis (full analysis set) was not reported in the published paper.
There were no significant differences between fluticasone/formoterol and fluticasone/salmeterol for most secondary outcomes. The time to onset of action for fluticasone/formoterol was found to be shorter than fluticasone/salmeterol throughout the 12 weeks of the study (hazard ratio 1.64, 95% CI 1.28 to 2.10, p<0.001). However, this was based on the full analysis set; the per protocol analysis was not reported.

Safety

In both studies, the side-effect profiles of fluticasone/formoterol and the comparators appeared similar, although the statistical significance of any possible differences was not reported. The overall rate of adverse events across all treatment groups was approximately 20% in study 1 and 24% in study 2. The majority of adverse events were considered 'mild or moderate', and most commonly related to infections. Adverse events considered to be severe were very rare (less than 2% across all groups).

Evidence strengths and limitations

Caution is needed when translating the results of these studies to clinical practice. Most people enrolled in the studies were treated at step 4 of the British guideline on the management of asthma at baseline (ICS dose above 800 micrograms/day of beclometasone equivalent plus a LABA). Approximately 75% of people in study 2 were initiated on a high dose ICS/LABA combination (step 4).

Only a small proportion of people with asthma need treatment at step 4\(^a\). There is limited experience of using fluticasone/formoterol in people with less severe asthma; for example, in people whose asthma is inadequately controlled on regular-dose ICS alone (step 2).

Both studies were designed to assess a disease-oriented measure of lung function as the primary outcome. No significant differences were observed in patient-oriented outcomes such as asthma exacerbations and serious adverse events. However, the studies were not designed to measure these outcomes and were unlikely to be large enough, or of sufficient duration, to detect any important differences that may exist.

A secondary outcome analysis in study 2 found that fluticasone/formoterol was superior to fluticasone/salmeterol in time to onset of action throughout the study. However, only the results of the full analysis set were presented. The actual times to onset of action were not stated in the published paper, therefore it is difficult to assess the relevance and clinical significance of this analysis.
In study 2, there was incomplete reporting of data in the published paper and only results of the per protocol analysis were presented for the primary outcome. Study 2 had an open-label design. For both studies allocation concealment was unclear, which may have introduced bias. Both studies also had a run-in phase and only people who could demonstrate correct inhaler technique were included.

There are currently no published long-term efficacy or safety data on the fluticasone/formoterol combination inhaler and no published papers on its use in children and young people under 18 years.

[7] See the British guideline on the management of asthma for more information on beclometasone equivalent doses. Fluticasone potency is approximately double that of beclometasone (except Qvar and Fostair devices) or budesonide.


[9] Bodzenta-Lukaszyk A, Dymek A, McAulay K et al. (2011) Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: an open-label, randomised study. BMC Pulmonary Medicine 11: 28


Context

Treatment alternatives

Fluticasone and formoterol are available in a range of separate inhaler devices.

Three other ICS/LABA combination inhalers are licensed in the UK:

- beclometasone/formoterol (Fostair) metered dose inhaler – not licensed for children and young people under 18 years

- fluticasone/salmeterol (Seretide) metered dose inhaler and dry powder inhaler – not licensed for children under 4 years
budesonide/formoterol (Symbicort) dry powder inhaler – not licensed for children under 6 years.

Costs of treatment alternatives

<table>
<thead>
<tr>
<th>120-dose units</th>
<th>Low strength</th>
<th>Medium strength</th>
<th>High strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flutiform metered dose inhaler</td>
<td>50/5 micrograms £18.00</td>
<td>125/5 micrograms £29.26</td>
<td>250/10 micrograms £45.56</td>
</tr>
<tr>
<td>Fostair metered dose inhaler</td>
<td>Not available</td>
<td>100/6 micrograms £29.32</td>
<td>Not available</td>
</tr>
<tr>
<td>Seretide metered dose inhaler</td>
<td>50/25 micrograms £18.00</td>
<td>125/25 micrograms £35.00</td>
<td>250/25 micrograms £59.48</td>
</tr>
<tr>
<td>Symbicort dry powder inhaler</td>
<td>100/6 micrograms £33.00</td>
<td>200/6 micrograms £38.00</td>
<td>400/12 micrograms £38.00 (60-dose unit)</td>
</tr>
</tbody>
</table>

1 100 micrograms of beclometasone in Fostair is approximately equivalent to 200 micrograms of beclometasone in a CFC-free inhaler[^1].

2 Seretide is also available as a dry powder inhaler.

Prices based on Drug Tariff, September 2012 and MIMS October 2012.

[^1]: SIGN/BTS (2012) British guideline on the management of asthma

Estimated impact for the NHS

Likely place in therapy

The British guideline on the management of asthma recommends a trial of ICS plus LABA for children aged 5 years and over and adults whose asthma is uncontrolled on an ICS alone. NICE guidance on ICS for asthma recommends that the decision on whether to prescribe a combination device or separate devices should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence[^1].

[^1]: SIGN/BTS (2012) British guideline on the management of asthma
There are more published data available for budesonide/formoterol (Symbicort) and fluticasone/salmeterol (Seretide)\textsuperscript{[12,13]}. However, the limited published data appear to suggest that the efficacy and safety of fluticasone/formoterol is similar to other ICS/LABA combination inhalers.

If a combination inhaler is appropriate, it is likely that the choice will depend largely on individual patient factors, for example:

- the availability of the drug and dose in the specific device
- the ability to develop and maintain an effective technique with the specific device
- suitability of the device to the person's lifestyle
- preference for and willingness to use a particular device.

If more than 1 device is suitable and acceptable to the person, NICE guidance on ICS for asthma recommends the least costly option should be chosen.

Switching a person's treatment from 1 combination inhaler to another, for example on economic grounds, does not appear to be a 'simple switch' and needs careful assessment and management. The British guideline on the management of asthma recommends stepping down therapy once asthma is controlled, but this recommendation is often not implemented, leaving some people overtreated. Regular review as treatment is stepped down is important\textsuperscript{[14]}.

**Estimated usage**

In the quarter up to December 2011, spending on all ICS/LABA combination inhalers was approximately £140 million in general practice in England\textsuperscript{[15]}. The manufacturer of Flutiform (Napp Pharmaceuticals) estimates that 1.3 million people are currently receiving an ICS/LABA combination inhaler for asthma in the UK\textsuperscript{[16]}. The company estimates that switching every person from Seretide to Flutiform could result in savings of up to £167,473 per year for an average primary care trust population (339,000). However, when considering the variables involved in switching inhaled therapies, it is not possible to provide an estimate of usage within localities.

\textsuperscript{[11]} National Institute for Health and Clinical Excellence (2008) Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over, NICE technology appraisal guidance 138
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For information about the process used to develop this evidence summary, see the Evidence summaries: new medicines – interim process statement.

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