

Chronic obstructive pulmonary disease: fluticasone furoate plus vilanterol

Evidence summary

Published: 18 June 2013

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Key points from the evidence

The content of this evidence summary was up-to-date in June 2013. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

Fluticasone furoate/vilanterol (Relvar Ellipta) is a once-daily corticosteroid and long-acting beta₂ agonist combination inhaler, which has been submitted for a marketing authorisation for the symptomatic treatment of adults with chronic obstructive pulmonary disease (COPD) and an exacerbation history despite regular bronchodilator therapy. There are currently no published studies comparing fluticasone furoate/vilanterol with other licensed treatments for COPD, which makes it difficult to assess its place in therapy in the NHS.

<p>Effectiveness</p> <ul style="list-style-type: none"> • No published studies comparing fluticasone furoate/vilanterol with other ICS/LABA combination inhalers licensed for use in COPD. • Fluticasone furoate/vilanterol 100/25 micrograms reduced the mean yearly rate of moderate and severe exacerbations, but not exacerbations requiring admission to hospital, compared with vilanterol 25 micrograms alone. • Fluticasone furoate/vilanterol 100/25 micrograms improved trough FEV₁ after 24 weeks' treatment compared with placebo but not compared with vilanterol alone. 	<p>Safety</p> <ul style="list-style-type: none"> • No statistical analysis of safety data from studies is available. • Local corticosteroid effects, pneumonia (including requiring admission to hospital) and non-traumatic fractures were seen more frequently with fluticasone furoate/vilanterol 100/25 micrograms than with vilanterol alone.
<p>Patient factors</p> <ul style="list-style-type: none"> • Administration is once-daily using a multi-dose dry powder inhalation device (the Ellipta device). The 2 combination inhalers in the same class currently licensed for use in COPD are for twice-daily use. 	<p>Cost</p> <ul style="list-style-type: none"> • Cost has yet to be determined.

Key points

Fluticasone furoate is a once-daily inhaled corticosteroid (ICS) and vilanterol is a once-daily inhaled long-acting beta₂ agonist (LABA). A combination multi-dose dry powder inhalation device (the Ellipta device) containing fluticasone furoate 100 micrograms and vilanterol 25 micrograms has been submitted for a marketing authorisation for the symptomatic treatment of COPD in adults who have an FEV₁ (forced expired volume in 1 second) of less than 70% and an exacerbation history despite regular bronchodilator therapy. A regulatory decision is expected in late 2013.

This evidence summary is based on studies that have been published in full. In a pre-specified pooled analysis of 2 [randomised, double-blind, parallel group studies](#) (total n=3255), [Dransfield et al. \(2013\)](#) found that fluticasone furoate/vilanterol 100/25 micrograms reduced the mean yearly

rate of moderate and severe exacerbations compared with vilanterol 25 micrograms alone in people with COPD and a history of such exacerbations (from 1.11 to 0.81, rate ratio was 0.7, 95% [confidence interval](#) [CI] 0.6 to 0.8, $p < 0.0001$). However, there was no statistically significant difference in the mean yearly rate of exacerbations requiring admission to hospital compared with vilanterol 25 micrograms alone.

[Kerwin et al. \(2013\)](#) (n=1030) found that fluticasone furoate/vilanterol 100/25 micrograms was statistically significantly superior to placebo in improving post-dose weighted mean FEV₁ (173 ml, 95% CI 123 to 224 ml, $p < 0.001$) and trough FEV₁ (115 ml, 95% CI 60 to 169 ml, $p < 0.001$) after 24 weeks' treatment. The lower limit in the confidence interval of trough FEV₁ is less than the 100 ml difference in FEV₁ considered in the [full NICE guideline on COPD](#) to be the minimum clinically important difference. There was no statistically significant difference in trough FEV₁ between fluticasone furoate/vilanterol 100/25 micrograms and vilanterol 25 micrograms.

An additional study ([Martinez et al. 2013](#)) had the same design as that by [Kerwin et al. \(2013\)](#), but for methodological reasons, statistical analysis of the results for fluticasone furoate/vilanterol 100/25 micrograms could not be performed.

Statistical analysis of safety data was not presented in any of the studies included in this review, which limits the conclusions that can be drawn. Local corticosteroid effects, pneumonia (including pneumonia requiring admission to hospital) and non-traumatic fractures were seen more frequently with fluticasone furoate/vilanterol 100/25 micrograms than with vilanterol alone.

The studies that have been published in full provide no information on the effectiveness of fluticasone furoate/vilanterol compared with available inhalers licensed for use in COPD. A further 12-week phase III trial (trial reference [NCT01342913](#)) comparing the spirometric effects of fluticasone furoate/vilanterol 100/25 micrograms once daily with fluticasone propionate/salmeterol 500/50 micrograms (Seretide 500 Accuhaler) twice daily has not yet been published in full. The exact dose equivalence between fluticasone furoate and fluticasone propionate (the currently licensed fluticasone salt) is not known (GlaxoSmithKline: personal communication May 2013).

The cost of the product has yet to be determined, so cost comparisons with other inhaled therapy licensed for use in COPD cannot be made at present. The exact place in therapy of fluticasone furoate/vilanterol is also difficult to assess, but if a UK marketing authorisation is granted it will represent an additional treatment option alongside existing inhaled therapies licensed for use in COPD.

Key evidence

Dransfield MT, Bourbeau J, Jones PW et al. (2013) [Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials](#). *The Lancet Respiratory Medicine* 1: 210–23 doi:10.1016/s2213-2600(13)70040-7

Kerwin EM, Scott-Wilson C, Sanford L et al. (2013) [A randomised trial of fluticasone furoate/vilanterol \(50/25 micrograms; 100/25 micrograms\) on lung function in COPD](#). *Respiratory Medicine* 107: 560–9

Update

The following information has become available since this ESNM was produced.

January 2014: Availability of fluticasone furoate/vilanterol (Relvar Ellipta) combination inhaler

[Relvar Ellipta 92 micrograms/22 micrograms](#) which is licensed for the treatment of chronic obstructive pulmonary disease and asthma was launched in the UK in January 2014. [Relvar Ellipta 184 micrograms/22 micrograms](#) is also available for the treatment of asthma. See [ESNM34: Asthma: fluticasone furoate/vilanterol \(Relvar Ellipta\) combination inhaler](#) for more information.

The Ellipta device contains 30 inhalations for 30 days of treatment. The cost of the Relvar Ellipta 92/22 microgram strength inhaler is £27.80. The cost of the Relvar Ellipta 184/22 microgram strength inhaler is £38.87. Costs (excluding VAT) taken from [MIMS](#), October 2014.

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

Fluticasone furoate/vilanterol 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](#).

Introduction

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 diagnosed COPD, and an estimated 2 million people have COPD that remains undiagnosed. COPD produces symptoms, disability and impaired quality of life, which may respond to pharmacological and other therapies that have limited or no impact on the airflow obstruction. Exacerbations often occur, during which there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations.

The NICE clinical guideline on [COPD](#) defines COPD as follows:

- Airflow obstruction is defined as a reduced FEV₁/FVC ratio (where FEV₁ is forced expired volume in 1 second and FVC is forced vital capacity), such that FEV₁/FVC is less than 0.7.
- If FEV₁ is 80% predicted normal or more, a diagnosis of COPD should be made only in the presence of respiratory symptoms, for example, breathlessness or cough.

Classification of severity of airflow obstruction in COPD according to the NICE clinical guideline is shown in table 1.

Table 1 NICE classification of severity of airflow obstruction in COPD

Severity of airflow obstruction		
Post-bronchodilator FEV ₁ /FVC	FEV ₁ % predicted	Post-bronchodilator
<0.7	≥80%	Stage 1: Mild ^a
<0.7	50–79%	Stage 2: Moderate
<0.7	30–49%	Stage 3: Severe
<0.7	<30%	Stage 4: Very severe ^b

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expired volume in 1 second; FVC, forced vital capacity.

^a Symptoms should be present to diagnose COPD in people with mild airflow obstruction.

^b Or FEV₁ <50% with respiratory failure.

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 does include the key recommendations that relate to this evidence summary and the likely place in therapy of fluticasone furoate/vilanterol.

- 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 FEV₁ is 50% predicted or more: either a long-acting beta₂ agonist (LABA) or a long-acting muscarinic antagonist (LAMA)
 - if FEV₁ is less than 50% predicted: either a LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or a LAMA.
- In people with stable COPD and an FEV₁ of 50% predicted or more who remain breathless or have exacerbations despite maintenance therapy with a LABA:
 - consider a LABA with an ICS in a combination inhaler
 - consider a LAMA in addition to a LABA where an ICS is declined or not tolerated.
- Offer a LAMA in addition to a LABA with an ICS to people with COPD who remain breathless or have exacerbations despite taking a LABA with an ICS, irrespective of their FEV₁.
- 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 FEV₁.
- 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

Relvar Ellipta is a combination inhaler containing 2 active ingredients not previously available: fluticasone furoate (an inhaled corticosteroid [ICS]) and vilanterol (a long-acting beta₂ agonist [LABA]). These are administered using the multi-dose, dry powder Ellipta inhalation device (GlaxoSmithKline: personal communication March 2013).

Proposed therapeutic indication

Fluticasone furoate/vilanterol (Relvar Ellipta, GlaxoSmithKline) was submitted to the [European Medicines Agency](#) (EMA) for evaluation for a marketing authorisation for the symptomatic treatment of chronic obstructive pulmonary disease (COPD) in adults with a FEV₁ (forced expired volume in 1 second) of less than 70% predicted normal (post-bronchodilator) and an exacerbation history despite regular bronchodilator therapy. A marketing authorisation for the use of this product in asthma has also been submitted. Evidence on the potential use of this product in asthma is not reviewed in this evidence summary.

The manufacturer expects a final authorisation decision by late 2013.

Proposed course and cost

The proposed dose is fluticasone furoate 100 micrograms plus vilanterol 25 micrograms once daily, which if approved will be licensed as fluticasone furoate 92 micrograms plus vilanterol 22 micrograms (dose delivered using the mouth piece of the device) (GlaxoSmithKline: personal communication March 2013).

The exact dose equivalence between fluticasone furoate and fluticasone propionate (the currently licensed fluticasone salt) is not known (GlaxoSmithKline: personal communication May 2013).

The cost of Relvar Ellipta is yet to be determined (GlaxoSmithKline: personal communication March 2013).

Evidence review

This evidence review is based on the 3 [randomised controlled trials](#) (RCTs) that provide the best published evidence for fluticasone furoate/vilanterol for treating chronic obstructive pulmonary disease (COPD) and that have been published in full. [Dransfield et al. \(2013\)](#) published results from two 52-week randomised, [double-blind](#), parallel group studies that investigated whether fluticasone furoate/vilanterol in combination (3 different doses of fluticasone furoate) would prevent more exacerbations compared with vilanterol alone.

A second RCT included in this evidence summary ([Kerwin et al. 2013](#)) compared 2 strengths of fluticasone furoate/vilanterol with the same strengths of the individual components and placebo in patients with COPD. The 2 co-primary outcomes were the weighted mean FEV₁ (forced expired volume in 1 second; 0 to 4 hours post-dose) on day 168, and the change from baseline in trough FEV₁ (23–24 hours post-dose) on day 169. An additional study ([Martinez et al. 2013](#)) had the same design as that by [Kerwin et al. \(2013\)](#) but for methodological reasons, statistical analysis of the results for fluticasone furoate/vilanterol 100/25 micrograms could not be performed.

A further relevant phase III trial has been completed, but results have not yet been published in full (trial reference [NCT01342913](#)). This trial assessed the 24-hour spirometry effect (FEV₁) of fluticasone furoate/vilanterol 100/25 micrograms once daily compared with fluticasone propionate/salmeterol 500/50 micrograms (Seretide 500 Accuhaler) twice daily over a 12-week treatment period in people with COPD.

[Dransfield et al. \(2013\)](#)

- Design: 2 simultaneous, replicate, 52-week, randomised, double-blind, parallel group studies. Each had a 4-week open-label run-in period using combination fluticasone propionate/salmeterol 250/50 micrograms twice daily. The method of allocation described suggests that this was concealed.
- Population: 1622 adults in study 1 and 1633 adults in study 2. Study 1 involved 167 sites in 15 countries and study 2 involved 183 sites in 15 countries. Participants were 40 years or older (mean 64 years) with COPD (post-bronchodilator FEV₁ 70% predicted or less, mean range 44.3% to 46.4%, and FEV₁/FVC [forced vital capacity] ratio 0.7 or less), a history of at least 1 COPD exacerbation in the previous year that needed systemic or oral corticosteroids, antibiotics or admission to hospital, and a smoking history of 10 or more pack-years.
- Intervention and comparison: participants were randomised in approximately equal numbers to 4 treatments, taken once daily using the Ellipta inhaler:

- fluticasone furoate 50 micrograms (emitted dose 44 micrograms) plus vilanterol 25 micrograms (emitted dose 22 micrograms)
 - fluticasone furoate 100 micrograms (emitted dose 92 micrograms) plus vilanterol 25 micrograms (emitted dose 22 micrograms)
 - fluticasone furoate 200 micrograms (emitted dose 184 micrograms) plus vilanterol 25 micrograms (emitted dose 22 micrograms)
 - vilanterol 25 micrograms (emitted dose 22 micrograms).
- Outcome: the primary efficacy end point was the yearly rate of moderate and severe COPD exacerbations. Moderate exacerbations were defined as worsening symptoms of COPD needing treatment with oral corticosteroids and/or antibiotics. Severe exacerbations were defined as those that needed hospital admission. Secondary and additional end points included the time to first moderate or severe exacerbation, yearly rate of severe exacerbations, the number of night-time awakenings due to symptoms, and dyspnoea score. Specific safety end points included haematological and clinical measurements, incidence of bone fractures and clinically diagnosed pneumonia. The 2 studies were analysed separately and in a predefined pooled analysis, based on the intention-to-treat population. Results of this pooled analysis are summarised in table 2.

Table 2 Summary of the pooled analysis, [Dransfield et al. \(2013\)](#)

	Fluticasone furoate/vilanterol once daily (micrograms)			Vilanterol 25 micrograms once daily
	50/25	100/25	200/25	
Efficacy (ITT population)	n=820	n=806	n=811	n=818
Primary outcome				
Moderate and severe exacerbations; LS mean yearly rate	0.93	0.81	0.85	1.11
LS mean yearly RR for moderate and severe exacerbations (95% CI) compared with vilanterol alone	0.8 (0.7 to 1.0), p=0.014	0.7 (0.6 to 0.8), p<0.0001	0.8 (0.7 to 0.9), p=0.0003	-
Selected secondary and additional outcomes				

Time to first moderate or severe exacerbation: HR (95% CI) compared with vilanterol alone	0.9 (0.8 to 1.0), p=0.114	0.8 (0.7 to 0.9), p=0.0002	0.8 (0.7 to 0.9), p=0.0001	–
Severe exacerbation LS mean yearly rate	0.08	0.09	0.08	0.10
LS mean yearly RR for severe exacerbations (95% CI) compared with vilanterol alone	0.8 (0.6 to 1.2), p=0.313	0.9 (0.6 to 1.4), p=0.695	0.8 (0.5 to 1.2), p=0.280	–
Night-time awakenings, LS mean difference (95% CI) from vilanterol alone	–0.06 (–0.10 to –0.01), p=0.011	–0.08 (–0.12 to –0.03), p=0.001	–0.07 (–0.12 to –0.03), p=0.002	–
Dyspnoea score ^a : LS mean difference (95% CI) from vilanterol alone	–0.08 (–0.12 to –0.03), p=0.0006	–0.09 (–0.014 to –0.05), p<0.0001	–0.11 (–0.16 to –0.07), p<0.0001	–
Safety (ITT population)	n=820	n=806	n=811	n=818
Adverse events leading to discontinuation or withdrawal ^b	6.5% (53/820)	7.7% (62/806)	7.5% (61/811)	5.5% (45/818)
Local corticosteroid effects ^b	17.3% (142/820)	15.0% (121/806)	17.3% (140/811)	11.7% (96/818)
Pneumonia ^b	5.9% (48/820)	6.3% (51/806)	6.8% (55/811)	3.3% (27/818)
Bone disorders (including fractures) ^b	2.9% (24/820)	3.3% (27/806)	2.6% (21/811)	1.1% (9/818)
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, Intention-to-treat; LS, least squares; RR, rate ratio.				
^a Dyspnoea was scored on a scale of –2 to +2, with –2 indicating 'much less than usual' and +2 indicating 'much more than usual'.				
^b No statistical analysis of safety outcomes was presented.				

Kerwin et al. (2013)

- Design: 24-week double-blind, placebo-controlled RCT. The method of allocation described suggests that this was concealed.
- Population: 1030 adults in 9 countries aged at 40 years or older (mean 63 years) with COPD (post bronchodilator FEV₁ 70% predicted or less, mean range 46.9–49.9%, and FEV₁/FVC ratio 0.7 or less), a smoking history of at least 10 pack-years, and a score of at least 2 on the Modified Medical Research Council Dyspnoea Scale. No previous history of COPD exacerbations was needed but about a quarter of participants had had at least 1 moderate exacerbation of COPD (needing treatment with oral corticosteroids and/or antibiotics but not hospital admission) and about 7% had had at least 1 severe exacerbation (needing hospital admission) in the year before trial entry.
- Intervention and comparison: participants were randomised in approximately equal numbers to 5 treatments, taken once daily in the morning using a dry powder inhaler:
 - fluticasone furoate 50 micrograms (emitted dose 44 micrograms) plus vilanterol 25 micrograms (emitted dose 22 micrograms)
 - fluticasone furoate 100 micrograms (emitted dose 92 micrograms) plus vilanterol 25 micrograms (emitted dose 22 micrograms)
 - fluticasone furoate 100 micrograms (emitted dose 92 micrograms)
 - vilanterol 25 micrograms (emitted dose 22 micrograms)
 - placebo.
- Outcomes: there were 2 co-primary outcomes: weighted mean FEV₁ (0–4 hours post-dose) on day 168, and the change from baseline in trough FEV₁ (23–24 hours post-dose) on day 169. The primary analysis was based on the intention-to-treat population split into 2 levels pre-specified by the authors to avoid spurious statistically significant findings arising through chance, given the number of possible comparisons:
 - The level 1 analysis consisted of 6 key comparisons of the co-primary end points for fluticasone furoate/vilanterol 100/25 micrograms and vilanterol 25 micrograms. These are summarised in the discussion of the evidence for [clinical effectiveness](#).
 - The authors specified that only if all comparisons reached statistical significance at level 1 would they move on to level 2 analyses, which included comparison with fluticasone furoate/vilanterol 50/25 micrograms. The level 1 analysis did not meet the pre-defined criteria and so no formal statistical testing was performed at level 2.

- Secondary and additional outcomes included changes in dyspnoea score, night-time awakenings and other symptom-related end points but the statistical hierarchy used in the analysis meant that no statistical significance can be inferred from the results for these outcomes.

Clinical effectiveness

Discussion of the evidence for clinical effectiveness focuses on fluticasone furoate/vilanterol 100/25 micrograms because that is the dose and strength that has been submitted for licensing. In their predefined pooled analysis, [Dransfield et al. \(2013\)](#) found that the mean yearly rate for moderate and severe exacerbations for fluticasone furoate/vilanterol 100/25 micrograms was 0.81 compared with 1.11 for vilanterol 25 micrograms alone. The yearly rate ratio was 0.7 (95% confidence interval [CI] 0.6 to 0.8), a reduction of 30% in relative terms. This was similar in people with a history of frequent exacerbations; defined as at least 2 moderate or severe exacerbations in the previous year (yearly rate ratio 0.7, 95% CI 0.6 to 0.9, $p=0.0005$). The [full NICE guideline on COPD](#) considered a relative reduction in the risk of exacerbations of 20% or more to be clinically important. This dose of fluticasone furoate/vilanterol also increased the time to first moderate or severe exacerbation compared with vilanterol 25 micrograms alone (hazard ratio 0.8, 95% CI 0.7 to 0.9, $p=0.0002$). However, it was not shown to reduce the mean yearly rate of severe exacerbations (those needing admission to hospital) compared with vilanterol 25 micrograms alone (rate ratio 0.9, 95% CI 0.6 to 1.4, $p=0.695$).

Compared with vilanterol 25 micrograms alone, fluticasone furoate/vilanterol 100/25 micrograms also produced statistically significant improvements in night-time awakenings (mean difference -0.08 , 95% CI -0.12 to -0.03 , $p=0.0012$) and dyspnoea (mean difference -0.09 , 95% CI -0.014 to -0.05 , $p<0.0001$, on a scale of -2 to $+2$, with -2 indicating 'much less than usual' and $+2$ indicating 'much more than usual').

[Kerwin et al. \(2013\)](#) found that fluticasone furoate/vilanterol 100/25 micrograms was statistically significantly superior to placebo in improving post-dose weighted mean FEV₁ (173 ml, 95% CI 123 to 224 ml, $p<0.001$) and trough FEV₁ (115 ml, 95% CI 60 to 169 ml, $p<0.001$) after 24 weeks' treatment. However, there was no statistically significant difference in trough FEV₁ between fluticasone furoate/vilanterol 100/25 micrograms and vilanterol 25 micrograms (48 ml, 95% CI -6.0 to 102ml, $p=0.082$).

A further study by [Martinez et al. \(2013\)](#) was of a similar design to that by [Kerwin et al. \(2013\)](#) and was intended to provide multiple statistical comparisons between fluticasone furoate/vilanterol 200/25 micrograms and fluticasone furoate/vilanterol 100/25 micrograms compared with their individual components and placebo. The authors used a similar hierarchy of statistical analysis to

[Kerwin et al. \(2013\)](#), which involved analysis of comparisons of fluticasone furoate/vilanterol 200/25 micrograms in the first stage. Pre-specified criteria were not met so the second stage, which would have included comparisons of fluticasone furoate/vilanterol 100/25 micrograms, was not conducted.

Safety

Statistical analysis of the safety data from all 3 of the studies was not presented, which therefore limits the conclusions that can be drawn.

In the pooled analysis of the RCT by [Dransfield et al. \(2013\)](#), 7.7% of patients receiving fluticasone furoate/vilanterol 100/25 micrograms experienced an adverse event leading to discontinuation or withdrawal from the study, compared with 5.5% of those receiving vilanterol 25 micrograms. As the [NICE guideline on COPD](#) notes, there are particular risks associated with long-term use of inhaled corticosteroids. Local corticosteroid effects, pneumonia and bone disorders (including fractures) were seen more frequently in the fluticasone furoate/vilanterol 100/25 microgram group than the vilanterol group.

There were 6 non-traumatic fractures in the fluticasone furoate/vilanterol 100/25 microgram group (0.74%) compared with 2 in the vilanterol group (0.24%). The incidence of pneumonia in the fluticasone furoate/vilanterol 100/25 microgram group was approximately double that in the vilanterol group (6.3% compared with 3.3%). Moreover, 3.1% (25/806) of patients in the fluticasone furoate/vilanterol 100/25 microgram group had pneumonia that required admission to hospital compared with 0.98% (8/818) of patients in the vilanterol 25 microgram group. There was 1 fatal pneumonia-related adverse event in the fluticasone furoate/vilanterol 100/25 microgram group compared with none in the vilanterol 25 microgram group. The potential risk of pneumonia or other infections of the lower respiratory tract associated with the use of inhaled corticosteroids in patients with COPD has previously been [highlighted](#) by the [Medicines and Healthcare products Regulatory Agency \(MHRA\)](#).

In the [Kerwin et al. \(2013\)](#) study, the same percentage of patients receiving fluticasone furoate/vilanterol 100/25 micrograms and placebo had an adverse event leading to discontinuation or withdrawal from the study (9%). Pneumonia occurred in 2% of the fluticasone furoate/vilanterol 100/25 microgram group compared with 1% of the placebo group.

Evidence strengths and limitations

[Kerwin et al. \(2013\)](#) demonstrated that fluticasone furoate/vilanterol 100/25 micrograms has beneficial effects on lung function as measured by trough FEV₁ in people with COPD compared with placebo, when used up to 24 weeks. However, the [full NICE guideline on COPD](#) considers 100 ml to be the minimum clinically important difference in FEV₁. The lower limit of the 95% confidence interval for the difference did not reach this limit.

The NICE guideline on [COPD](#) advises that the effectiveness of bronchodilator therapy should not be assessed by lung function alone but should include a variety of other measures, such as improvement in symptoms, activities of daily living, exercise capacity, and rapidity of symptom relief. [Dransfield et al. \(2013\)](#) demonstrated that fluticasone furoate/vilanterol 100/25 micrograms reduces the yearly rate of moderate and severe exacerbations compared with vilanterol 25 micrograms alone and the time to first moderate or severe exacerbation, but not the rate of exacerbations requiring admission to hospital. There were statistically significant benefits from fluticasone furoate/vilanterol 100/25 micrograms on symptomatic measures (night-time awakening and dyspnoea scores) but the differences were small in absolute terms and are of questionable clinical significance. [Kerwin et al. \(2013\)](#) also assessed effects on dyspnoea but observed differences were less than the minimally clinically important difference and the results could not be assessed statistically.

The studies by [Dransfield et al. \(2013\)](#) and [Kerwin et al. \(2013\)](#) also had several methodological limitations that affect their usefulness in assessing the place in therapy of fluticasone furoate plus vilanterol in the NHS. The rationale for the design of the studies by [Dransfield et al. \(2013\)](#), encompassing 2 simultaneous, replicate trials of a common condition with a very large number of centres relative to the number of patients recruited (such that each centre would recruit only a small number of patients) is unclear. The primary end point depended in part on local practice (whether or not to start systemic corticosteroids or antibiotics, or admit to hospital) and this may have varied between sites. The comparator in all the studies was placebo or vilanterol 25 micrograms, and not established combination therapy or monotherapy licensed for use in COPD.

One trial that has not yet been published in full (trial reference [NCT01342913](#)) compared fluticasone furoate/vilanterol 100/25 micrograms once daily with fluticasone propionate/salmeterol 500/50 micrograms (Seretide 500 Accuhaler) twice daily. This trial was relatively short term (12 weeks) and it measured a disease-orientated outcome (24-hour spirometric effect [FEV₁]), which will therefore limit the conclusions that can be drawn from it.

Context

Treatment alternatives

Inhaled treatments for chronic obstructive pulmonary disease (COPD) recommended by NICE are outlined in the [introduction](#).

There are 2 long-acting beta₂ agonist (LABA) and inhaled corticosteroid (ICS) combination inhalers currently licensed for use in COPD in the UK:

- fluticasone propionate/salmeterol 500/50 micrograms dry powder inhalation (Seretide 500 Accuhaler)
- budesonide/formoterol dry powder inhaler (Symbicort 200/6 Turbohaler and Symbicort 400/12 Turbohaler).

Other combined ICS and LABA inhalers are licensed for use in asthma but not COPD.

Costs of treatment alternatives

Drug	Usual dosage ^{a,b}	30-day cost excluding VAT ^c
Fluticasone propionate 500 micrograms/salmeterol 50 micrograms (Seretide 500 Accuhaler)	1 inhalation twice daily	£40.92
Budesonide 200 micrograms/formoterol fumarate dihydrate 6 micrograms (Symbicort Turbohaler 200/6)	2 inhalations twice daily	£38.00
Budesonide 400 micrograms /formoterol fumarate dihydrate 12 micrograms (Symbicort Turbohaler 400/12)	1 inhalation twice daily	£38.00
<p>^a Doses taken from the relevant summary of product characteristics.</p> <p>^b The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.</p> <p>^c Costs taken from Drug Tariff May 2013.</p>		

Estimated impact for the NHS

Likely place in therapy

The NICE guideline on [chronic obstructive pulmonary disease \(COPD\)](#) recommends that the choice of drug treatment should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and costs.

Currently, published efficacy and safety data for fluticasone furoate/vilanterol are limited to short-term, placebo-controlled trials with disease-orientated primary outcomes and 1 study of the effect of fluticasone furoate/vilanterol on rates of moderate and severe exacerbations compared with vilanterol alone. These trials provide no information on the effectiveness of fluticasone furoate/vilanterol compared with available licensed inhaled therapy for COPD.

In addition, the cost of the product has yet to be determined; therefore at present, cost comparisons with other inhaled corticosteroid (ICS)/long-acting beta₂ agonist (LABA) combination inhalers licensed for use in COPD cannot be made. At present, the exact place in therapy of fluticasone furoate/vilanterol is difficult to assess but if a UK marketing authorisation is granted, it will represent an additional treatment option alongside existing inhaled therapies licensed for use in COPD.

Estimated usage

If a marketing authorisation is granted, the manufacturer expects fluticasone furoate/vilanterol to be used in patients new to this class of drugs or in patients on existing treatments who are symptomatic on their current regimen and may benefit from a once-daily product (GlaxoSmithKline: personal communication March 2013).

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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**.

For information about the process used to develop this evidence summary, see [Evidence summaries: new medicines – interim process statement](#).

Changes after publication

November 2014: Minor maintenance.

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