LMMG New Medicine Assessment

Fluticasone furoate/vilanterol (Relvar Ellipta®▼) combination inhaler
Asthma in adults and children aged 12 and over

Recommendation:

Fluticasone furoate/vilanterol (Relvar Ellipta) combination inhaler is not recommended for use to treat adults and children aged 12 years and over with asthma. **BLACK**

Summary of supporting evidence:

- Relvar Ellipta is a once-daily dry-powder inhaler containing fluticasone furoate, an inhaled corticosteroid (ICS), and vilanterol, a long-acting beta-2 agonist (LABA). It is licensed for regular treatment of asthma in adults and adolescents aged 12 years and older who are not adequately controlled with ICS and 'as needed' inhaled short-acting beta-2 agonists (i.e. uncontrolled at step 2 of British asthma guidelines). It is available in two strengths, 92/22 micrograms and 184/22 micrograms.

- Although studies lasting up to 12 months have shown fluticasone furoate/vilanterol improves lung function compared with placebo in patients with asthma and reduces the rate of severe asthma exacerbations significantly more than fluticasone furoate alone, it is unclear how many patients were uncontrolled at step 2 of asthma guidelines as details of the ICS doses taken by patients before study entry were available in only one study and two studies enrolled patients on medium- or high-dose ICS.

- No adequately powered studies have compared the effects of Relvar Ellipta with other ICS/LABA combination inhalers or currently available ICS monotherapy on patient-orientated outcomes such as exacerbation rate. One study assessing effect on lung function showed there was no significant difference between Relvar Ellipta 92/22 micrograms once daily and fluticasone propionate/salmeterol 250/50 micrograms twice daily. There are limited published efficacy data available for the higher-strength inhaler, particularly in children aged 12 to 17 years.

- Relvar Ellipta is not easily amenable to use in accordance with British asthma guidelines because it is not available in a strength equivalent to a low dose of ICS. Guidelines recommend that patients uncontrolled on low-dose ICS should be started on a LABA and then the ICS dose titrated up if necessary. Once asthma is controlled, the ICS dose should be stepped down if possible. The lowest daily dose of ICS via Relvar Ellipta (92 micrograms fluticasone furoate) is equivalent to 500 micrograms fluticasone propionate, which is classed as medium-dose ICS. Because there is no strength lower than the 92/22 inhaler, patients will receive an excessive dose of ICS if prescribed Relvar Ellipta and once controlled cannot be stepped down to a dose equivalent to a low-dose of ICS. Also,

it is sometimes more practical to prescribe separate LABA and ICS inhalers – this flexibility is not possible with Relvar Ellipta as its constituents (fluticasone furoate and vilanterol) are not available alone in separate inhalers.

- Inadvertent dosing errors are considered a risk with Relvar Ellipta by some respiratory specialists because the manufacturer markets the 92/22 dose as equivalent to low- to medium-dose ICS. Also, patients may mistakenly use Relvar Ellipta on an 'as needed' basis because it has a grey and blue cover, and patients in the UK are educated that blue inhalers are relievers, and the name 'Relvar' sounds similar to 'reliever'. There is also a risk of medication error because of confusion over differing potencies and dosing frequencies with fluticasone furoate and fluticasone propionate.

- The most common adverse events with Relvar Ellipta in patients with asthma are headache, nasopharyngitis and upper respiratory tract infection. Incidence of pneumonia in studies was low with all strengths of Relvar Ellipta (less than 1.1%), and similar to that seen with fluticasone propionate/salmeterol 250/50 micrograms twice daily. There was a higher rate of cardiovascular adverse events in patients taking 184/22 micrograms once daily than in those on the lower dose due to a higher incidence of extrasystoles. Adrenal suppression is a potential risk although data on the effects of Relvar Ellipta on cortisol excretion are inconsistent.

- Relvar Ellipta is the only ICS/LABA combination inhaler licensed for once daily administration. However, there are no data showing patient compliance is better with Relvar Ellipta than with twice-daily ICS/LABA combination inhalers.

- Unlike other ICS/LABA combination inhalers available in the UK, Relvar Ellipta is not licensed for use in patients already controlled on an ICS plus LABA because no studies have adequately compared Relvar Ellipta with a licensed ICS/LABA combination inhaler.

- At current prices, Relvar Ellipta 92/22 micrograms inhaler is more expensive than low-dose ICS/LABA combination inhalers, and less expensive than other medium-dose ICS/LABA combination inhalers. Relvar Ellipta 184/22 micrograms inhaler is less expensive than other high-dose ICS/LABA combination inhalers.

Details of Review

Name of medicine (generic & brand name) **[manufacturer]:**

Fluticasone furoate and vilanterol (Relvar Ellipta®▼) combination inhaler [GlaxoSmithKline]

Strength(s) and form(s):

Two strengths are available:

- fluticasone furoate 92 micrograms plus vilanterol (as trifenatate) 22 micrograms (the delivered dose leaving the mouthpiece), and
- fluticasone furoate 184 micrograms plus vilanterol (as trifenatate) 22 micrograms (the delivered dose leaving the mouthpiece).

These are administered using the multi-dose, dry-powder Ellipta inhalation device. The inhaler is light grey with a blue mouthpiece.

Dose and administration:

One inhalation once a day.

The starting dose of 92/22 micrograms once daily should be considered for patients who require a low- to medium-dose of inhaled corticosteroid (ICS) in combination with a long-acting beta-2 agonist (LABA). If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms once daily. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

BNF therapeutic class / mode of action

3.2 Corticosteroids / 3.1.1.1 Selective $beta_2$ agonists

Licensed indication(s):

Regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (LABA and ICS) is appropriate, that is patients not adequately controlled with ICS and 'as needed' inhaled short-acting beta-2 agonists.

Course and cost:

The cost of 30 days' treatment is £27.80 for patients receiving 92/22 micrograms once daily, and £38.87 for patients receiving 184/22 micrograms once daily. Respective annual costs are £333.60 and £667.20.

Current standard of care/comparator therapies:

Four other ICS/LABA combination inhalers are licensed in the UK for treating asthma:

- Seretide – fluticasone propionate/salmeterol metered-dose inhaler and dry-powder inhaler
- Flutiform – fluticasone propionate/formoterol metered-dose inhaler
- Symbicort – budesonide/formoterol dry-powder inhaler
- Fostair – beclometasone/formoterol metered-dose inhaler.

Relevant NICE guidance:

- British Thoracic Society and Scottish Intercollegiate Guidelines Network (2012). British guideline on the management of asthma. SIGN guideline 101. (Accredited by NICE)
- National Institute for Health and Clinical Excellence (2008). Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over. NICE technology appraisal guidance 138.

Background and context

Asthma is a chronic disorder, characterised by reversible airflow obstruction and increased responsiveness of the airways to various stimuli [1]. Symptoms are variable, intermittent, usually worse at night, and include recurring episodes of wheezing, breathlessness, chest tightness and coughing. The age-standardised prevalence of treated asthma is 7% in men and 8% in women [1].

The British guideline on the management of asthma recommends low-dose ICS as first-line regular preventer therapy for adults and children aged five years and over, with a short-acting beta-2 agonist used as needed (step 2) [2]. If asthma is uncontrolled by low-dose ICS alone, patients should be given a trial of LABA in addition to low-dose ICS (step 3). Adding a LABA should be considered before going above a daily dose of 400 micrograms beclometasone dipropionate (BDP) given via a chlorofluorocarbon (CFC) containing inhaler (equivalent to 200 micrograms fluticasone propionate [FP]), and certainly before going above 800 micrograms BDP-CFC (400 micrograms FP) (step 4). NICE recommends that for patients who need an ICS plus LABA, combination devices are an option [1]. The decision to use a combination device or two agents in separate devices should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence. The least costly device suitable for the individual is recommended. Four ICS/LABA combination inhalers are licensed in the UK for treating asthma [3]:

- Flutiform – FP/formoterol metered-dose inhaler
- Fostair – beclometasone/formoterol metered-dose inhaler
- Seretide – FP/salmeterol (SM) dry-powder inhaler and metered-dose inhaler
- Symbicort – budesonide/formoterol dry-powder inhaler.

Relvar Ellipta is a once-daily dry-powder inhaler [4] containing fluticasone furoate (FF), a novel ICS with greater affinity for glucocorticoid receptors and longer retention in respiratory tissues than FP [5], and vilanterol (VI), a novel LABA which is a thousand times more selective for beta-2 receptors than beta-1 or beta-3 receptors [6]. It is licensed for regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination ICS/LABA inhaler is appropriate, that is patients not adequately controlled with ICS and 'as needed' inhaled short-acting beta-2

agonists [4]. Unlike other combination inhalers, it is not licensed for use in patients already controlled on an ICS plus LABA [7]. It is available in two strengths [4]:

- fluticasone furoate 92 micrograms plus vilanterol (as trifenatate) 22 micrograms, and
- fluticasone furoate 184 micrograms plus vilanterol (as trifenatate) 22 micrograms.

FF 92 micrograms once daily is approximately equivalent to FP 250 micrograms twice daily; FF 184 micrograms once daily is approximately equivalent to FP 500 micrograms twice daily [4]. This compares with approximate equivalent daily doses in British and international guidelines of [2,8]:

- *Low-dose ICS:* BDP-CFC 200-500; FP 100-250
- *Medium-dose ICS:* BDP-CFC >500-1,000; FP >250-500
- *High-dose ICS:* BDP-CFC >1,000-2,000; FP >500-1,000

Explanation of terms (used in the text and Table of trials):

[a]**AQLQ+12 (Asthma Quality of Life +12 Questionnaire):** contains 32 questions answered on a scale ranging from 1 (severe impairment) to 7 (no impairment). Overall AQLQ score is the mean of all 32 responses. The minimal clinically important difference is 0.5 [7].

[b]**ACQ (Asthma Control Questionnaire):** contains five questions about symptoms, one about rescue treatment and one about FEV_1. A score of 0.75 or less indicates asthma has been well controlled over the past week, and a score of 1.5 or higher indicates asthma has been inadequately controlled. The minimal clinically important difference is 0.5 [2].

[c]**Minimum FEV_1 reversibility:** reversibility of FEV_1 after short-acting beta-2 agonist inhalation should be at least 12% to 15%, and 200 mL to diagnose asthma [10].

[d]**Severe exacerbation:** deterioration of asthma needing use of systemic corticosteroids for at least three days, or inpatient hospitalisation, or hospital visit owing to asthma needing systemic corticosteroids [11].

[e]**Trough FEV_1:** Pre-bronchodilator, pre-dose FEV_1 [9].

Summary of evidence

Summary of efficacy data in proposed use:

Three pivotal studies and two supportive studies were submitted in support of a licence for Relvar Ellipta for treating patients with asthma when a combination of an ICS and LABA is appropriate (i.e. switch and step-up indications) [9]. The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) considered there were insufficient data to support switching as none of the studies had adequately compared Relvar Ellipta with a licensed ICS/LABA combination inhaler.

Four of the studies (studies one to four below) were randomised, double-blind studies involving patients aged 12 years and over with persistent asthma who had been using ICS/LABA or ICS alone for at least 12 weeks before study entry, with a stable dose for the previous four weeks [5,9,11,12]. In one study [11], patients had been on a low- to high-dose of ICS (200 micrograms to 1,000 micrograms FP daily or equivalent), in two studies [5,12], patients had been on a medium- to high-dose ICS (at least 500 micrograms FP daily) or ICS/LABA, and in the other study [9] they

had been on a low- to medium-dose ICS or ICS/LABA. Diagnosis of asthma was confirmed by each patient meeting a *minimum FEV_1 reversibility*[c] requirement. Each study had a two- to four-week run-in period during which LABAs were stopped; in studies one, two and four, the patients' current ICS was replaced with an equivalent dose of FP [5,9,12]. Asthma was confirmed as uncontrolled in all patients except in one study [11], as shown by presence of asthma symptoms and rescue use of salbutamol during run-in periods. Rescue use of salbutamol was allowed in all studies. All analyses were done on intention-to-treat (ITT) populations. To account for multiplicity in three studies which had a large number of arms (studies one, two and four), statistical analyses followed a step-down, closed-testing procedure in which analysis of secondary outcomes was only done if the difference between arms for the primary outcome was significant.

Pivotal studies (see also Table of trials)

Study one [9]

- This 12-week study (n=609) compared FF/VI 92/22 micrograms once daily with FF 92 micrograms once daily and placebo. The co-primary outcomes were mean change from baseline in *trough FEV_1*[e] and post-dose weighted mean 0–24 hour serial FEV_1. Compared with placebo, FF/VI and FF significantly increased mean *trough FEV_1*[e] from baseline (difference from placebo, 172mL; p<0.001, and 136mL; p=0.002, respectively). There was no significant difference between FF/VI and FF. A similar pattern was seen with weighted mean 0–24 hour serial FEV_1; mean difference between FF/VI and placebo was 302mL (p<0.001), between FF and placebo it was 186mL (p=0.003), and between FF/VI and FF it was 116mL (p=0.06). Statistical analysis of secondary outcomes was consequently not allowed, but differences between FF/VI and the other two groups in number of symptom-free and rescue-free days were minimal.

Study two [5] O'Byrne et al. 2013

- This 24-week study (n=586) compared FF/VI 184/22 micrograms once daily with FF 184 micrograms once daily and FP 500 micrograms twice daily. Baseline mean *trough FEV_1*[e] in this study did not indicate that patients with more severe disease were enrolled than in study one, which assessed the lower dose of FF. FF/VI produced a clinically and statistically significant improvement in the co-primary outcome of mean *trough FEV_1*[e] compared with FF and FP; difference in mean change from baseline was 193mL (95% CI 108 to 277; p<0.001) vs. FF, and 210mL (127 to 294; p<0.001) vs. FP. There was also a statistically significant improvement in the co-primary outcome of weighted mean 0–24 hour serial FEV_1 with FF/VI compared with FF and FP; difference in mean change from baseline was 136mL (1 to 270; p=0.048) vs. FF, and 206mL (73 to 339; p=0.003) vs. FP. For the secondary outcome measure of mean change from baseline in percentage of rescue-free days there was a statistically significant difference between FF/VI and FF but not between FF/VI and FP.

The CHMP noted the contradictory lung function results with the two doses of Relvar Ellipta in these studies: FF/VI 92/22 micrograms was not significantly more effective than FF alone at increasing mean *trough FEV_1*[e], but FF/VI 184/22 micrograms once daily was significantly more effective than both FF 184 micrograms once daily and FP 500 micrograms twice daily [9]. The manufacturer suggested this could be due to VI's effect not being maintained throughout the 24 hour period, and patients achieving near maximal bronchodilation with FF alone. The CHMP

concluded that the effects seen with both doses of Relvar Ellipta are similar to those obtained with other ICS/LABA combination inhalers.

Study three [11] Bateman et al. (2013)

- This variable duration study (mean 52.0 to 52.7 weeks) enrolled 2,019 patients with at least one asthma exacerbation that needed systemic corticosteroids or a hospital visit in the previous year. Patients were randomised to FF/VI 92/22 micrograms once daily or FF 92 micrograms once daily. The primary outcome was time to first *severe exacerbation*[d] (as judged by a central blinded committee), and the study was designed to finish after 330 *severe exacerbations*[d] had occurred. The adjusted risk of having a *severe exacerbation*[d] by 52 weeks was 12.8% in the FF/VI group compared with 15.9% in the FF group. This is an absolute reduction of 3.1%, and a relative reduction of 20%. The rate of *severe exacerbations*[d] per patient per year was significantly lower in the FF/VI group compared with the FF group (0.14 vs. 0.19, respectively; rate reduction 25% [5 to 40]; p=0.014). 154 (15%) patients in the FF/VI group had 200 *severe exacerbations*[d] and 186 (18%) patients in the FF group had 271 exacerbations.

The CHMP noted that the reduction in rate of *severe exacerbations*[d] is small but considered it to be clinically relevant. It also noted that, when data from adolescents were analysed separately, more patients receiving FF/VI had a *severe exacerbation*[d] compared with those receiving FF alone; however no conclusions can be drawn from this as there were so few adolescents.

Supportive studies

Study four [12] Woodcock et al. (2013)

- In this 24-week study, 806 patients previously on medium-dose ICS (31%) or ICS/LABA, were randomised to FF/VI 92/22 micrograms once daily or FP/salmeterol (SM) 250/50 micrograms twice a day. The primary efficacy outcome was change from baseline in post-dose weighted mean 0–24 hour serial FEV_1. The study was a superiority study designed to detect a difference of 80 mL between FF/VI and FP/SM – no statistically significant difference was found. Compliance with treatments was very high and no benefit from once-daily dosing compared with twice-daily dosing was seen.

Study five [9]

- This six-week study assessed the effects of both doses of Relvar Ellipta (92/22 and 184/22 microgram) compared with prednisolone 10mg and placebo on the hypothalamic-pituitary-adrenal axis system. It will not be discussed further in this review.

Summary of safety data:

The most common adverse events with Relvar Ellipta in patients with asthma are headache, nasopharyngitis and upper respiratory tract infection [9]. There was a higher rate of cardiovascular adverse events in patients taking a dose of 184/22 micrograms once daily than in the other study arms which was due to a higher incidence of extrasystoles [9]. Adrenal suppression is a potential risk although data on the effects of Relvar Ellipta on cortisol excretion are inconsistent.

Pneumonia

Evidence from a direct comparison of Relvar Ellipta 92/22 micrograms once daily with FP/SM 250/50 micrograms twice daily suggests no difference in risk of pneumonia [9]. In the 24-week comparative study, there were no cases of pneumonia in the Relvar Ellipta group vs. two in the FP/SM group [12]. In studies assessed by the CHMP, overall incidence of pneumonia was low (less than 1.1%) in all study groups but dose-related – in an analysis of 17 clinical studies involving Relvar Ellipta, the rate of community-acquired pneumonia with the 184/22 micrograms dose (18.4 subjects with an event per 1,000 patient-years) was higher than with the 92/22 microgram dose and very similar to that seen with FP/SM 250/50 micrograms twice daily (19.7 subjects per 1,000 patient-years; integrated analysis of 46 studies) [9].

Long-term data

In a published 52-week study, safety and tolerability of FF/VI 92/22 micrograms and 184/22 micrograms once daily was assessed in comparison with FP 500 micrograms twice daily in 503 adults and adolescents (16%) with asthma (mean age 39 years), most of whom were previously on medium-dose ICS [13]. Statistical analysis was performed on the ITT population but was not provided for most outcomes [7].

The incidence of any on-treatment adverse event was similar across all three groups (66% to 73%), as was the withdrawal rate due to an adverse event. Headache, upper respiratory tract infection and nasopharyngitis were most common, with similar rates in all groups. Oral/oropharyngeal candidiasis was more common with FF/VI at both strengths than with FP (6 to 7% compared with 3%). Most patients had normal or no change from baseline in 24 hour urine-free cortisol excretion at any assessment (70% to 81% across the groups). However, some patients would already have adrenal suppression due to previous use of high-dose ICS prior to randomisation, making detection of subtle changes in cortisol excretion less likely [14].

No clinically important changes were reported for non-fasting glucose, potassium levels, QT interval (corrected using Fridericia's formula) or ophthalmic assessments. Cardiovascular adverse events were more common with FF/VI 184/22 micrograms once daily (18%) than with a dose of 92/22 micrograms once daily (12%) or FP (10%), principally due to extrasystoles noted during Holter monitoring. Pulse rate, measured ten minutes after a dose rather than over 24 hours, was significantly increased from baseline in both FF/VI groups (by 3.4 beats per minute) compared with the FP group. Non-sustained ventricular tachycardia was seen in two patients from each FF/VI group and sustained supraventricular tachycardia was seen in three patients in the FF/VI 184/22 microgram group. During the study, three patients (1%) in the FF/VI 92/22 microgram group, six patients (3%) in the FF/VI 184/22 microgram group and three patients (3%) in the FP group had a severe asthma exacerbation.

Strengths and limitations of the evidence:

Population

- The studies enrolled patients with a wide range of asthma severity – but it is unclear how many were uncontrolled at step 2 of asthma guidelines [2,8]. Details of the ICS doses taken by patients before study entry were available in only one study [5] so it is not

possible to confirm that the study populations reflect patients in clinical practice. However, in two studies patients were enrolled if they were on medium- or high-dose ICS [5,12], and in another study, 60% of patients were uncontrolled on an ICS/LABA combination inhaler during the run-in period [11]. In these three studies, it is therefore possible that some patients were already at step 3 or 4 of asthma guidelines [5,11,12]. Caution is needed in extrapolating the results to people with less severe asthma. Relvar Ellipta is licensed for patients uncontrolled with ICS and 'as needed' inhaled short-acting beta-2 agonists, but it is not clear that data from these studies support its use at step 2 of asthma guidelines.

- In all four studies, asthma was confirmed as uncontrolled at baseline in all patients by presence of asthma symptoms and use of rescue salbutamol, which patients recorded during the run-in periods [5,9,11,12].
- Only 23 adolescents (4% of 586) were involved in the study assessing the higher dose of FF/VI [9].

Intervention

- In the 52-week study, the authors noted that some patients would have received a step-up in ICS dose after randomisation [13]. This also possibly occurred in the other studies that enrolled patients previously on low-dose ICS (studies one and three). Management of patients in this way does not reflect asthma guidelines, which recommend adding a LABA before increasing ICS dose [2,8].
- There are limited efficacy and safety data available for the higher strength inhaler. Only one study has assessed the efficacy of FF/VI 184/22 micrograms, and the primary outcome was not patient-orientated [5].
- The duration of all studies, except one (study one), is sufficient to assess the efficacy of Relvar Ellipta. The minimum duration recommended when assessing efficacy of controller medicines for asthma is six months, and a minimum of 12 months is advised if measuring exacerbation rates [10].

Comparator

- None of the studies compared the effect of Relvar Ellipta with other licensed ICS/LABA combination inhalers or currently available ICS monotherapy on patient-orientated outcomes. Instead, Relvar was compared with FF alone which is not licensed for use as ICS monotherapy, and no licence application for monotherapy has been submitted [9].
- In the 52-week study designed to evaluate safety and tolerability of Relvar Ellipta the comparator was FP 500 micrograms twice daily [13]. This high dose is rarely used in the UK, and almost never without concomitant therapy such as a LABA [15].

Outcomes

- The outcomes assessed in the studies included disease-orientated measures (*trough* FEV_1[e]) and patient-orientated measures (symptoms and exacerbations). Both are appropriate and recommended for studies of asthma medicines by the EMA [10].

Summary of evidence on cost effectiveness:

None published yet.

The Scottish Medicines Consortium plans to issue advice on Relvar Ellipta for treatment of patients with asthma on 09 June 2014, and their review will include an analysis of comparative health economic evidence [16].

Prescribing and risk management issues:

- Inadvertent dosing errors are considered a risk with Relvar Ellipta by some respiratory specialists because the manufacturer markets the 92/22 dose as equivalent to low- to medium-dose ICS [17]. They also do not consider Relvar Ellipta appropriate for patients at step 3 of British Asthma Guidelines [2]. FF 92 micrograms once daily is considered equivalent to FP 250 micrograms twice daily [3], which is classed in asthma guidelines as a medium-dose ICS (not low-dose) [2,8]. Because there is no strength lower than the 92/22 inhaler, some patients will receive an excessive dose of ICS if prescribed Relvar Ellipta.
- Relvar Ellipta is not easily amenable to use in accordance with British asthma guidelines because it is not available in a strength equivalent to a low dose of ICS. Guidelines recommend that patients uncontrolled on low-dose ICS should be started on a LABA and then the dose of ICS titrated up if necessary [2,8]. Once asthma is controlled, a combination inhaler should be considered as this ensures patients do not use a LABA without an ICS [2,8]. It is also recommended that therapy is stepped down if possible, with the dose of ICS reduced by approximately 25% to 50% every three months [2]. Because there is no strength lower than the 92/22 inhaler, some patients will receive an excessive dose of ICS if prescribed Relvar Ellipta or will have to switch to a different ICS in order to step down. It is sometimes more practical to prescribe separate LABA and ICS inhalers – this flexibility is not possible with Relvar Ellipta as its constituents (FF and VI) are not available alone in separate inhalers.
- There is a risk of medication error because of confusion over differing potencies and dosing frequencies with FF and FP [7].
- There is a risk that patients may mistakenly use Relvar Ellipta on an ‘as needed’ basis because it has a grey and blue cover, and patients in the UK are educated that blue inhalers are relievers [17]. In addition, the name ‘Relvar’ sounds similar to ‘reliever’. The manufacturer has argued that no safety concerns were raised about the colour or name of Relvar Ellipta during clinical trials [18]. They consider that patients are unlikely to confuse Relvar Ellipta with a reliever inhaler because it is a dry-powder inhaler and most relievers are metered-dose inhalers. Patients will have to be given clear advice that Relvar Ellipta must be used regularly and not ‘as needed’. UK Medicines Information has produced a safety assessment report for Relvar Ellipta listing recommendations for the manufacturer, NHS organisations, prescribers and patients [19].
- The maximum dose of Relvar Ellipta in patients with moderate or severe liver impairment is 99/22 micrograms once daily [4].
- Clinically significant drug interactions are unlikely but use of Relvar Ellipta should be avoided in patients taking strong CYP3A4 inhibitors which may increase systemic exposure to FF and VI [4].
- Patients should rinse their mouth without swallowing, after using Relvar Ellipta [4].

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per 30 days (ex VAT)
Low-dose inhaled corticosteroid **Equivalent to beclometasone dipropionate CFC* equivalent: 200 to 500 micrograms daily**			
Relvar Ellipta dry-powder inhaler	Not available	-	-
Flutiform metered-dose inhaler	50/5 micrograms 2 puffs twice a day	£18.00 120-dose unit	£18.00
Fostair metered-dose inhaler**	100/6 micrograms 1 puff twice a day	£29.32 120-dose unit	£14.66
Seretide Accuhaler	100/50 micrograms 1 inhalation twice a day	£18.00 60-dose unit	£18.00
Symbicort dry-powder inhaler	200/6 micrograms 1 inhalation twice a day	£38.00 120-dose unit	£19.00
Medium-dose inhaled corticosteroid **Equivalent to beclometasone dipropionate CFC* equivalent: >500 to 1,000 micrograms daily**			
Relvar Ellipta dry-powder inhaler	92/22 micrograms 1 inhalation once a day	£27.80 30-dose unit	£27.80
Flutiform metered-dose inhaler	125/5 micrograms 2 puffs twice a day	£29.26 120-dose unit	£29.26
Fostair metered-dose inhaler**	100/6 micrograms 2 puffs twice a day	£29.32 120-dose unit	£29.32
Seretide Accuhaler	250/50 micrograms 1 inhalation twice a day	£35.00 60-dose unit	£35.00
Symbicort dry-powder inhaler	400/12 micrograms 1 inhalation twice a day	£38.00 60-dose unit	£38.00
High-dose inhaled corticosteroid **Equivalent to beclometasone dipropionate CFC* equivalent: >1,000 to 2000 micrograms daily**			
Relvar Ellipta dry-powder inhaler	184/22 micrograms 1 inhalation once a day	£38.87 30-dose unit	£38.87
Flutiform metered-dose inhaler	250/10 micrograms 2 puffs twice a day	£45.56 120-dose unit	£45.56
Fostair metered-dose inhaler**	Not available	-	-
Seretide Accuhaler	500/50 1 inhalation twice a day	£40.92 60-dose unit	£40.92
Symbicort dry-powder inhaler	400/12 micrograms 2 inhalations twice a day	£38.00 60-dose unit	£76.00
Costs based on MIMS list prices March 2014.			
* Beclometasone dipropionate (BDP)-chlorofluorocarbon (CFC) inhalers are no longer available. **100 micrograms of beclometasone in Fostair is approximately equivalent to 200 micrograms of BDP-CFC [2]. The ICS/LABA combination inhalers listed above differ in their licensing status and recommended dosing for use in children and young people aged under 18 years.			

Associated additional costs or available discounts:

None.

Productivity, service delivery, implementation:

Not applicable.

Anticipated patient numbers and net budget impact:

There are an estimated 5.2 million people with asthma in the UK [1]. Lifetime prevalence of diagnosed asthma is 16% in women and 13% in men. 1998 figures from the General Practice Research Database, which sampled 211 general practices in England and Wales, estimated the age-standardised prevalence of treated asthma to be 7% in men and 8% in women.

The manufacturers of Relvar Ellipta estimate that there are currently 935,000 people with asthma who are prescribed ICS monotherapy (plus as-needed short-acting beta-2 agonists), i.e. at step 2 of asthma guidelines [7]. They estimate that 40% of these people have poorly controlled asthma. Therefore, approximately 374,000 people may be eligible for combined ICS/LABA treatment, i.e. step 3 of asthma guidelines.

Assuming there are 600 patients per 100,000 population with uncontrolled asthma eligible for ICS/LABA combination therapy, the annual cost of Relvar Ellipta 92/22 micrograms once daily per 100,000 people is about £200,000.

Innovation, need, equity:

Not applicable.

References

1. National Institute for Health and Clinical Excellence. Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over. NICE technology appraisal guidance 138; 2008. Accessed 03 March 2014 at: http://guidance.nice.org.uk/TA138.
2. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. SIGN guideline 101; 2012. Accessed 03 March 2014 at: www.sign.ac.uk/guidelines/fulltext/101/index.html.
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Table of trials: Summary of pivotal Relvar Ellipta RCTs relevant to use in asthma

Ref	Trial design	Trial population and treatment	Efficacy results	FF/VI 92/22	FF 92	Placebo	p value$	Grading of evidence (SORT criteria)*
9	12-week, randomised, multicentre, double-blind, parallel-group study. The study consisted of: • A 4-week run-in period during which patients on ICS/LABA were switched to same-dose ICS alone, • A 12-week treatment period with patients randomised (1:1:1) to FF/VI 92/22, or FF 92, or placebo, all once daily. **Inclusion criteria:** • Patients aged ≥12 years with uncontrolled asthma. • Use of ICS or ICS/LABA for ≥12 weeks with stable low- to medium-dose ICS (FP 200-500 daily) or low-dose ICS/LABA (FP/SM 200/100 daily) for ≥4 weeks. • Best pre-bronchodilator FEV_1 40% to 90% of predicted normal. • FEV_1 reversibility after salbutamol inhalation of ≥12% and ≥200mL. **Exclusion criteria:** • Life-threatening asthma in past 10 years. • Respiratory infection not resolved within 4 weeks of the study which led to a change in asthma management, • Concurrent respiratory disease. • Asthma exacerbation requiring hospitalisation or A&E visit in past 6 months, or oral corticosteroids in past 12 weeks. • Visual evidence of oral candidiasis.	610 patients randomised; 515 (85%) completed the study. ITT population, n=609. • 58% women. • 84% white. • Mean age 40 years. • 13% aged 12 to 17 years. • Mean duration of asthma 11-13 years. • % of patients previously on ICS/LABA not stated. • Mean daily dose of FF/VI and FF not stated. **Baseline data (FF/VI; FF; placebo):** • Trough FEV_1 (mL) 2,334; 2,290; 2,344	**Co-primary outcomes**					
			Trough FEV_1 (mL)					
			Change from baseline to week 12, LS mean (± SE)	368 (30.4)	332 (30.2)	196 (31.0)	-	
			Treatment difference vs. FF 92, mean [95% CI]	36 [-48-120]	-	-	=0.405*	
			Treatment difference vs. placebo, mean [95% CI]	172 [87-258]	136 [51-222]	-	<0.001	
			0-24 hour $wmFEV_1$ (mL)					
			Change from baseline to week 12, LS mean (± SE)	513 (43.0)	398 (43.2)	212 (45.6)	-	
			Treatment difference vs. FF 92, mean [95% CI]	116 [-5-236]	-	-	=0.06*	
			Treatment difference vs. placebo, mean [95% CI]	302 [178-426]	-	-	<0.001	
			Secondary outcomes (powered)					
			Rescue-free 24 hour periods (%)					3
			Change from baseline to week 12, LS mean (± SE)	37.1 (2.3)	26.5 (2.3)	17.8 (2.3)		
			Treatment difference vs. FF 92, mean [95% CI]	10.6 [4.3-16.8]	-	-		
			Treatment difference vs. placebo, mean [95% CI]	19.3 [13.0-25.6]	-	-		
			Symptom-free 24 hour periods (%)					
			Change from baseline to week 12, LS mean (± SE)	32.5 (2.1)	20.4 (2.1)	14.6 (2.2)		
			Treatment difference vs. FF 92, mean [95% CI]	12.1 [6.2-18.1]	-	-		
			Treatment difference vs. placebo, mean [95% CI]	18.0 [12.0-23.9]	-	-		
			AQLQ+12[a] total score					
			Change from baseline to week 12, LS mean (± SE)	0.91 (0.06)	0.76 (0.06)	0.61 (0.06)		
			Treatment difference vs. FF 92, mean [95% CI]	0.15 [-0.01-0.3]	-	-		
			Treatment difference vs. placebo, mean [95% CI]	0.30 [0.13-0.46]	-	-		

Abbreviations: AQLQ+12 Asthma Quality of Life +12 Questionnaire; CI confidence interval; FF/VI fluticasone furoate/vilanterol; FP fluticasone propionate; ICS inhaled corticosteroid; ITT intention-to-treat; LABA long-acting beta-2 receptor agonist; LS least squares; SM salmeterol; SE standard error; $wmFEV_1$ weighted mean forced expiratory volume in 1 second ; ***Note 1***: All doses in micrograms; ***Note 2****: Failure to achieve p<0.05 meant significance could not be inferred from further analyses; ***Note 3***[$]: p value is for comparisons with FF/VI.

Ref	Trial design	Trial population and treatment	Efficacy results	FF/VI 184/22	FF 184	FP 1,000	p value$	Grading of evidence (SORT criteria)*
5,9	24-week, randomised, multicentre (63), double-blind, double-dummy, parallel-group study. The study consisted of: • A 4-week run-in period during which patients on ICS/LABA were switched to same-dose ICS alone, • A 24-week treatment period with patients randomised (1:1:1) to FF/VI 184/22 once daily plus placebo, or FF 184 once daily plus placebo, or FP 500 twice daily plus placebo. **Inclusion criteria:** • Patients aged ≥12 years with asthma. • Use of ICS or ICS/LABA for ≥12 weeks with stable high-dose ICS (FP 1,000 daily) or medium-dose ICS/LABA (FP/SM 500/100 daily) for ≥4 weeks. • Evening pre-bronchodilator FEV_1 40% to 90% of predicted normal. • FEV_1 reversibility after salbutamol inhalation of ≥12% and ≥200mL. **Exclusion criteria:** • As in the study above.	587 patients randomised; 476 (81%) completed the study. ITT population, n=586. • 59% women. • 84% white. • Mean age 46 years. • 4% aged 12 to 17 years. • Mean duration of asthma 15.5 years. • 76% previously on ICS/LABA. • Mean daily dose of FP in run-in 551 to 583mcg. **Baseline data (FF/VI; FF; FP):** • Trough FEV_1 (mL) 2,129; 2,190; 2,138 • Rescue-free 24hour periods (%) 7.6; 7.8; 6.3 • Symptom-free 24hour periods (%) 5.1; 4.7; 2.7	**Co-primary outcomes**					
			Trough FEV_1 (mL)					
			Change from baseline to week 24, LS mean (± SE)	394 (30.2)	201 (30.3)	183 (30.0)	-	
			Treatment difference vs. FF 184, mean [95% CI]	193 [108-277]	-	-	<0.001	
			Treatment difference vs. FP 1,000, mean [95% CI]	210 [127-294]	18 [-66-102]	-	<0.001	
			0-24 hour $wmFEV_1$ (mL)					
			Change from baseline to week 24, LS mean (± SE)	464 (47.0)	328 (49.3)	258 (48.3)	-	
			Treatment difference vs. FF 184, mean [95% CI]	136 [1-270]	-	-	=0.048	
			Treatment difference vs. FP 1,000, mean [95% CI]	206 [73-339]	-	-	=0.003	
			Secondary outcomes (powered)					
			Rescue-free 24 hour periods (%)					3
			Change from baseline to week 24, LS mean (± SE)	38.2 (2.42)	26.6 (2.5)	31.9 (2.5)	-	
			Treatment difference vs. FF 184, mean [95% CI]	11.7 [4.9-18.4]	-	-	<0.001	
			Treatment difference vs. FP 1,000, mean [95% CI]	6.3 [-0.4-13.1]	-	-	=0.067	
			Symptom-free 24 hour periods (%)					
			Change from baseline to week 24, LS mean (± SE)	29.3 (2.29)	21.0 (2.3)	24.5 (2.3)	-	
			Treatment difference vs. FF 184, mean [95% CI]	8.4 [2.0-14.8]	-	-	=0.01	
			Treatment difference vs. FP 1,000, mean [95% CI]	4.9 [-1.6-11.3]	-	-	=0.137	
			AQLQ+12[a] total score					
			Change from baseline to week 24, LS mean (± SE)	0.93 (0.065)	0.88 (0.07)	0.90 (0.07)	-	
			Treatment difference vs. FF 184, mean [95% CI]	0.05 [-0.14-0.24]	-	-	=0.587*	
			Treatment difference vs. FP 1,000, mean [95% CI]	0.03 [-0.16-0.21]	-	-	=0.786	

Abbreviations: AQLQ+12 Asthma Quality of Life +12 Questionnaire; CI confidence intervals; FF/VI fluticasone furoate/vilanterol; FP fluticasone propionate; ICS inhaled corticosteroid; ITT intention-to-treat; LABA long-acting beta-2 receptor agonist; LS least squares; SM salmeterol; SE standard error; $wmFEV_1$ weighted mean forced expiratory volume in 1 second ; ***Note 1***: All doses in micrograms; ***Note 2****: Failure to achieve p<0.05 meant significance could not be inferred from further analyses; ***Note 3$***: p value is for comparisons with FF/VI; superiority for FF/VI vs. FF and non-inferiority for FF/VI vs. FP.

Ref	Trial design	Trial population and treatment	Efficacy results				Grading of evidence (SORT criteria)*
				FF/VI 92/22	FF 92	p value	
9,11	Variable duration (6-18 months), randomised, multicentre (167), double-blind, parallel-group study. The study consisted of: • A 2-week run-in period during which baseline checks were done, • A minimum 24-week treatment period with patients randomised (1:1) to FF/VI 92/22 once daily, or FF 92 once daily. **Inclusion criteria:** • Patients aged ≥12 years with uncontrolled asthma. • Use of ICS or ICS/LABA for ≥12 weeks with stable low- to high-dose ICS (FP 200-1,000 daily) or low- to medium-dose ICS/LABA (FP/SM 200/100-500/100 daily) for ≥4 weeks. • At least one asthma exacerbation in the past year requiring hospitalisation or A&E visit or systemic corticosteroids (but not during run-in). • Best pre-bronchodilator FEV_1 50% to 90% of predicted normal. • FEV_1 reversibility after salbutamol inhalation of ≥12% and ≥200mL. **Exclusion criteria:** • Life-threatening asthma in past 5 years. • Concurrent respiratory disease. • Visual evidence of oral candidiasis.	2,020 patients randomised; 1,748 (87%) completed the study. ITT population, n=2,019. • 67% women. • 73% white. • Mean age 42 years. • 14% aged 12 to 17 years. • Mean duration of asthma 15.5 years. • 60% previously on ICS/LABA. • 43% had a history of >1 exacerbation in the past year. • Mean daily dose of FF/VI and FF not stated. **Baseline data (FF/VI; FF):** • Trough FEV_1 (mL) 2,216; 2,193 • Mean ACQ-7[b] score 2.169; 2.154 • Proportion with well-controlled asthma (ACQ-7[b] score≤0.75) 2%; 2% • Nil re: symptom- or rescue-free days.	**Primary outcome**				1
			Time to first severe asthma exacerbation Adjusted probability of a severe exacerbation by 52 weeks, % [95% confidence interval]	12.8 [10.7-14.9]	15.9 [13.5-18.2]	=0.036	
			Hazard ratio [95% confidence interval]	0.795 [0.642-0.985]			
			Secondary outcomes				
			Rate of severe asthma exacerbations per patient per year	0.14	0.19	=0.014	
			Rate reduction, % [95% confidence interval]	25 [5-40]			
			Patients who had one or more on-treatment severe asthma exacerbations, number (%)	154 (15%)	186 (18%)	NR	
			Patients with well-controlled asthma (ACQ[b] score ≤0.75) at end of the trial, %	44	36	<0.001	
			Odds ratio [95% confidence interval]	1.5 [1.23-1.82]			
			Safety outcomes				
			Patients reporting serious adverse events, %	4.1	2.9	NR	
			Adverse events leading to discontinuation or withdrawal, %	1.6	1.9	NR	
			Asthma-related serious adverse events, %	1	0.7	NR	

Abbreviations: ACQ Asthma Control Questionnaire; FEV_1 forced expiratory volume in 1 second ; FF/VI fluticasone furoate/vilanterol; FP fluticasone propionate; ICS inhaled corticosteroid; ITT intention-to-treat; LABA long-acting beta-2 receptor agonist; SM salmeterol; ***Note 1***: All doses in micrograms.

Grading of evidence (based on SORT criteria):

Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies
Level 3	Disease-oriented evidence or evidence from: • consensus guidelines • expert opinion • case series

Midlands and Lancashire Commissioning Support Unit,
Jubilee House, Lancashire Business Park, Leyland, PR26 6TR
Tel: 01772 644 400 | www.staffordshirelancashirecsu.nhs.uk