Evidence Review for Prescribing Clinical Network
Treatment: Relvar Ellipta® 92 micrograms/22micrograms in COPD
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Topic Submitted by: Noreen Devanney
Date: 5TH March 2014

Summary page

- How strong is the evidence for claimed efficacy?
  **Grade A** = > 1 RCT or meta-analysis
- Potential advantages:

  This combination provides an alternative once daily cost effective option for patients who are indicated to have treatment with combined LABA/ICS as per National Institute of Clinical Excellence (NICE²) or Global Initiative for Chronic Obstructive Lung Disease (GOLD⁴) Guidelines.

- Is there a clear place in therapy / treatment pathway?
  
  A) as per NICE² for patients for patients with FEV1<50% or FEV1 ≥50% with persistent exacerbations or breathlessness on LABA or LAMA.
  
  B) as per GOLD⁴ for patients with FEV1<50% at high risk of exacerbations( ≥ 2 exacerbation per year ) or ≥ 1 hospitalization and more symptoms , mMRC ≥ 2 or CAT ≥10 (CAT: COPD Assessment Test, MRC: Medical research Council Scale)

- Is monitoring for toxicity required? No

- Is monitoring for efficacy required? Desirable to assess efficacy. Review people with mild or moderate COPD at least once a year and those with very severe COPD at least twice a year.

- Is dose titration required? No

- Traffic light status -Green

- Role of the specialist (if applicable)?

- Role of GP (if applicable)?

- Financial implications? Cost effective compared to currently available ICS/LABA.

- National Guidance available :NICE²/ GOLD⁴ as above

**Recommendation:**

Relvar Ellipta® 92micrograms/ 22micrograms to be placed as an option in COPD in addition to Symbicort Turbohaler® 400 and Seretide Accuhaler 500®.
1. Purpose of the Review

To review the evidence for Relvar Ellipta® 92 micrograms /22 micrograms (dry powder for inhalation) fluticasone furoate 92 micrograms / vilanterol trifenate 22 micrograms / inhalation in COPD. This is a black triangle combination ▼ and intensively monitored by the CHM (Commission on Human Medicines) and the MHRA (Medicines and Healthcare products Regulatory Agency).

2.1 Indication: COPD (Chronic Obstructive Pulmonary Disease)

Relvar Ellipta® is licensed for the symptomatic treatment of adults with COPD with a FEV₁<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. (SPC)¹

2.2 The problem: An estimated 3 million people chronic obstructive pulmonary disease (COPD) in the UK. About 900,000 have diagnosed COPD and an estimated 2 million people have COPD which remains undiagnosed have. Most patients are not diagnosed until they are in their fifties.²

Definition: COPD is characterised by airflow obstruction that is not fully reversible. The airflow obstruction does not change markedly over several months and is usually progressive in the long term. COPD is predominantly caused by smoking. Other factors, particularly occupational exposures, may also contribute to the development of COPD. Exacerbations often occur, where there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations.

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.

COPD is the preferred term for the conditions in patients with airflow obstruction who were previously diagnosed as having chronic bronchitis or emphysema.²

Effects and prognosis:

- The natural history of COPD varies among individuals. However, COPD is progressive, especially if the person’s exposure to noxious agents continues. Stopping exposure to these agents may slow or halt the progression of the disease. However, once developed, it cannot be cured.
- About 30,000 people each year in the UK die of COPD, accounting for 5% of all deaths.
- The true mortality rate due to COPD is difficult to quantify, as many people with COPD die with the disease rather than because of it. Nevertheless, mortality from COPD increases with age, severity of disease, and socioeconomic deprivation.³

COPD is heterogeneous, so no single measure can give an adequate assessment of the true severity of the disease in an individual patient. Severity assessment is, nevertheless, important because it has implications for therapy and relates to prognosis.

Disability in COPD can be poorly reflected in the FEV₁. A more comprehensive assessment of severity includes the degree of airflow obstruction and disability, the
frequency of exacerbations and the following known prognostic factors: FEV\textsubscript{1}, T\textsubscript{L}CO, breathlessness (MRC scale), health status, exercise capacity (for example, 6-minute walk test), BMI, partial pressure of oxygen in arterial blood (PaO\textsubscript{2}), cor pulmonale. The BODE index (BMI, airflow obstruction, dyspnoea and exercise capacity) is used to assess prognosis where its component information is currently available\textsuperscript{3}.

**Gradation of severity of airflow obstruction**

<table>
<thead>
<tr>
<th>Post-bronchodilator FEV\textsubscript{1}/FVC</th>
<th>GOLD 2014 *</th>
<th>NICE CG101 * (2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post-bronchodilator</td>
<td>Post-bronchodilator</td>
</tr>
<tr>
<td>&lt; 0.7</td>
<td>≥ 80%</td>
<td>Stage 1 – Mild</td>
</tr>
<tr>
<td>&lt; 0.7</td>
<td>50–79%</td>
<td>Stage 2 – Moderate</td>
</tr>
<tr>
<td>&lt; 0.7</td>
<td>30–49%</td>
<td>Stage 3 – Severe</td>
</tr>
<tr>
<td>&lt; 0.7</td>
<td>&lt; 30%</td>
<td>Stage 4 – Very severe**</td>
</tr>
</tbody>
</table>

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

**Or FEV\textsubscript{1} < 50% with respiratory failure.**

**Aetiology:**
- **Tobacco smoking:** This is the major risk factor for development of chronic obstructive pulmonary disease (COPD). Although COPD can occur in people who have never smoked, about 90% of cases are caused by cigarette smoking.
- **Occupational exposure:** Exposure to dust, chemicals, noxious gases, and particles) has been implicated in the development of COPD; the association is independent of smoking.
- **Air pollution:** Indoor and outdoor air pollution may also contribute to the development of COPD.
- **Genetics:** The genetic risk of homozygous α\textsubscript{1}-antitrypsin deficiency accounts for less than 1% of COPD cases. However, it is the best-documented genetic risk factor for COPD. Severe α\textsubscript{1}-antitrypsin deficiency is linked with premature and accelerated development of COPD in smokers and non-smokers, but lung function decline occurs more rapidly in smokers. Although no gene for COPD has been identified, there is likely to be a genetic influence in the development of the disease. A significant familial risk of airflow obstruction has been reported in smoking siblings of people with severe COPD.\textsuperscript{3}

**Diagnosis:**
There is no single diagnostic test for COPD. The diagnosis is suspected on the basis of symptoms and signs and supported by spirometry.
A diagnosis of COPD should be considered in patients over the age of 35 who have a risk factor (generally smoking) and who present with one or more of the following symptoms:
- exertional breathlessness
- chronic cough
• regular sputum production
• frequent winter ‘bronchitis’
• wheeze

Patients in whom a diagnosis of COPD is considered should also be asked about the presence of the following factors: weight loss, effort intolerance, waking at night, ankle swelling, fatigue, occupational hazards, chest pain, and haemoptysis.

NB These last two symptoms are uncommon in COPD and raise the possibility of alternative diagnoses.

Spirometry:
Spirometry should be performed:
• at the time of diagnosis
• to reconsider the diagnosis, if patients show an exceptionally good response to treatment.
Post-bronchodilator spirometry should be performed to confirm the diagnosis of COPD.

Alternative diagnoses or investigations should be considered in:
• older people without typical symptoms of COPD where the FEV₁/FVC ratio is < 0.7
• younger people with symptoms of COPD where the FEV₁/FVC ratio is ≥ 0.7.

2.3 The Intervention:
Inhaled bronchodilators such as LABAs (Long-acting β₂ agonists) and LAMAs (Long-acting muscarinic antagonists) reduce breathlessness and improve exercise tolerance without producing large improvements in forced expiratory volume in 1 second (FEV₁).
Inhaled corticosteroids (ICSs) have been shown to reduce rates of exacerbations, improve quality of life and give short-term improvements in FEV₁.

How does it work?
Vilanterol is a long-acting beta 2 agonist (LABA). LABAs stimulate β₂ receptors resulting in relaxation of bronchial smooth muscle.
Fluticasone Furoate is an inhaled corticosteroid (ICS). The primary mechanism of action in COPD is unclear however ICS have a potent anti-inflammatory effect and act on multiple cell types involved in inflammation such as eosinophils, macrophages, lymphocytes and mediators such as cytokines and chemokines. COPD is characterised by inflammation in the smooth muscle of the airways.
Molecular interactions occur between corticosteroids and LABAs, whereby steroids activate the beta₂-receptor gene, increasing receptor number and sensitivity and LABAs prime the glucocorticoid receptor for steroid-dependent activation and enhance cell nuclear translocation. This results in synergistic actions when ICS/LAMA are used.¹

Care setting: Relvar Ellipta® may be initiated in primary or secondary care.

Frequency: Relvar Ellipta® is administered once-daily by inhalation using an Ellipta® device. 1 inhalation (delivered dose) of fluticasone furoate 92 micrograms once daily is approximately equivalent to fluticasone propionate 250 micrograms twice daily.⁵
2.4 Alternative treatments:
Combination LABA/ICS currently licensed for the treatment of COPD in the UK:
Symbicort Turbohaler ®200/6 ² puffs bd (Budesonide/formoterol)
Symbicort Turbohaler @400/12 ³1 puff bd (Budesonide/formoterol)
Seretide Accuhaler® 500 ⁷1 puff bd (Fluticasone/salmeterol)

3. Effectiveness

3.1 Expected benefits
GOLD: ICS/LABA combination reduces serious outcomes. The addition of regular treatment with inhaled glucocorticosteroid to bronchodilator treatment has been shown to reduce the frequency of exacerbations and thus improve health status (Evidence A) ⁴
GOLD: combination therapy is better than monotherapy Inhaled glucocorticosteroid combined with a long-acting beta 2-agonist is more effective than the individual components (Evidence A) ⁴

Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. There is no additional benefit of the 184/22 micrograms dose compared to the 92/22 micrograms dose and there is a potential increased risk of pneumonia and systemic corticosteroid-related adverse reactions (see sections 3.3).

3.2 Is there a plausible biological basis for effectiveness?
Yes as per 2.3

3.3 Side-effects/complications
Special warnings and precautions due to pharmacological actions of the two drug classes are highlighted in the SPC ¹ as for other LABA/ICS. These are cardiovascular effects, hypoglycaemia, systemic corticosteroids effects, paradoxical bronchospasm, caution in hepatic impairment

Summary of selected side effects of Relvar Ellipta ®192, Symbicort Turbohaler ®400, Seretide Accuhaler ®500 (common and very common only).

Data from large asthma and COPD clinical trials were used to determine the frequency of adverse reactions associated with fluticasone furoate/vilanterol. In the asthma clinical development program a total of 7,034 patients were included in an integrated assessment of adverse reactions. In the COPD clinical development programme a total of 6,237 subjects were included in an integrated assessment of adverse reactions.

The most commonly reported adverse reactions with fluticasone furoate and vilanterol were headache and nasopharyngitis. With the exception of pneumonia and fractures, the safety profile was similar in patients with asthma and COPD. During clinical studies, pneumonia and fractures were more frequently commonly observed in patients with COPD.
See SPCs \(^1,^6,^7\) for comprehensive lists of all side effects.

(very common (≥1/10), common (≥1/100 and <1/10))

<table>
<thead>
<tr>
<th></th>
<th>Relvar(^8^1)</th>
<th>Symbicort(^8^6)</th>
<th>Seretide(^8^7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>common</td>
<td></td>
<td>common</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td></td>
<td>common</td>
<td>common</td>
</tr>
<tr>
<td>Candidiasis of mouth and throat</td>
<td></td>
<td>(Pneumonia not on list but referred to under selected ADRs, see P.8)</td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>common</td>
<td>common</td>
<td>common</td>
</tr>
<tr>
<td><strong>Respiratory and Thoracic Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>very common</td>
<td>common</td>
<td>very common</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>common</td>
<td></td>
<td>common</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>common</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>common</td>
<td>Muscle cramps: common</td>
<td>common</td>
</tr>
<tr>
<td>Back pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture (See P.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>common</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Description of selected adverse reactions /
**Risk of Pneumonia (from Summary of Product Characteristics)** The risk of pneumonia in COPD is reported in the SPCs of Relvar Ellipta®, Symbicort® and Seretide®.

**Relvar Ellipta SPC** Integrated analysis of the two replicate one year studies in COPD with an exacerbation in the preceding year (n = 3255)

<table>
<thead>
<tr>
<th></th>
<th>FF/VI 184/22</th>
<th>FF/VI 92/22</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pneumonia events per 1000 patient years</td>
<td>97.9</td>
<td>85.7</td>
<td>42.3</td>
</tr>
<tr>
<td>Severe Pneumonia events per 1000 patient years</td>
<td>33.6</td>
<td>35.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Serious events per 1000 patient years</td>
<td>35.1</td>
<td>42.9</td>
<td>12.1</td>
</tr>
<tr>
<td>Fatal events per 1000 patient years</td>
<td>8.8</td>
<td>1.5</td>
<td>0</td>
</tr>
</tbody>
</table>

Four 12 week comparison studies with Fluticasone Propionate/Salmeterol Combination FP/Sal occurrence of pneumonia with Relvar® in patients with COPD

<table>
<thead>
<tr>
<th></th>
<th>FF/VI 100/25</th>
<th>FP/SAL 250/50mcg</th>
<th>FP/SAL 500/50mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n</td>
<td>1190</td>
<td>934</td>
<td>262</td>
</tr>
<tr>
<td>Patients with pneumonia</td>
<td>7&lt;1%(2 serious)</td>
<td>4(&lt;1%)(4 serious)</td>
<td>2(&lt;1%)(2 serious)</td>
</tr>
</tbody>
</table>

In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of pneumonia per 1000 patient years was 18.4 for FF/VI 184/22 versus 9.6 for FF/VI 92/22 and 8.0 in the placebo group.

**Seretide® SPC: Data from the Torch study** The estimated 3-year probability of having pneumonia reported as an adverse event was 12.3% for placebo, 13.3% for salmeterol, 18.3% for FP and 19.6% for Seretide® (Hazard ratio for Seretide® vs placebo: 1.64, 95% CI: 1.33 to 2.01, p<0.001). There was no increase in pneumonia related deaths; deaths while on treatment that were adjudicated as primarily due to pneumonia were 7 for placebo, 9 for salmeterol, 13 for FP and 8 for Seretide®.
Symbicort® SPC: In a 3-year clinical trial with budesonide in COPD, pneumonia occurred at a frequency of 6%, compared with 3% in the placebo group (p<0.001 and p<0.01, respectively).

Studies Relating to the Incidence of Pneumonia in COPD

A Cochrane Review 9 published in 2012, analysed data of 14 studies involving salmeterol/fluticasone propionate and budesonide/formoterol. An increase in pneumonia was reported from 12 studies but there was no significant difference demonstrated between salmeterol/fluticasone and budesonide/formoterol or any indication of dose response effect.

The matched cohort PATHOS 10 and recently published SUISSA 11 studies suggest that this risk varies between agents and is more marked with fluticasone.

Fractures (from Summary of Product characteristics) 1, 6, 7

Relvar®- In two replicate 12 month studies in a total of 3,255 patients with COPD the incidence of bone fractures overall was low in all treatment groups, with a higher incidence in all Relvar Ellipta® groups (2%) compared with the vilanterol 22 micrograms group (<1%). Although there were more fractures in the Relvar Ellipta groups compared with the vilanterol 22 micrograms group, fractures typically associated with corticosteroid use (e.g., spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% of the Relvar Ellipta® and vilanterol treatment arms.

Seretide®- There was no significant difference in probability of bone fracture (5.1% placebo, 5.1% salmeterol, 5.4% FP and 6.3% Seretide; Hazard ratio for Seretide vs placebo: 1.22, 95% CI: 0.87 to 1.72, p=0.248.

Symbicort®- Long-term studies with inhaled budesonide in children at mean daily doses of 400 micrograms (metered dose) or in adults at daily doses of 800 micrograms (metered dose) have not shown any significant effects on bone mineral density. No information regarding the effect of Symbicort® at higher doses is available.

In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of fractures was <1%, and usually associated with trauma.

Relvar Ellipta®: Interaction with CYP3A4 inhibitors

(Similar to currently available LABA/ICS)

Fluticasone furoate and vilanterol are both rapidly cleared by extensive first pass metabolism mediated by the liver enzyme CYP3A4.
### 3.4 Efficacy: Tables 1-3 below summary of trial evidence

<table>
<thead>
<tr>
<th>Study design</th>
<th>Patient population</th>
<th>Primary endpoint assessment</th>
<th>Phase 3 results</th>
</tr>
</thead>
</table>
| **COPD phase 3 data: 24 hour spirometric effect of Relvar 92/22mcg (fluticasone furoate/vilanterol)** | This was a phase III, multicentre, randomised, double blind, placebo controlled crossover study designed to evaluate the 24-hour spirometric effect of fluticasone furoate/vilanterol (Relvar) once daily in patients with COPD. Subjects completed a 2 week placebo run-in period prior to randomisation. Each treatment was inhaled once a day in the morning for 28 days using the Ellipta dry powder device. Treatment periods were separated by 2-week, single-blind, placebo washout periods. | Clinical history of COPD | **Patient Population**

33 patients were assigned to the fluticasone furoate/vilanterol (Relvar) 92/22mcg OD arm and 51 patients to the placebo OD arm.

The mean patient age was 57.9 years and 46% were male and 89% caucasian. 83% were current smokers and 53% had had COPD for ≥ 5 years. Mean post bronchodilator % predicted FEV₁ at baseline was 49.8%.

**Primary efficacy endpoint**

Fluticasone furoate/vilanterol (Relvar) 92/22mcg OD demonstrated significantly higher 0 to 24-hour weighted mean (wm) FEV₁ vs placebo OD at the end of the 28 day treatment period (220mL; 95% CI (0.165,0.275); p<0.001). |
<p>| <strong>Phase 3 results</strong> | Time-adjusted (weighted mean) 0 to 24-hour FEV₁ at the end of the 28-day treatment period | | |
| <strong>Primary endpoint</strong> | This was calculated from pre-dose FEV₁ and post-dose FEV₁, after 5, 15, 30, and 60 minutes and 2, 4, 6, 8, 12, 16, 20, 22, 23, and 24 hours. | | |</p>
<table>
<thead>
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</thead>
<tbody>
<tr>
<td>A randomised, multicentre, double blind, double dummy, parallel group comparative efficacy/safety study comparing once daily Relvar 92/22mcg (fluticasone furoate/vilanterol) in the morning, versus twice daily Seretide Accuhaler 500/50mcg (fluticasone propionate/salmeterol) in patients with moderate to very severe COPD. Patients were randomised 1:1 to receive study medication for 12 weeks. Randomisation was preceded by a 2 week placebo run-in period. This was a superiority study with the hypothesis that Relvar 92/22mcg would demonstrate superior efficacy over Seretide 500/50mcg of improvement from baseline in 0-24 hour weighted mean (wm) EV</td>
<td>Clinical history of COPD in accordance with ERS definition Post salbutamol FEV₁/FVC ratio of ≤ 0.70 and FEV₁ ≤ 70% predicted normal ≥ 10 pack years smoking history Hospitalised or treated with oral corticosteroids or antibiotics for at least one COPD exacerbation within 3 years of screening Male and female adults ≥ 40 years of age. The Intention to Treat (ITT) study population included 266 patients who received once daily fluticasone furoate/vilanterol (Relvar) 92/22mcg via an Ellipta and 262 patients who received twice daily fluticasone propionate/salmeterol (Seretide) 500/50mcg via an Accuhaler.</td>
<td>24 hour effect on lung function of Relvar 92/22mcg OD compared to Seretide 500/50mcg BD after 12 weeks of treatment. This was assessed through the change from baseline in wmFEV₁, measured serially over 24 hours on day 84. <strong>Secondary efficacy endpoint assessments</strong> Time to 100ml increase from baseline from 0-4 hours on day 1 Change from baseline in trough FEV₁ on day 85 <strong>Other efficacy endpoint assessments included:</strong> Quality of Life measured by the St George’s Respiratory Questionnaire (SGRQ) for COPD patients (SGRQ). This is a COPD specific questionnaire designed to measure impact of COPD and its treatment on the subject’s health related quality of life.</td>
<td><strong>Primary efficacy endpoint</strong> A clinically meaningful improvement from baseline in 0-24 h wmFEV₁ (day 84) was observed with both Relvar (mean ± SD = 130 ± 222 mL) and Seretide (mean ± SD = 109 ± 221 mL). The primary endpoint of superiority was not met because the difference in improvement between the two arms (22 mL) did not reach statistical significance (95% CI (-18, 63); p=0.282). The bar chart below shows the mean change in FEV₁ of Relvar 92/22mcg OD versus Seretide Accuhaler 500/50 mcg BD at 12 weeks. <strong>Secondary efficacy endpoints</strong> Because statistical significance was not achieved for the primary endpoint it cannot be inferred for comparisons of secondary efficacy endpoints. The details below should be considered as descriptive only: The median time to 100ml improvement in wmFEV₁ from baseline was 16 minutes in the fluticasone furoate/vilanterol (Relvar) arm and 28 minutes in the fluticasone propionate/salmeterol (Seretide) arm (p=ns)</td>
</tr>
</tbody>
</table>
### Study design
Two identically designed and analysed multicentre, randomised, double blind, parallel group studies were conducted comparing once daily Relvar 92/22mcg (fluticasone furoate/vilanterol) with once daily vilanterol 22mcg in the reduction of moderate and severe exacerbations. Treatments were given in the morning using the Ellipta dry powder inhaler. Both studies had a 4 week run-in period during which all subjects received open-label fluticasone propionate/salmeterol 250/50 mcg twice daily to standardise COPD pharmacotherapy and stabilise disease. Pooled data from the two studies is reported below. Patient population:
Clinical history of COPD in accordance with ERS definition
Post salbutamol FEV₁/FVC ratio of ≤ 0.70 and FEV₁ ≤ 70% predicted normal
≥ 10 pack years smoking history
At least one COPD exacerbation in the 12 months prior to screening that required either systemic/oral corticosteroids, antibiotics and/or hospitalisation
Outpatients aged 40 years or older

### Patient population

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<td><strong>COPD phase 3 data: Relvar (fluticasone furoate/vilanterol) vs LABA alone (vilanterol) for prevention of exacerbations of COPD.</strong>&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td></td>
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</tbody>
</table>

This page summarises the key points of the Dransfield MT et al. 2013 phase 3 study. Please see references for full citation.

Exacerbations of COPD are important events that are associated with accelerated loss of lung function and poor health status.

Single agent vilanterol is not licensed for the treatment of COPD.

### Primary efficacy endpoint assessments
The yearly rate of moderate and severe exacerbations

Moderate exacerbations were defined as worsening symptoms of COPD (≥2 consecutive days) necessitating treatment with oral corticosteroids or antibiotics, or both

Severe exacerbations were similar events that necessitated hospital admission

### Secondary efficacy endpoint assessments
Time to first on treatment moderate or severe exacerbation

Yearly rate of exacerbations necessitating systemic or oral corticosteroids

Change from randomisation in trough FEV₁ at week 52

These results are consistent with previous studies of twice daily ICS/LABA combinations that established the added value of ICS for these endpoints<sup>13</sup>

### Table 3: COPD phase 3 data: Relvar (fluticasone furoate/vilanterol) vs LABA alone (vilanterol) for prevention of exacerbations of COPD<sup>13</sup>

<table>
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Exacerbations of COPD are important events that are associated with accelerated loss of lung function and poor health status.

Single agent vilanterol is not licensed for the treatment of COPD.

### Primary efficacy endpoint
Fluticasone furoate/vilanterol (Relvar) OD significantly reduced the mean yearly rate of moderate and severe exacerbations versus vilanterol alone (0.81 vs 1.11; 27% reduction; AR 0.3; p<0.0001)

The graph below shows the reduction in moderate/severe exacerbation rates over 52 weeks

### Secondary efficacy endpoints
Compared to vilanterol, fluticasone furoate/vilanterol (Relvar) OD significantly reduced the risk in time to first on treatment moderate/severe exacerbation (Hazard ratio 0.8; 95% CI 0.7,1.0;p=0.0002)

Compared to vilanterol, fluticasone furoate/vilanterol (Relvar) OD significantly reduced the annual rate of on treatment exacerbations requiring oral or systemic corticosteroids by 30% (0.7; 95% CI (0.6,0.8);p<0.0001)

Compared to vilanterol OD, fluticasone furoate/vilanterol (Relvar) OD demonstrated significantly greater improvements in trough FEV₁ at 52 weeks (40ml difference; 95% CI (0.02, 0.06); p=0.0003).

These results are consistent with previous studies of twice daily ICS/LABA combinations that established the added value of ICS for these endpoints<sup>13</sup>
4. Summary of Key Points for Consideration

4.1a National guidance:
NICE\textsuperscript{2} and GOLD \textsuperscript{4} guidance for COPD. Long acting bronchodilators/inhaled corticosteroid (LABA and ICS) are included in both guidance recommendations.

**NICE May 2010**

**FEV1 ≥ 50%**
LABA or LAMA if breathless or exacerbations on short acting bronchodilators
If still symptomatic or exacerbations then use \textbf{combination LABA/ICS}.
If still symptomatic or exacerbations use LAMA + LABA/ICS
LABA + LAMA used if ICS is declined or not tolerated

**FEV1 < 50%**
LAMA or LABA/ICS, then LAMA + LABA/ICS if still symptomatic

**GOLD December 2013** \textsuperscript{4} advises that combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.
GOLD has segmented patients into four groups according to whether the risk of exacerbation is low or high and whether the symptomatic impact of the disease in the patient is low or high in relation to the patients’ spirometric classification.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Characteristic</th>
<th>Spirometric Classification</th>
<th>Exacerbations Per year</th>
<th>mMRC (Medical research Council)</th>
<th>CAT (COPD assessment test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low risk Less symptoms</td>
<td>GOLD1-2</td>
<td>≤ 1</td>
<td>0-1</td>
<td>&lt;10</td>
</tr>
<tr>
<td>B</td>
<td>Low risk * More symptoms</td>
<td>GOLD1-2</td>
<td>≤ 1</td>
<td>≥2</td>
<td>≥10</td>
</tr>
<tr>
<td>C</td>
<td>High Risk Less symptoms</td>
<td>GOLD 3-4</td>
<td>≥ 2</td>
<td>0-1</td>
<td>&lt;10</td>
</tr>
<tr>
<td>D</td>
<td>High Risk More symptoms</td>
<td>GOLD 3-4</td>
<td>≥ 2</td>
<td>≥2</td>
<td>≥10</td>
</tr>
</tbody>
</table>

**Group C:** High risk of exacerbations and fewer symptoms:
first choice - LAMA or ICS+ LABA
second choice - LAMA + LABA

**Group D:** High risk of exacerbations and more symptoms:
first choice - LAMA or ICS + LABA;
second choice - ICS + LABA + LAMA or
ICS + LABA + phosphodiesterase inhibitor or
LAMA + LABA or LAMA + phosphodiesterase inhibitor
4.2 Efficacy

Summary Efficacy data

**Compared to Seretide® 500/50mcg:** (528 patients total: 266 Relvar®, 262 Seretide®) 12 weeks

NB Short 12 week trial with disease orientated primary outcome (24 hour spirometric effect on FEV1)

Primary endpoint: 24 hour effect on lung function after 12 weeks of treatment. The primary endpoint of superiority was not met because although there was an improvement of 22ml (130ml v 108ml) in the Relvar® arm compared to Seretide®, the difference in improvement between the two arms did not reach statistical significance. NB because statistical significance was not met for the primary endpoint it cannot be inferred for comparisons of secondary endpoints.

Secondary Endpoint: Median time to 100ml improvement from baseline was 16 minutes in the fluticasone furoate/vilanterol (Relvar®) arm and 28 minutes in the fluticasone propionate/salmeterol (Seretide®) arm.

Secondary Endpoint: Non significant improvement of 23mls (111ml v 88ml) in baseline trough at day 85 in the Relvar® arm.

Quality of life: Saint George Respiratory Questionnaire no significant difference

**Compared to vilanterol alone:** (1624 patients total: 806 Relvar®, 818 vilanterol alone) 52 weeks

Relvar® significantly reduced the mean yearly rate of moderate and severe exacerbations

Reduced risk in time to first moderate/severe exacerbation

Reduced annual rate of exacerbations requiring oral or systemic corticosteroids

Significantly higher trough FEV1 at 52 weeks compared to vilanterol alone

**Compared to placebo:** (84 patients total: 33 Relvar®, 51 placebo) 28 days

Relvar® demonstrated significantly higher 0-24-hour FEV1 v placebo at the end of the 28 day treatment period

4.3 Potential Benefits over existing therapy.

- Once daily dosing.
- Potential cost savings compared to other LABA/ICS combinations.

4.4 Potential disadvantages

- Fluticasone furoate and vilanterol are both newly licensed drugs in the UK therefore lack long term efficacy and safety data.
- This is relevant in particular in relation to increased incidence of pneumonia with inhaled corticosteroids in patients with COPD.
- In common with other ICS/LABA combinations there is an increased risk of pneumonia in patients with COPD treated with Relvar®.
- Fluticasone furoate is a high affinity steroid. One inhalation (delivered dose) of fluticasone furoate 92 micrograms once daily is approximately equivalent to fluticasone propionate...
250 micrograms twice daily. As well as conferring higher potency it is not known if there are long term safety implications due to increased potency.

- Trial lengths were short.
  - 28 days (v placebo for spirometric effect), and
  - 12 months (v vilanterol measuring yearly rate of moderate and severe exacerbations)
  - 12 weeks (v Seretide® 500 measuring change in FEV$_1$)

- Trials comparing Relvar Ellipta® 92® to Seretide 500 Accuhaler® in COPD, as well as being short term (12 week), measure disease orientated outcome i.e. 24 hour spirometry effect FEV$_1$. There is no data comparing reductions in exacerbations or hospitalisations compared to Seretide 500 Accuhaler®. Data comparing incidence of pneumonia between Relvar Ellipta 92® and Seretide 500 Accuhaler® only come from 12 week studies.

- When inhaler has been started the shelf life is six weeks only. This may increase risk of patient using expired inhaler.

4.5 Budgetary Impact

4.5.1 Cost:

**Table 3: compared to licensed ICS/LABA combinations in COPD**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per 30 days (£)</th>
<th>Cost per year (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seretide 500 Accuhaler®</td>
<td>One puff bd</td>
<td>40.92</td>
<td>491.04</td>
</tr>
<tr>
<td>Symbicort 400 Turbohaler®</td>
<td>One puff bd</td>
<td>38</td>
<td>456</td>
</tr>
<tr>
<td>Relvar Ellipta® 92ug</td>
<td>One puff daily</td>
<td>27.80</td>
<td>333.60</td>
</tr>
</tbody>
</table>

4.5.2 Precedent setting:

None

Scottish Medicines Consortium will report in April 2014

Conclusions and Recommendations

Relvar Ellipta® 92micrograms/ 22micrograms is a new once daily inhaled corticosteroid/long acting beta 2 agonist formulated in an easy to use dry powder device. In clinical trials Relvar® met primary and secondary endpoints compared to placebo and vilanterol alone. When compared to Seretide®, there was a clinically meaningful improvement from baseline FEV$_1$ with both Relvar® and Seretide®. Although Relvar® showed a greater improvement (130ml v 108ml) this did not reach statistical significance. Fluticasone furoate and vilanterol are both newly licensed drugs in the UK and, as is usual with new drugs, lack long term efficacy and safety data. In common with other ICS/LABA combinations there is an increased risk of pneumonia in patients with COPD treated with Relvar Ellipta®. Relvar Ellipta® may offer a cost effective alternative choice of ICS/LABA in COPD.

Recommendation

Relvar Ellipta® 92micrograms/ 22micrograms to be placed as an option in COPD in addition to Symbicort Turbohaler® 400 and Seretide Accuhaler 500®.
### Appendix 1: Evidence search

Search terms used:

<table>
<thead>
<tr>
<th>Resource</th>
<th>Used in this review?</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Library for Health (NHL)</td>
<td>N/A</td>
</tr>
<tr>
<td>A gateway site with access to other resources such as Reviews (Bandolier, Cochrane, CRD etc), Guidelines (e.g. NICE), Clinical Knowledge Summaries (CKS) and Journals including AMED, British Nursing Index, CINAHL, E-books, EMBASE, HMIC, MEDLINE, My Journals, PsycINFO, PubMed, Databases from Dialog.</td>
<td></td>
</tr>
<tr>
<td>National Institute of Health and Clinical Excellence (NICE)</td>
<td>✓ (through NHL)</td>
</tr>
<tr>
<td>NICE produces national guidance in three areas of health:</td>
<td></td>
</tr>
<tr>
<td>1. Public health - guidance on the promotion of good health and the prevention of ill health</td>
<td></td>
</tr>
<tr>
<td>2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS</td>
<td></td>
</tr>
<tr>
<td>3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS.</td>
<td></td>
</tr>
<tr>
<td>Bandolier</td>
<td>N/A</td>
</tr>
<tr>
<td><a href="http://www.medicine.ox.ac.uk/bandolier/index.html">http://www.medicine.ox.ac.uk/bandolier/index.html</a></td>
<td></td>
</tr>
<tr>
<td>Bandolier is a website about the use of evidence in health, healthcare, and medicine. Information comes from systematic reviews, meta-analyses, randomised trials, and from high quality observational studies.</td>
<td></td>
</tr>
<tr>
<td>Centre for Reviews and Dissemination</td>
<td>N/A</td>
</tr>
<tr>
<td><a href="http://www.york.ac.uk/inst/crd/">http://www.york.ac.uk/inst/crd/</a></td>
<td></td>
</tr>
<tr>
<td>CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care. Databases maintained by CRD include Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database</td>
<td></td>
</tr>
<tr>
<td>Scottish Intercollegiate Guidelines Network (SIGN)</td>
<td>N/A</td>
</tr>
<tr>
<td><a href="http://www.sign.ac.uk/">http://www.sign.ac.uk/</a></td>
<td></td>
</tr>
<tr>
<td>Scottish equivalent of NICE</td>
<td>N/A</td>
</tr>
<tr>
<td>Medical Services Advisory Committee (Australia)</td>
<td>N/A</td>
</tr>
<tr>
<td>The principal role of the Medical Services Advisory Committee</td>
<td></td>
</tr>
</tbody>
</table>
(MSAC) is to advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures.

Canadian Agency for Drugs and Technologies in Health (CADTH)
http://www.cadth.ca/index.php/en/home

The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada’s federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.

Appendix 2: Grading of evidence

- Ia: systematic review or meta-analysis of randomised controlled trials
- Ib: at least one randomised controlled trial
- IIa: at least one well-designed controlled study without randomisation
- IIb: at least one well-designed quasi-experimental study, such as a cohort study
- III: well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case–control studies and case series
- IV: expert committee reports, opinions and/or clinical experience of respected authorities

Appendix 3: References

1. Summary of Product Characteristics (SPC): Relvar Ellipta 92 micrograms/22micrograms inhalation powder (GSK)
   https://www.medicines.org.uk/emc/medicine/28496/SPC/Relvar-Ellipta+92+micrograms+22+micrograms+inhalation+powder%2c+pre-dispensed/


3. Clinical Knowledge Summaries (CKS): COPD:


5. British national Formulary February 2014
   http://www.medicinescomplete.com/mc/bnf/current/PHP34311-relvar-ellipta.htm?q=relvar&t=search&ss=text&p=1#PHP34311-relvar-ellipta

   https://www.medicines.org.uk/emc/medicine/11882/SPC/Symbicort+Turbohaler+400+12%2c+Inhalation+powder./

7. Summary of Product Characteristics (SPC) : Seretide Accuhaler 500
   https://www.medicines.org.uk/emc/medicine/2317/SPC/Seretide+100%2c+250%2c+500+Accuhaler/


11. Inhaled corticosteroids in COPD and the risk of serious pneumonia Samy Suissa, Valérie Patenaude, Francesco Lapi, Pierre Ernst downloaded from thorax.bmj.com on October 15, 2013 - Published by group.bmj.com
