

Asthma in adults: beclometasone/formoterol dry powder inhaler (Fostair NEXThaler)

Evidence summary

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[nice.org.uk/guidance/esnm53](https://www.nice.org.uk/guidance/esnm53)

Key points from the evidence

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

Summary

Fostair NEXThaler is an inhaled corticosteroid (ICS)/ long-acting beta-2 agonist (LABA) combination dry powder inhaler containing extrafine beclometasone/formoterol. Evidence from an 8-week randomised controlled trial suggests that in adults with stable asthma it is non-inferior to the pressurised metered dose inhaler (Fostair), and superior to non-extrafine beclometasone dry powder inhaler in terms of change from baseline in mean pre-dose morning peak expiratory flow with no difference in adverse events. There are no published comparative studies at the higher licensed dose, or with other available ICS/LABA combination inhalers or studies with patient orientated primary outcomes.

Regulatory status: Fostair pressurised metered dose inhaler has been licensed in the UK since 2007. Fostair NEXThaler is a new dry powder formulation inhaler licensed for the regular treatment of asthma in adults aged 18 years and over where use of a combination product (ICS and LABA) is appropriate. It was launched in September 2014.

<p>Effectiveness</p> <ul style="list-style-type: none"> • In an 8-week, double-<u>blind</u>, <u>randomised controlled trial</u> (RCT; n=755) in adults with stable asthma, extrafine beclometasone/formoterol 100/6 micrograms, 1 inhalation twice daily administered via a dry powder inhaler was non-inferior to the pressurised metered dose inhaler in terms of change from baseline in mean pre-dose morning peak expiratory flow. • In the same RCT, both extrafine formulations (dry powder and pressurised metered dose inhaler) of beclometasone/formoterol were statistically significantly superior to non-extrafine beclometasone dry powder inhaler for the same outcome ($p < 0.001$). 	<p>Safety</p> <ul style="list-style-type: none"> • The <u>summary of product characteristics</u> (SPC) states that the most common adverse reaction with beclometasone/formoterol dry powder inhaler is tremor. • In an 8-week RCT, 6 severe asthma exacerbations were observed in the non-extrafine beclometasone group, 4 in the extrafine beclometasone/formoterol dry powder inhaler group and 3 in the extrafine beclometasone/formoterol pressurised metered dose inhaler group. • The proportion of people experiencing treatment emergent adverse events was low and similar across all 3 treatment groups. Adverse events included headache, nasopharyngitis and pharyngitis.
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Patient factors	Resource implications
<ul style="list-style-type: none"> • Fostair NEXThaler contains beclometasone in an extrafine particle formulation. Dose adjustment may be required if people are transferred to Fostair NEXThaler inhalation powder from other inhalers containing non-extrafine beclometasone or different ICS medicines. • In a usability study with a number of limitations, more people preferred to use the NEXThaler device compared with Turbuhaler (Turbohaler) and Diskus (Accuhaler). • Extrafine beclometasone/formoterol dry powder inhaler has similar contraindications, cautions and interactions to other ICS/LABA combination inhalers. • No reliever treatments are available which use the NEXThaler device. Patients would therefore need to use a different inhaler device for their reliever and preventer medications. The British guideline on the management of asthma states this may lead to increased errors in inhaler use. • Unlike Fostair pressurised metered dose inhaler, Fostair NEXThaler is not licensed for maintenance and reliever therapy in adults with asthma. 	<ul style="list-style-type: none"> • The cost for 30-days treatment with Fostair NEXThaler ranges from £14.66 to £29.32 depending on the dose. • The cost of other licensed ICS/LABA combination inhalers at approximately similar doses ranges from £14.66 to £38.00 depending on the dosage and the product. See the cost of treatment alternatives section for more information.

Introduction and current guidance

The [British guideline on the management of asthma](#) (SIGN guideline 141) recommends that ICS are the first-choice regular preventer therapy for adults and children. If asthma is not adequately controlled on an ICS alone (at step 2), add-on therapy may be needed (step 3). For adults and children aged 5 years and over, an ICS and a LABA should be considered.

If treatment with an ICS and LABA is considered appropriate, [inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over](#) (NICE technology

appraisal guidance 138) recommends that using a combination inhaler within its marketing authorisation is an option. NICE recommends that the decision to use a combination inhaler or the 2 agents in separate inhalers should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence. If a combination inhaler is chosen, then the least costly device that is suitable for the individual is recommended.

The [British guideline on the management of asthma](#) recommends that in adults, administering ICS using a pressurised metered dose inhaler plus a spacer is as effective as using any dry powder inhaler. The guideline advises that there is no evidence to guide the order in which different devices should be tested in people who cannot use a pressurised metered dosed inhaler, and the most important points to consider are patient preference and cost. The person should have their ability to use an inhaler device assessed by a competent healthcare professional, and inhaler technique should be reassessed as part of a structured clinical review.

[Full text of introduction and current guidance.](#)

Product overview

[Fostair NEXThaler](#) (Chiesi Limited) is a dry powder inhaler containing 100 micrograms of beclometasone dipropionate (an ICS) and 6 micrograms of formoterol fumarate (a LABA).

The beclometasone in Fostair NEXThaler is an extrafine particle formulation, therefore dose adjustment is required when people are transferred to Fostair NEXThaler inhalation powder from a formulation with a non-extrafine particle size distribution. People who are transferred to Fostair NEXThaler inhalation powder from Fostair pressurised metered dose inhaler do not need dose adjustment because both inhalers use the extrafine particle formulation.

Fostair NEXThaler is licensed for the regular treatment of asthma in adults aged 18 years and over where use of a combination product (ICS and LABA) is appropriate:

- people not adequately controlled with ICS and 'as needed' inhaled short-acting beta2-agonist or
- people already adequately controlled on both ICS and LABAs.

The recommended dosage of Fostair NEXThaler is 1–2 inhalations twice daily and the maximum daily dose is 4 inhalations daily. People should be advised to keep a separate short-acting bronchodilator available at all times for the treatment of acute asthma attacks.

It should be noted that unlike Fostair pressurised metered dose inhaler; Fostair NEXThaler is **not licensed** for maintenance and reliever therapy in adults with asthma.

Fostair NEXThaler costs £29.32 for 1 inhaler containing 120 doses ([MIMS](#), December 2014; excluding VAT).

[Full text of product overview.](#)

Evidence review

- This evidence summary includes an RCT ([Kanniess et al. 2014](#)) that compared the efficacy and safety of extrafine beclometasone/formoterol dry powder inhaler (Fostair NEXThaler) at the lower licensed dose (1 inhalation twice daily) with extrafine beclometasone/formoterol pressurised metered dose inhaler (Fostair) and non-extrafine beclometasone dry powder inhaler; and a study ([Voshaar et al. 2014](#)) that compared the usability of the NEXThaler device with a Turbuhaler (Turbohaler) and Diskus (Accuhaler) device.
- [Kanniess et al. \(2014\)](#) was an 8-week, double-blind RCT in 755 adults with stable asthma. The study found that extrafine beclometasone/formoterol dry powder inhaler (Fostair NEXThaler) was non-inferior to the same combination administered by pressurised metered dose inhaler (Fostair) for the primary outcome of change from baseline in mean pre-dose morning peak expiratory flow (mean difference between the dry powder and pressurised metered dose inhaler groups –1.84 litres/minute, 95% [confidence interval](#) [CI] –6.73 to 3.05). Both extrafine formulations (dry powder and pressurised metered dose inhaler) of beclometasone/formoterol were statistically significantly superior to non extrafine beclometasone dry powder inhaler for the same outcome ($p < 0.001$). Some secondary patient orientated outcomes statistically significantly improved in both the extrafine beclometasone/formoterol dry powder groups compared with non-extrafine beclometasone alone, as would be expected. However there were no statistically significant differences for patient-orientated outcomes between the 2 extrafine beclometasone/formoterol groups.
- [Voshaar et al. \(2014\)](#) was a randomised crossover study that investigated the usability of the NEXThaler device, compared with 2 other dry powder inhalers in 66 adults with asthma and no previous experience of using dry powder inhalers. The study did not consider active treatment, had a number of limitations and is not considered in detail in this evidence summary. Statistically significantly more participants reported that if they had to pick one of the devices to use every day, they would choose NEXThaler (75.4%) compared with an Accuhaler (16.9%; $p < 0.001$) or a Turbuhaler (7.7%; $p < 0.001$).

- In [Kanniess et al. \(2014\)](#), 26 asthma exacerbations were reported during the trial, 13 of which were classed as severe. Of these, 6 were observed in the non-extrafine beclometasone group, 4 in the extrafine beclometasone/formoterol dry powder inhaler group and 3 in the extrafine beclometasone/formoterol pressurised metered dose inhaler group. The percentage of people reporting treatment-emergent adverse events was low in all 3 treatment groups (0.8% in the beclometasone/formoterol dry powder inhaler group and 1.2% in both the extrafine beclometasone/formoterol pressurised metered dose inhaler and non-extrafine beclometasone groups). Treatment-emergent adverse events reported in the extrafine beclometasone/formoterol dry powder inhaler, beclometasone/formoterol pressurised metered dose inhaler group and non-extrafine beclometasone groups included headache (1, 4 and 5 people respectively), nasopharyngitis (2, 6 and 6 people respectively) and pharyngitis (7, 3 and 2 people respectively).
- The [SPC](#) reports that the most common adverse reaction with beclometasone/formoterol dry powder inhaler is tremor. The SPC states that in a 12-week trial, tremor was mild in intensity, was only observed with the higher dosage (2 inhalations twice daily) and occurred most frequently at the beginning of treatment.
- [Kanniess et al. \(2014\)](#) was a large RCT (n=755). The primary outcome of this study, change from baseline to the entire 8-week treatment period in average pre-dose morning peak expiratory flow, was a disease orientated outcome. Patient orientated effects such as asthma symptoms and [asthma control questionnaire](#) score were reported as secondary outcomes. This study investigated the lower licensed dosage (1 inhalation twice daily) of extrafine beclometasone/formoterol dry powder inhaler. There are no published studies investigating the higher licensed dosage (2 inhalations twice daily) and so the efficacy and safety of this dosage cannot be determined from the available published evidence.

[Full text of evidence review.](#)

Context

Six ICS/LABA combination inhalers are licensed in the UK for treating asthma (see the relevant [summaries of product characteristics](#) for more information):

- extrafine beclometasone/formoterol (Fostair) metered dose inhaler and dry powder inhaler
- budesonide/formoterol (DuoResp Spiromax) dry powder inhaler
- budesonide/formoterol (Symbicort) dry powder inhaler

- fluticasone furoate/vilanterol (Relvar Ellipta) dry powder inhaler
- fluticasone propionate/formoterol (Flutiform) metered dose inhaler
- fluticasone propionate/salmeterol (Seretide) metered dose inhaler and dry powder inhaler.

[Full text of context.](#)

Estimated impact for the NHS

Extrafine beclometasone/formoterol administered using a dry powder inhaler (Fostair NEXThaler) has been shown to be non-inferior to the pressurised metered dose inhaler (Fostair) for a disease orientated outcome (change in peak expiratory flow). However there are no published comparative studies with the higher licensed dose or with other available ICS/LABA combination inhalers or studies with patient orientated primary outcomes. Unlike some other ICS/LABA combination inhalers, Fostair NEXThaler is only licensed for use in adults aged 18 years and above. In addition, Fostair NEXThaler is not licensed for maintenance and reliever therapy in adults with asthma.

The [British guideline on the management of asthma](#) recommends that for adults, a pressurised metered dose inhaler plus a spacer is as effective as any dry powder inhaler for administering ICS. For people who cannot use a pressurised metered dose inhaler, the guideline advises that the most important points to consider are patient preference and cost, and the choice of device may be determined by the choice of drug.

The [British guideline on the management of asthma](#) advises that using the same type of device to deliver preventer and reliever treatments may improve outcomes. Currently, no reliever medications are available in the NEXThaler device, whereas for some other ICS/LABA dry powder inhaler devices (such as Accuhaler and Turbohaler) there are reliever inhalers available using the same device.

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using extrafine beclometasone/formoterol dry powder inhaler (NEXThaler) or another ICS/LABA combination inhaler.

[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 [British guideline on the management of asthma](#) (SIGN guideline 141) recommends a stepwise approach for the treatment of asthma. Before starting a new drug or stepping up treatment, adherence to existing therapies, assessment of inhaler technique, and elimination of trigger factors should be addressed. Inhaled corticosteroids (ICS) are the first-choice regular preventer therapy for adults and children. If asthma is not adequately controlled on an ICS alone (at step 2), add-on therapy may be needed (step 3). For adults and children aged 5 years and over, an ICS and a long-acting beta-2 agonist (LABA) should be considered.

In adults and children aged over 12 years, if poor control persists after the options at step 3 have been tried (including increasing the dose of ICS to 800 micrograms of beclometasone dipropionate or equivalent), high-dose ICS treatment (up to 2000 micrograms of beclometasone dipropionate or equivalent) or the addition of a fourth drug should be considered (step 4).

LABAs are recommended as first choice add-on therapy to improve lung function, symptoms, and decrease asthma attacks. However, Cochrane reviews of regular treatment of chronic asthma with [formoterol](#) and [salmeterol](#) found a small absolute increased risk of serious adverse events with LABAs, which does not appear to be completely abolished when an ICS is used concurrently.

After an assessment of the risks and benefits of LABAs in asthma, the MHRA concluded in a [Drug Safety Update](#) that the benefits of using a LABA with an ICS outweigh any apparent risks. The Commission on Human Medicines has issued [advice on the use and safety of LABAs for treating chronic asthma](#) for prescribers.

If treatment with an ICS and LABA is considered appropriate, [inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over](#) (NICE technology appraisal guidance 138) recommends that using a combination inhaler within its marketing authorisation is an option. NICE recommends that the decision to use a combination inhaler or the

2 agents in separate inhalers should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence. If a combination inhaler is chosen, then the least costly device that is suitable for the individual is recommended.

The [British guideline on the management of asthma](#) advises that prescribing mixed inhaler types may cause confusion and lead to increased errors in use, and that using the same type of device to deliver preventer and reliever treatments might improve outcomes.

Product overview

Drug action

[Fostair NEXThaler](#) (Chiesi Limited) is a dry powder inhaler containing 100 micrograms of beclometasone dipropionate (an ICS) and 6 micrograms of formoterol fumarate (a LABA).

The beclometasone in Fostair NEXThaler is an extrafine particle formulation, therefore dose adjustment is required when people are transferred to Fostair NEXThaler inhalation powder from a formulation with a non-extrafine particle size distribution. People who are transferred to Fostair NEXThaler inhalation powder from Fostair pressurised metered dose inhaler do not need dose adjustment because both inhalers use the extrafine particle formulation.

The bronchodilating effect of formoterol is rapid, occurring within 1–3 minutes after inhalation, and it has a duration of action of 12 hours after dose administration.

Licensed therapeutic indication

Fostair pressurised metered dose inhaler has been licensed in the UK since 2007. Fostair NEXThaler is a new dry powder formulation inhaler that was launched in September 2014. It is licensed for the regular treatment of asthma in adults aged 18 years and over where use of a combination product (ICS and LABA) is appropriate:

- people not adequately controlled with ICS and 'as needed' inhaled short-acting beta2-agonist or
- people already adequately controlled on both ICS and LABAs.

It should be noted that unlike Fostair pressurised metered dose inhaler, Fostair NEXThaler is **not licensed** for maintenance and reliever therapy in adults with asthma.

Course and cost

The recommended dosage of Fostair NEXThaler is 1–2 inhalations twice daily and the maximum daily dose is 4 inhalations daily. People should be advised to keep a separate short-acting bronchodilator available at all times for the treatment of acute asthma attacks.

Fostair NEXThaler costs £29.32 for 1 inhaler containing 120 doses ([MIMS](#), December 2014; excluding VAT).

The cost for 30-days treatment at a dosage of 1 inhalation twice daily is £14.66. The cost for 30-days treatment at a dosage of 2 inhalations twice daily is £29.32.

Evidence review

This evidence summary is based on a [randomised controlled trial](#) (RCT; [Kanniess et al. 2014](#)) that compared the efficacy and safety of extrafine beclometasone/formoterol dry powder inhaler (Fostair NEXThaler) at the lower licensed dosage (1 inhalation twice daily) with extrafine beclometasone/formoterol pressurised metered dose inhaler (Fostair) and non-extrafine beclometasone dry powder inhaler. Also included is a study ([Voshaar et al. 2014](#)) that compared the usability of the NEXThaler device with a Turbuhaler (Turbohaler) and Diskus (Accuhaler) device. This study did not consider active treatment or comparator and is therefore not discussed in detail in this evidence summary.

A study ([NCT01570478](#)) comparing extrafine beclometasone/formoterol 100/6 micrograms dry powder inhaler (Fostair NEXThaler) with fluticasone/salmeterol 250/50 micrograms dry powder inhaler (Seretide Accuhaler) in adults with has been completed but has not been published. Another study ([NCT00862394](#)) comparing the efficacy and safety of extrafine beclometasone/formoterol dry powder inhaler (Fostair NEXThaler) at the lower and higher licensed dosages (2 inhalations twice daily) with extrafine beclometasone/formoterol pressurised metered dose inhaler (Fostair) in people aged 12 years and over with moderate to severe asthma has been completed but has not been published. Neither of these unpublished studies are included in this evidence summary.

[Kanniess et al. \(2014\)](#)

- Design: 8-week, double-[blind](#), triple-dummy, 3-arm RCT in 104 centres in 7 European countries.

- Population: 755 non-smoking adults (aged 18 years and over, mean age 44 years) with a diagnosis of stable asthma for at least 6 months before screening. Participants had to have a smoking history of less than 5 pack-years, normal lung function (defined as a forced expired value in 1 second [FEV₁] greater than 80% predicted) after wash out of bronchodilators, and be receiving treatment with regular medium doses of ICS (up to 1000 micrograms/day of non-extrafine beclometasone dipropionate or equivalent), or fixed combinations of ICS/LABAs (up to fluticasone/salmeterol 500/100 micrograms/day or equivalent). In addition, participant's asthma needed to be controlled as demonstrated by a score of less than 1.25 on the 7 question version of [asthma control questionnaire](#) (ACQ-7; a measure of asthma control over the previous week. The score is the average of seven, 7 point questions, 5 on symptoms, 1 on bronchodilator use and 1 on FEV₁% predicted. The [British guideline on the management of asthma](#) states that a score of 0.75 or less indicates well controlled asthma and a score of 1.5 or greater indicates inadequately controlled asthma).
- Intervention and comparison: the study involved a 4-week run-in during which participant's current asthma therapy was replaced with extrafine beclometasone dipropionate/formoterol fumarate 100/6 micrograms pressurised metered dose inhaler (Fostair) at a dosage of 1 inhalation twice daily. Participants with an FEV₁% predicted of more than 80% after wash out of bronchodilators, and with an ACQ-7 score of less than 1.25 after the run-in were randomised (allocation concealed) 1:1:1 to 8-weeks treatment with:
 - extrafine beclometasone dipropionate/formoterol fumarate 100/6 micrograms dry powder inhaler (Fostair NEXThaler), 1 inhalation twice daily (n=251)
 - extrafine beclometasone dipropionate/formoterol fumarate 100/6 micrograms pressurised metered dose inhaler (Fostair), 1 inhalation twice daily (n=252)
 - non-extrafine beclometasone dipropionate dry powder inhaler 100 micrograms, 1 inhalation twice daily (n=252).

Salbutamol as a rescue therapy was allowed throughout the study for symptom relief.

- Outcomes: the primary outcome was to demonstrate non-inferiority of extrafine beclometasone/formoterol dry powder inhaler (Fostair NEXThaler) compared with the same administered by pressurised metered dose inhaler (Fostair) in terms of change from baseline to the entire 8-week treatment period in average pre-dose morning peak expiratory flow (calculated from daily home-based peak flow measurements). The pre-specified non-inferiority margin was –15 litres/minute. Superiority of extrafine beclometasone/formoterol dry powder inhaler (Fostair NEXThaler) over non-extrafine beclometasone dry powder inhaler in terms of the primary outcome was assessed as a secondary outcome to confirm assay sensitivity.

Secondary outcomes included average use of rescue medication, percentage of rescue medication use-free days, average total morning and evening symptom scores, percentage of asthma symptom-free days, percentage of asthma control days (no symptoms or rescue medication use), change in ACQ-7 score and safety outcomes.

Table 1 Summary of *Kanniess et al. (2014)*

	Extrafine beclometasone/formoterol DPI (Fostair NEXThaler)	Extrafine beclometasone/formoterol pMDI (Fostair)	Non-extrafine beclometasone DPI	Analysis
Randomised	n=251	n=252	n=252	
Efficacy (ITT population) ^a	n=251	n=251	n=252	
Primary outcome: adjusted mean change from baseline to entire 8-week treatment period in average pre-dose PEF (non-inferiority)	Adjusted mean difference from baseline: 2.00 L/min, 95% CI -1.80 to 5.81 L/min	Adjusted mean difference from baseline: 3.84 L/min, 95% CI -0.00 to 7.69 L/min	Not applicable for primary outcome	Adjusted mean difference between treatments: -1.84 L/min, 95% CI -6.73 to 3.05 L/min. Non-inferiority of extrafine beclometasone/formoterol DPI compared with pMDI was demonstrated because the lower limit of the 95% CI was within the pre-specified margin of -15 L/min
Selected secondary outcomes:				

<p>Secondary outcome 1: adjusted mean change from baseline to entire 8-week treatment period in average pre-dose PEF (superiority)</p>	<p>Adjusted mean difference from baseline: 2.00 L/min, 95% CI -1.80 to 5.81 L/min</p> <p>Adjusted mean difference between extrafine beclometasone/formoterol DPI compared with non-extrafine beclometasone DPI: 9.96 L/min, 95% CI 5.07 to 14.86 L/min</p>	<p>Adjusted mean difference from baseline: 3.84 L/min, 95% CI -0.00 to 7.69 L/min</p> <p>Adjusted mean difference between extrafine beclometasone/formoterol pMDI compared with non-extrafine beclometasone DPI: 11.81 L/min, 95% CI 6.92 to 16.69 L/min</p>	<p>Adjusted mean difference from baseline: -7.96 L/min, 95% CI -11.75 to -4.17 L/min</p>	<p>Superiority of extrafine beclometasone/formoterol DPI and pMDI compared with non-extrafine beclometasone DPI was demonstrated ($p < 0.001$ for both comparisons)</p>
<p>Secondary outcome 2: adjusted mean percentage change in asthma control days from baseline to the entire treatment period^b</p>	<p>8.9% ($p < 0.05$)</p>	<p>9.6% ($p < 0.05$)</p>	<p>5.6% ($p < 0.05$)</p>	<p>A statistically significant difference was found between the extrafine beclometasone/formoterol pMDI and non-extrafine beclometasone groups ($p < 0.05$)</p>

Secondary outcome 3: adjusted mean change in ACQ-7 score from baseline to week 8 ^c	-0.026 points	-0.028 points	0.058 points (p<0.05)	A statistically significant difference was found between the non-extrafine beclometasone DPI and extrafine beclometasone/formoterol DPI (-0.084, p<0.05) and pMDI (-0.085, p<0.05) groups
Safety^d	n=251	n=251	n=252	
Number of participants experiencing a severe asthma exacerbation ^e	1.6% (4/251)	1.2% (3/251)	2.4% (6/252)	No statistical analysis reported
Number of participants reporting treatment related adverse events	0.8% (2/251)	1.2% (3/251)	1.2% (3/252)	No statistical analysis reported

Abbreviations: ACQ-7, 7 question asthma control questionnaire; CI, confidence interval; DPI, dry powder inhaler; ITT, intention-to-treat; L, litre; min, minute; p, p-value; PEF, peak expiratory flow; pMDI, pressurised metered dose inhaler.

^aThe intention-to-treat population included all randomised participants who took at least 1 dose of study medication and had post-randomisation efficacy data.

^bAsthma control days were defined as days with no asthma symptoms or rescue medication use.

^cThe ACQ-7 is a measure of asthma control over the previous week. The score is the average of seven, 7 point questions, 5 on symptoms, 1 on bronchodilator use and 1 on FEV1% predicted. Increased scores represent worsening asthma control.

^dThe safety population included all randomised participants who took at least 1 dose of study medication.

^e The definition of a severe asthma exacerbation was one which required the administration of systemic corticosteroids or an increase from a stable maintenance dose for at least 3 days, or a hospitalisation or emergency room visit with the use of systemic steroids

Voshaar et al. (2014)

- Design: randomised crossover comparison study, performed at 3 sites in the UK.
- Population: 66 adults aged 18 years or older (mean age 42.9 years) with a diagnosis of asthma who were using a pressurised metered dose inhaler for at least 3 months before enrolment on the study. Participants had never used dry powder inhalers before, and had not had an asthma attack requiring a visit to the GP or hospital admission within the 3 months before enrolment on the study.
- Intervention and comparison: participants were presented in a randomised order with NEXThaler, Turbohaler and Accuhaler empty devices (containing no medication). Participants were given instructions for use to read each time they were presented with an inhaler, and were timed (up to a maximum of 5 minutes) on how long it took to familiarise themselves with the instructions. No verbal instruction on inhaler use was provided. Participants were then asked to use the device by carrying out the steps detailed in the instructions for use, and thinking aloud to explain what they were doing. An experimenter observed the participant using the device and took note of any errors made using the devices. The participant repeated using the same device a second and third time, before moving on to the next device and repeating the same steps.

- **Outcomes:** the effectiveness outcomes were the number of steps failed, and the number of people who were able to use the device without making any critical errors (defined as any error that prevented a dose from being delivered). Efficiency outcomes included the time it took for the participants to set up the device and the time it took to read the instructions for use. Participant satisfaction was measured using a preference questionnaire including questions on the easiest device to use, and preference to own.

Clinical effectiveness

Kanniess et al. (2014) found that extrafine beclometasone/formoterol dry powder inhaler (Fostair NEXThaler) was non-inferior to the same combination administered by pressurised metered dose inhaler (Fostair) for the primary outcome of change from baseline in mean pre-dose morning peak expiratory flow (mean difference between the dry powder and pressurised metered dose inhaler groups -1.84 litres/minute, 95% confidence interval [CI] -6.73 to 3.05 . Non-inferiority was demonstrated because the lower limit of the 95% CI was within the pre-specified margin of -15 litres/minute). Both extrafine formulations (dry powder and pressurised metered dose inhaler) of beclometasone/formoterol were statistically significantly superior to non-extrafine beclometasone dry powder inhaler for the same outcome ($p < 0.001$ for both). The authors report that these findings were confirmed by analyses in the per-protocol population. Average total daytime and night-time symptom scores statistically significantly improved from baseline to the entire treatment period in both extrafine beclometasone/formoterol groups, and daytime score statistically significantly improved in the non-extrafine beclometasone group ($p < 0.05$ for all comparisons). However, there was no statistically significant difference between any of the groups.

Average use of rescue medication and percentage of rescue medication-free days statistically significantly improved from baseline in both extrafine beclometasone/formoterol groups ($p < 0.05$ for both), but neither outcome reached statistical significance in the non-extrafine beclometasone group. There was no statistically significant difference between the 2 extrafine beclometasone/formoterol groups for these outcomes; however, there was a statistically significant difference between both extrafine beclometasone/formoterol groups compared with the non-extrafine beclometasone group. The percentage of asthma symptom free days, and asthma control days statistically significantly improved in all groups from baseline to the entire treatment period ($p < 0.05$ for all comparisons). The extrafine beclometasone/formoterol pressurised metered dose inhaler group was statistically significantly better than the non-extrafine beclometasone group for the percentage of asthma control days ($p < 0.05$). There was no statistically significant difference between the extrafine beclometasone/formoterol pressurised metered dose group and the dry powder inhaler group, or between the extrafine beclometasone/formoterol dry powder inhaler and non-extrafine beclometasone groups for this outcome.

ACQ-7 score change from baseline to the entire treatment period in both extrafine beclometasone/formoterol groups was not statistically significant. In the non-extrafine beclometasone group, ACQ-7 score statistically significantly worsened by 0.058 points ($p < 0.05$). The difference between the non-extrafine beclometasone group and the extrafine beclometasone/formoterol dry powder inhaler (-0.084 points) and pressurised metered dose inhaler (-0.085 points) groups was statistically significant ($p < 0.05$ for both). However these differences were not clinically important according to the British guideline on the management of asthma which states that the minimal important difference is 0.5 points.

Voshaar et al. (2014) report that the overall number of steps failed improved for all inhaler devices between the first and second use ($p < 0.001$). The mean number of steps failed during first and second use was statistically significantly less for NEXThaler compared with Turbohaler ($p < 0.001$) and Accuhaler ($p < 0.001$). Figures were displayed graphically and no data were provided. The number of people who completed an inhalation without any critical errors was statistically significantly greater during the first use for NEXThaler (and Accuhaler), compared with Turbohaler ($p < 0.05$). During the second use, the percentage of people completing an inhalation without critical errors was 71% for NEXThaler, 59% for Accuhaler and 47% for Turbohaler (no statistical analysis reported).

The time taken to set up the device was statistically significantly longer for Turbohaler (8.69 seconds) and Accuhaler (7.85 seconds) compared with NEXThaler (6.02 seconds, $p < 0.001$ compared with Turbohaler and Accuhaler). Time to read the instructions for use was reported as the average reading duration per syllable, and was statistically significantly less for NEXThaler (0.15 seconds) compared with Accuhaler (0.32 seconds; $p < 0.001$) and Turbohaler (0.2 seconds; $p < 0.001$).

Overall, the device which was reported by participants as the easiest to use was statistically significantly greater for NEXThaler (74.2%) compared with Accuhaler (16.7%; $p < 0.001$) and Turbohaler (9.1%; $p < 0.001$). In addition, statistically significantly more participants reported that they if they had to pick one of the devices to use every day, they would choose NEXThaler (75.4%) compared with an Accuhaler (16.9%; $p < 0.001$) or a Turbohaler (7.7%; $p < 0.001$).

Safety and tolerability

In Kanniess et al. (2014), 26 asthma exacerbations were reported during the trial, 13 of which were classed as severe. Of these, 6 were observed in the non-extrafine beclometasone group, 4 in the extrafine beclometasone/formoterol dry powder inhaler group and 3 in the extrafine

beclometasone/formoterol pressurised metered dose inhaler group (no statistical analyses reported).

The percentage of people reporting treatment-emergent adverse events was low and similar across the groups (0.8% in the beclometasone/formoterol dry powder inhaler group and 1.2% in both the extrafine beclometasone/formoterol pressurised metered dose inhaler and non-extrafine beclometasone groups). Treatment-emergent adverse events reported in the extrafine beclometasone/formoterol dry powder inhaler, beclometasone/formoterol pressurised metered dose inhaler group and non-extrafine beclometasone groups included headache (1, 4 and 5 people respectively), nasopharyngitis (2, 6 and 6 people respectively) and pharyngitis (7, 3 and 2 people respectively).

The [summary of product characteristics](#) (SPC) states that, as with other inhalers containing LABAs, beclometasone/formoterol dry powder inhaler should not be started in people who are experiencing an acute exacerbation of asthma, or in people with significantly worsening or deteriorating asthma. The SPC states that, as with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing, cough and shortness of breath after dosing. This should be treated with a fast-acting bronchodilator and beclometasone/formoterol dry powder inhaler should be discontinued immediately.

Systemic effects of ICS may occur (such as Cushing's syndrome, adrenal suppression, psychological and behavioural effects), particularly at high doses prescribed for prolonged periods. Therefore the dose of ICS should be titrated to the lowest that effectively maintains control of asthma symptoms ([SPC](#) for beclometasone/formoterol dry powder inhaler [Fostair NEXThaler]).

The [SPC](#) advises that the most common adverse reaction with beclometasone/formoterol dry powder inhaler is tremor. Adverse event information listed in the SPC includes safety data from the published [Kanniess et al. \(2014\)](#) 8-week RCT that investigated the lower licensed dosage of Fostair NEXThaler, and from the unpublished 12-week RCT ([NCT00862394](#)) that investigated the lower and higher licensed dosages of Fostair NEXThaler. The SPC states that in the 12-week trial, tremor was mild in intensity, was only observed with the higher dosage (2 inhalations twice daily) and occurred most frequently at the beginning of treatment.

Evidence strengths and limitations

[Kanniess et al. \(2014\)](#) was a large (n=755) RCT. Key strengths included the double-blind triple dummy design and inclusion of a non-extrafine beclometasone group to confirm assay sensitivity. Allocation to treatment was concealed, therefore avoiding an important potential source of bias.

The non-inferiority analysis was in the intention-to-treat (ITT) population, and the authors report that findings were supported by analysis in the per protocol population, although no data were provided for this. The European Medicine Agency guidance on the [points to consider on switching between superiority and non-inferiority](#) advises that, although in a superiority study the ITT analysis is the analysis of choice, in a non-inferiority study the ITT and per-protocol analyses have equal value and their use should lead to similar conclusions for a robust interpretation of the results.

The primary outcome of this study, change from baseline to the entire 8-week treatment period in average pre-dose morning peak expiratory flow, is a disease orientated outcome. Patient orientated outcomes such as asthma symptoms and ACQ-7 score were reported as secondary outcomes. In a study with a duration of 8 weeks, the data on key patient-orientated outcomes in asthma is of limited value. Although the differences in ACQ-7 between the non-extrafine beclometasone group and the extrafine beclometasone/formoterol dry powder inhaler and pressurised metered dose inhaler groups were statistically significant, they were not [clinically important](#) according to the [British guideline on the management of asthma](#) which states that the minimal important difference is 0.5 points.

[Kanniess et al. \(2014\)](#) investigated the lower dosage (1 inhalation twice daily) of extrafine beclometasone/formoterol dry powder inhaler and this may explain the low incidence of adverse events reported in the trial. There are no published studies investigating the higher licensed dosage (2 inhalations twice daily) and so the efficacy and safety of this dosage cannot be determined from the available published evidence.

It is not known how the efficacy and safety of extrafine beclometasone/formoterol dry powder inhaler compares with other ICS/LABA combination inhalers. There are no published studies directly comparing it with such licensed alternatives and extrapolation of data from different populations using different interventions may not be valid.

Extrafine beclometasone/formoterol dry powder inhaler is administered using the NEXThaler device. [Voshaar et al. \(2014\)](#) was a randomised crossover study designed to investigate the usability of the NEXThaler compared with other dry powder devices. The other dry powder devices assessed were Turbuhaler and Diskus. These devices are the same as the Turbohaler, and Accuhaler devices that are available in the UK.

The results reported in the NEXThaler usability study ([Voshaar et al. \(2014\)](#)) had a number of limitations. For example effectiveness of device handling was assessed by describing step failures and critical errors during the first and second use of the inhaler devices in people who had never

used these devices before increasing the likelihood of errors. In addition, subjective assessment of step failures and critical errors by an observer could have introduced bias. Time taken to read the instructions for use was reported as the average reading duration per syllable, rather than total time so the relevance of this finding is unclear.

In [Voshaar et al. \(2014\)](#), people were not trained on how to use the respective inhaler devices but were provided with instructions for use leaflets. The [British guideline on the management of asthma](#) recommends that people should receive training in the use of their inhaler device and should have their ability to use the device assessed by a competent healthcare professional. However, a [Drug and Therapeutics Bulletin](#) from 2012 discusses the concerns that many health professionals do not know how to use inhalers correctly and are therefore not in a position to coach inhaler technique effectively. Nevertheless, if people in the study by [Voshaar et al. \(2014\)](#) had received a training intervention from a competent healthcare professional, the usability results may have been different. The results of this study may not be applicable to usual UK clinical practice because of these limitations.

Context

Alternative treatments

Six ICS/LABA combination inhalers are licensed in the UK for treating asthma (see the relevant [summaries of product characteristics](#) for more information):

- extrafine beclometasone/formoterol (Fostair) metered dose inhaler and dry powder inhaler
- budesonide/formoterol (DuoResp Spiromax) dry powder inhaler
- budesonide/formoterol (Symbicort) dry powder inhaler
- fluticasone furoate/vilanterol (Relvar Ellipta) dry powder inhaler
- fluticasone propionate/formoterol (Flutiform) metered dose inhaler
- fluticasone propionate/salmeterol (Seretide) metered dose inhaler and dry powder inhaler.

NICE has published evidence summaries: new medicines on [fluticasone propionate/formoterol \(Flutiform\) combination inhaler in asthma](#), [fluticasone furoate/vilanterol \(Relvar Ellipta\) combination inhaler in asthma](#), and [beclometasone/formoterol \(Fostair\) pressurised metered dose inhaler for maintenance and reliever treatment in asthma](#).

Table 2 Costs of alternative treatments

	Non-extrafine beclometasone dipropionate 400 micrograms total daily dose approximate equivalent ^a	Non-extrafine beclometasone dipropionate 800 to 1000 micrograms total daily dose approximate equivalent ^a
DuoResp Spiromax (dry powder inhaler)	160/4.5 micrograms 1 inhalation twice a day £14.99 for 30 days Based on a 120-dose unit at £29.97 ^b	320/9 micrograms 1 inhalation twice a day £29.97 ^b for 30 days 60-dose unit
Fostair NEXThaler (dry powder inhaler)	100/6 micrograms 1 inhalation twice a day £14.66 for 30 days Based on a 120-dose unit at £29.32 ^b	100/6 micrograms 2 inhalations twice a day £29.32 ^b for 30 days 120-dose unit
Fostair (pressurised metered dose inhaler)	100/6 micrograms 1 inhalation twice a day £14.66 for 30 days Based on a 120-dose unit at £29.32 ^c	100/6 micrograms 2 inhalations twice a day £29.32 ^c for 30 days 120-dose unit
Flutiform (pressurised metered dose inhaler)	50/5 micrograms 2 inhalations twice a day £18.00 ^c for 30 days 120-dose unit	125/5 micrograms 2 inhalations twice a day £29.26 ^c for 30 days 120-dose unit
Relvar Ellipta ^d (dry powder inhaler)		92/22 micrograms 1 inhalation once a day £ 27.80 ^b for 30 days 30-dose unit
Seretide Evohaler (pressurised metered dose inhaler)	50/25 micrograms 2 inhalations twice a day £18.00 ^c for 30 days 120-dose unit	125/25 micrograms 2 inhalations twice a day £35.00 ^c for 30 days 120-dose unit

Seretide Accuhaler (dry powder inhaler)	100/50 micrograms 1 inhalation twice a day £18.00 ^c for 30 days 60-dose unit	250/50 micrograms 1 inhalation twice a day £35.00 ^c for 30 days 60-dose unit
Symbicort Turbohaler (dry powder inhaler)	200/6 micrograms 1 inhalation twice a day £19.00 for 30 days Based on a 120-dose unit at £38.00 ^c	400/12 micrograms 1 inhalation twice a day £38.00 ^c for 30 days 60-dose unit
<p>^a Doses do not represent the full range that can be used. Dose equivalents estimated using information from the British guideline on the management of asthma and the relevant summaries of product characteristics.</p> <p>^b Costs based on MIMS, December 2014; excluding VAT.</p> <p>^c Costs based on the drug tariff, December 2014; excluding VAT.</p> <p>^d Relvar Ellipta contains the ICS fluticasone furoate. Fluticasone furoate 92 micrograms once a day is approximately equivalent to fluticasone propionate 250 micrograms twice a day. The British guideline on the management of asthma indicates that 250 micrograms fluticasone propionate twice a day is approximately equivalent to 1000 micrograms non-extrafine beclometasone dipropionate per day.</p>		

Estimated impact for the NHS

Likely place in therapy

The [British guideline on the management of asthma](#) (SIGN guideline 141) recommends add-on therapy (step 3) for people whose asthma is not adequately controlled on an ICS alone (at step 2). For adults and children aged 5 years and over a LABA is the first-choice add-on therapy. The guideline recommends combination ICS/LABA inhalers to guarantee that the LABA is not taken without the ICS, and to improve inhaler adherence.

Extrafine beclometasone/formoterol dry powder inhaler (Fostair NEXThaler) has been shown to be non-inferior to extrafine beclometasone/formoterol pressurised metered dose inhaler (Fostair) for the primary outcome of change in mean pre-dose morning peak expiratory flow. However there are no published comparative studies with the higher licensed dose or other available ICS/LABA combination inhalers or studies with patient orientated primary outcomes. Unlike some other ICS/LABA combination inhalers, Fostair NEXThaler is only licensed for use in adults aged 18 years and

above. In addition, Fostair NEXThaler is not licensed for maintenance and reliever therapy in adults with asthma.

The [British guideline on the management of asthma](#) recommends that for adults, a pressurised metered dose inhaler plus a spacer is as effective as any dry powder inhaler for administering ICS. For people who cannot use a pressurised metered dose inhaler, the guideline advises that there is no evidence to dictate the order in which devices should be tested. The most important points to consider are patient preference and cost. The choice of device may be determined by the choice of drug.

Extrafine beclometasone/formoterol dry powder inhaler (Fostair NEXThaler) has a lower acquisition cost for 30-days treatment compared with some other ICS/LABA combination inhalers. A usability study, with some limitations, found that more people preferred the NEXThaler device compared with using a Turbohaler or Accuhaler device.

The [British guideline on the management of asthma](#) advises that prescribing mixed inhaler types may cause confusion and lead to increased errors in use. Using the same type of device to deliver preventer and reliever treatments may improve outcomes. Currently, no reliever medications are available in the NEXThaler device, whereas for some other ICS/LABA dry powder inhaler devices (such as Accuhaler and Turbohaler) there are reliever inhalers available using the same device.

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using extrafine beclometasone/formoterol dry powder inhaler (NEXThaler) or another ICS/LABA combination inhaler for treating asthma in adults.

Estimated usage

The manufacturers (Chiesi Limited) estimate that approximately 70,000 Fostair NEXThaler devices will be prescribed in 2015 (at a cost of around £2 million) and approximately 185,000 devices will be prescribed in 2016 (at a cost of around £5.4 million).

Relevance to NICE guidance programmes

Beclometasone/formoterol dry powder inhaler (Fostair NEXThaler) was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has published the following technology appraisal relating to the use of ICS in asthma in adults:

- [Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over](#) (NICE technology appraisal guidance 138).

NICE is developing a clinical guideline on [asthma - diagnosis and monitoring](#) (expected publication date June 2015).

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Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

John Haughney has received reimbursements for attending symposia, fees for speaking at and 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.

He has co-authored academic papers in areas of current interest relating to pharmaceutical products manufactured by Almirall, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck Sharp & Dohme, Mundipharma, Novartis, and Teva.

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Kevin Gruffydd Jones has acted as a consultant for and spoken on behalf of GlaxoSmithKline, AstraZeneca, Chiesi, Almirall, Mundipharma, Boehringer Ingelheim, Teva and Novartis.

Peter Calverley has acted as a speaker at meetings about chronic obstructive pulmonary disease supported by GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Novartis and Takeda. His department has received funding in support of clinical trials in chronic obstructive pulmonary disease from GSK, Boehringer Ingelheim and Takeda.

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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