Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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fluticasone furoate / vilanterol 92/22, 184/22 micrograms inhalation powder (Relvar Ellipta®)

SMC No. (966/14)

GlaxoSmithKline UK

09 May 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

fluticasone furoate / vilanterol (Relvar Ellipta®) is accepted for use within NHS Scotland.

Indication under review: the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta$_2$-agonists.

There was no statistically significant difference between fluticasone furoate/vilanterol 92/22 micrograms daily and another inhaled corticosteroid/long acting beta$_2$-agonist combination (ICS/LABA) inhaler for 0 to 24 hour serial weighted mean forced expiratory volume in one second, at 24 weeks.

Some alternative ICS/LABA combination inhalers are available at a lower daily cost.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

The regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta$_2$-agonists.

Dosing Information

One inhalation of fluticasone furoate/vilanterol 92/22 or 184/22 micrograms once daily.

A starting dose of fluticasone furoate/vilanterol 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta$_2$-agonist. If patients are inadequately controlled on fluticasone furoate/vilanterol 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control.

Fluticasone furoate/vilanterol 184/22 micrograms should be considered for adults and adolescents 12 years and over who require a higher dose of inhaled corticosteroid in combination with a long-acting beta$_2$-agonist.

Product availability date

8 January 2014

Summary of evidence on comparative efficacy

Fluticasone furoate/vilanterol is one of a number of inhaled corticosteroid (ICS)/long acting beta$_2$-agonist (LABA) combination inhalers licensed for the treatment of asthma. British guidance recommends adding an inhaled LABA in adult patients taking ICS at doses of 200 to 800 micrograms of beclometasone dipropionate per day (or equivalent) who are not adequately controlled on ICS alone.[1]

Evidence to support efficacy of fluticasone furoate/vilanterol for the treatment of asthma come from three, randomised, 12 to 24 week studies and one longer-term study where patients were treated for up to 76 weeks.[2-5] All studies recruited patients aged ≥12 years with asthma (reversibility of forced expiratory volume in one second [FEV$_1$] of at least 12% and 200mL) and a pre-bronchodilator FEV$_1$ of 40% (or 50%) to 85% (or 90%) predicted normal. The studies included a four-week run-in period where patients were treated with a stable dose of ICS and a short acting beta$_2$-agonist (SABA) when required.

Study HZA113091 was a double-blind, comparative, 24-week study, which randomised 806 patients to treatment with fluticasone furoate/vilanterol 92/22 micrograms once daily (n=403) or fluticasone propionate/salmeterol 250/50 micrograms twice daily (n=403) for 24 weeks.[2-4] Patients were required to be taking ICS for ≥12 weeks, with a stable medium dose of ICS (fluticasone propionate 250 micrograms twice daily or equivalent) for ≥4 weeks. The primary end-point was change from baseline in 0 to 24 hour serial weighted mean (wm) FEV$_1$ after 24 weeks of treatment. Superiority of fluticasone furoate/vilanterol versus fluticasone

propionate/salmeterol was not shown. For all secondary end-points there were also no significant differences between treatments. See Table 1 for results of primary and some secondary endpoints

Table 1: results of primary and some secondary endpoints for study HZA113091

	Fluticasone furoate vilanterol 92/22 micrograms daily (n=403)	**Fluticasone propionate/salmeterol 250/50 micrograms twice daily (n=403)**	**Difference/HR/OR**
Primary endpoint: 0 to 24 hour wm serial FEV_1 at week 24			
LS mean change in 0 to 24 hour wm serial FEV_1 at week 24	0.341L	0.377L	Difference: -0.037L (95% CI -0.088L to 0.015L, p=0.162
Secondary endpoints			
Time to onset of bronchodilator effect	61 minutes	59 minutes	HR: 0.95 (95% CI 0.80 to 1.13)
LS mean change in 0 to 4 hour serial wm FEV_1 post-dose at week 24 (±SE)	0.360L ±0.0184	0.394L ±0.0186	Difference: -0.034 (95% CI -0.086 to 0.017)
% obtaining ≥12% and ≥200 mL increase from baseline in FEV_1 at 24 hours at week 24	51%	50%	OR: 1.09 (95% CI 0.80 to 1.48)

LS=least square, HR=hazard ratio, OR=odds ratio, CI=confidence interval, wm=weighted mean

Quality of life was measured using the Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ +12), the Asthma Control Test (ACT) and the European Quality of Life 5 Dimensions questionnaire (EQ-5D). There were improvements from baseline in the AQLQ+12, ACT, and EQ-5D asthma health outcomes assessments for both groups, with no difference between treatments.

Two double-blind studies (HZA106827 and HZA106829) recruited patients who had been receiving an ICS, with or without LABA, for at least 12 weeks and on a stable dose for at least 4 weeks prior to screening.[3,4] Study HZA106827 required patients to be either maintained on a stable low to medium dose of an ICS (fluticasone propionate 100 to 250 micrograms twice daily or equivalent) or on a stable dose of an ICS/LABA low-dose combination (e.g. fluticasone propionate/salmeterol 100/50 micrograms twice daily). In study HZA106829, patients were required to be on fluticasone propionate 500 micrograms twice daily or equivalent, or on a stable dose of an ICS/LABA mid-dose combination (e.g. fluticasone propionate/salmeterol 250/50 micrograms twice daily). Eligible patients were randomised (stratified by use of LABA) to treatment with fluticasone furoate/vilanterol 92/22 micrograms daily (n=201), fluticasone furoate 92 micrograms daily (n=205) or placebo (n=203) for 12 weeks (in study HZA106827) and fluticasone furoate/vilanterol 184/22 micrograms daily (n=197), fluticasone furoate 184 micrograms daily (n=194) or fluticasone propionate 500 micrograms twice daily (n=195) for 24 weeks (in study HZA106829). The co-primary outcomes were the mean change from baseline in trough FEV_1 in all patients and 0 to 24 hours wm serial FEV_1 in a subset of patients who

performed serial FEV_1 measurements at week 12 (HZA106827) or week 24 (HZA106829). Results are presented in Table 2, below.

Table 2: results of co- primary outcomes for studies HZA106827 and HZA106829

Study HZA106827			
	Fluticasone furoate/ vilanterol 92/22 micrograms	**Fluticasone furoate 92 micrograms**	**Placebo**
Trough FEV_1			
LS mean trough FEV_1 at week 12	2.70L	2.66L	2.52L
LS mean change ±SE	0.37 ±0.03	0.33 ±0.03	0.20 ±0.03
Difference versus placebo	0.172L (95% CI 0.087 to 0.258, p<0.001)	-	-
Difference versus fluticasone furoate	0.036L (95% CI -0.048 to 0.120, p=0.405)	-	-
0 to 24 hour serial FEV_1			
n	108	106	95
0 to 24 hour wm serial FEV_1 at week 12	2.84L	2.73L	2.54L
LS mean change ±SE	0.51L ±0.04	0.40L ±0.04	0.21L ±0.05
Difference versus placebo	0.302L (95% CI 0.178 to 0.426, p<0.001)		
Difference versus fluticasone furoate	0.116L (95% CI -0.005 to 0.236, p=0.06)		
Study HZA106829			
	Fluticasone furoate/vilanterol 184/22 micrograms	**Fluticasone furoate 184 micrograms**	**Fluticasone propionate 500 micrograms twice daily**
Trough FEV_1			
LS mean trough FEV_1 at week 24	2.55L	2.36L	2.34L
LS mean change ±SE	0.39L ±0.03	0.20L ±0.03	0.18L ±0.03
Difference versus fluticasone furoate	0.193L (95% CI 0.108 to 0.277, p<0.001)		
Difference versus fluticasone propionate	0.210L (95% CI 0.127 to 0.294, p<0.001)		
0 to 24 hour serial FEV_1			
n	89	83	86
0 to 24 hour wm serial FEV_1 at week 24	2.67L	2.53L	2.46L

LS mean change ±SE	0.46L ±0.05	0.33L ±0.05	0.26L ±0.05
Difference versus fluticasone furoate	0.136L (95% CI 0.001 to 0.270, p=0.048)	-	-
Difference versus fluticasone propionate	0.206L (95% CI 0.073 to 0.339, p=0.003)	-	-

LS=least square, SE=standard error, CI=confidence interval, wm=weighted mean

HZA106837 was a phase III, long-term, double-blind, comparative study in patients with asthma for at least one year and receiving fluticasone propionate 200 to 1,000 micrograms/day (or equivalent) or fluticasone propionate/salmeterol 200/100 to 500/100 micrograms/day (or equivalent) for at least 12 weeks prior to screening.[3-5] After the run-in period patients were randomised to fluticasone furoate/vilanterol 92/22 micrograms daily (n=1,009) or fluticasone furoate 92 micrograms daily (n=1,010) for 24 to 76 weeks. The primary end-point was time to first severe asthma exacerbation defined as deterioration of asthma requiring the use of systemic corticosteroids (oral or injection) for at least three days or an inpatient hospitalisation or emergency department visit due to asthma that required systemic corticosteroids. Courses of corticosteroids separated by one week or more were treated as separate severe asthma exacerbations. Patients were withdrawn from the study if they experienced three severe asthma exacerbations in any six-month period or four severe asthma exacerbations during the double-blind treatment period.

The adjusted probability for one or more asthma exacerbations by 52 weeks was 13% (95% CI 11% to 15%) for fluticasone furoate/vilanterol and 16% (95% CI 14% to 18%) for fluticasone furoate; hazard ratio (adjusted for interim analysis) 0.79, 95% CI 0.64 to 0.98, p=0.036.[7] Superiority of fluticasone furoate/vilanterol 92/22 micrograms versus fluticasone furoate 92 micrograms was shown. Analysis in the PP population gave similar results. The rate of severe asthma exacerbations per patient per year was 0.14 in the fluticasone furoate/vilanterol group and 0.19 in the fluticasone furoate group. The ratio of the exacerbation rate from the negative binomial analysis for fluticasone furoate/vilanterol versus fluticasone furoate was 0.75 (95% CI 0.60 to 0.94), p=0.014.[5]

Summary of evidence on comparative safety

In study HZA113091, any adverse event (AE) was reported in 53% (213/403) of fluticasone furoate/vilanterol treated patients and 49% (198/403) of fluticasone propionate/salmeterol treated patients and there were 19 versus 15 treatment related AE in the respective groups. Adverse events occurring in ≥3% of either group included: nasopharyngitis (11% [46/403] versus 11% [46/403]), headache (8.4% [34/403] versus 10% [41/403]), upper respiratory tract infection (6.4% [26/403] versus 4.0% [16/403]), cough (3.7% [15/403] versus 3.2% [13/403]), sinusitis (3.0% [12/403] versus 1.7% [7/403]) and pyrexia (3.2% [13/403] versus 1.2% [5/403]). There were four serious adverse events (SAE) in the fluticasone furoate/vilanterol group versus six in the fluticasone propionate/salmeterol group, with none considered related to treatment.[2]

A 52-week safety study (HZA106839) was conducted in patients with asthma on regular ICS (500 to 1,000 micrograms/day or equivalent).[6] Patients were randomised to fluticasone furoate/vilanterol 92/22 micrograms daily (n=201), fluticasone furoate/vilanterol 184/22 micrograms daily (n=202), or fluticasone propionate 500 micrograms twice daily (n=100).

Treatment related AE occurred in 13% (27/201), 14% (29/202) and 14% (14/100) of patients respectively. Treatment related AE included; oral/oropharyngeal candidiasis (5.5% [11/201] versus 4.5% [9/202] versus 2.0% [2/100]), dysphonia (3.0% [6/201] versus 1.0% [2/202] versus none]), extrasystoles (<1% [1/201] versus 2.5% [5/202] versus none), and cough (1.5% [3/201] versus none versus 2.0% [2/100]). AE leading to study withdrawal occurred in five, three and six patients in the fluticasone furoate/vilanterol 92/22, fluticasone furoate/vilanterol 184/22 and fluticasone propionate groups respectively. The proportion of on-treatment SAE was 1.5% (3/201), <1% (1/202) and 7.0% (7/100) for the fluticasone furoate/vilanterol 92/22, fluticasone furoate/vilanterol 184/22 and fluticasone propionate groups respectively. One SAE was considered possibly treatment related: worsening hepatitis B in the fluticasone propionate group. No deaths were reported in the study.

The EMA commented on the higher incidence of cardiovascular events seen in the fluticasone furoate/vilanterol 184/22 micrograms group related to a higher incidence of extrasystoles. They noted that cardiovascular events, and particularly tachycardia, are known adverse events related to LABAs.[3]

Summary of clinical effectiveness issues

The British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidance recommends, at step 3 of their treatment algorithm, adding an inhaled LABA in adult patients taking ICS at doses of 200 to 800 micrograms beclometasone dipropionate/day who are not adequately controlled on ICS alone.[1] Combination inhalers are recommended to guarantee that the LABA is taken with the ICS and to improve inhaler adherence.

There are a number of comparator ICS/LABA combination inhalers available which are licensed for the regular treatment of asthma where use of a combination product (LABA and ICS) is appropriate, in patients not adequately controlled with ICS and 'as needed' inhaled SABA or in patients already adequately controlled on both ICS and LABA. However the European Medicines Agency (EMA) did not consider there were data for fluticasone furoate/vilanterol in patients already adequately controlled on both ICS and LABA.[3] As a result only the “step-up” indication was approved by the EMA. The exact equivalence of fluticasone furoate to other ICS is not known. The British National Formulary (February 2014) notes that fluticasone furoate 92 micrograms once daily is approximately equivalent to fluticasone propionate 250 micrograms twice daily.[7] This implies that the fluticasone dose in the fluticasone furoate/vilanterol 92/22 micrograms formulation approximates to a medium dose of ICS. Therefore the use of a low dose ICS (plus LABA) would not be possible with fluticasone furoate/vilanterol. Furthermore, as fluticasone furoate (and vilanterol) are not licensed individually for the treatment of asthma, patients will require a change to their ICS when commenced on fluticasone furoate/vilanterol.

One 24-week study compared fluticasone furoate/vilanterol 92/22 micrograms with fluticasone propionate/salmeterol 250/50 micrograms twice daily and no significant difference between treatments was shown for change from baseline in 0 to 24 hour serial wm FEV_1 at 24 weeks. This study was not designed to test non-inferiority. Furthermore, in another study no significant difference was demonstrated in the co-primary endpoints for fluticasone furoate/vilanterol 92/22 micrograms versus fluticasone furoate 92 micrograms after 12 weeks treatment. However, in a 24-week study fluticasone furoate/vilanterol 184/22 micrograms was significantly superior to fluticasone furoate 184 micrograms and to fluticasone propionate 500 micrograms twice daily. In addition, the exacerbation study demonstrated superiority of fluticasone furoate/vilanterol

92/22 micrograms versus fluticasone furoate 92 micrograms for the probability for one or more asthma exacerbations by week 52. While the 12-week study (HZA106827) may be considered to be shorter than recommended by in EMA guidance (which notes that chronic treatment of asthma studies should be of at least 6 months) [11], overall the EMA, in its European Public Assessment Report for Relvar Ellipta, considered the study durations were acceptable[3].

All studies (except the comparative study of fluticasone furoate/vilanterol versus fluticasone propionate/salmeterol and the safety study) recruited patients who were receiving ICS ±LABA. The proportion of patients on ICS plus LABA was approximately 40% in study HZA106827, 75% in study HZA106829 and 51% for study HZA106837.[5,8,9] However, the licensed indication is for patients not adequately controlled with ICS and 'as needed' inhaled SABA.[10] Therefore, patients receiving ICS plus LABA who were recruited to these studies would not be eligible for fluticasone furoate/vilanterol in clinical practice. All studies did include a four-week run-in period prior to randomisation in which patients received ICS (plus when required SABA).

There are limited direct comparative data and none comparing fluticasone furoate/vilanterol 184/22 micrograms with ICS/LABA combination inhalers. Consequently, Bayesian hierarchical mixed treatment comparisons (MTC) were conducted to compare (when data permitted):

- Fluticasone furoate/vilanterol (daily dose 92/22 micrograms) with medium dose ICS/LABA; fluticasone propionate/salmeterol, budesonide/formoterol fumarate dihydrate, beclomethasone/ formoterol fumarate dihydrate and fluticasone propionate/ formoterol fumarate dihydrate.
- Fluticasone furoate/vilanterol (daily dose 184/22 micrograms) with high dose ICS/LABA; fluticasone propionate/salmeterol, budesonide/formoterol fumarate dihydrate and fluticasone propionate/ formoterol fumarate dihydrate.

The MTC included studies of patients on an ICS or ICS/LABA at screening and analysed four outcomes: mean change from baseline in peak expiratory flow (PEF), FEV_1 (both primary outcomes), mean rate of moderate and severe exacerbations and mean change from baseline in AQLQ total score. The results of the MTC indicated that fluticasone furoate/vilanterol 92/22 micrograms and 184/22 micrograms had a high probability of non-inferiority versus other ICS/LABA combinations for PEF, FEV_1 and AQLQ outcomes. The evidence for non-inferiority for the exacerbation rate outcome was not robust due to high study-to-study variability. Another limitation of the MTC was heterogeneity in outcomes in common control arms between the studies. However, overall the MTC was considered to be acceptable.

Fluticasone furoate/vilanterol delivered by the Ellipta® device is the first ICS/LABA combination inhaler to be licensed only for once daily use in the treatment of asthma. A once daily dosing regimen of ICS/LABA combination inhaler may be preferred by patients and provide benefits in terms of treatment compliance over a twice daily dosing regimen which may be required for the comparators. However, the double-dummy design of the comparative study of once daily fluticasone furoate/vilanterol versus twice daily fluticasone propionate/salmeterol means that this, as well as inhaler device preference, was not assessed. Clinical experts consulted by SMC considered that the place in therapy of fluticasone furoate/vilanterol would be as an alternative to existing ICS/LABA combination inhalers where once daily administration is preferred. It was noted that, once in-use, the shelf life of the fluticasone furoate/vilanterol inhaler is relatively short at just six weeks.

The EMA considered the most frequent adverse events (headache, nasopharyngitis and upper respiratory tract infections) observed with fluticasone furoate/vilanterol in the treatment of asthma (and COPD) were similar to those reported for other approved ICS/LABA combination

products. However the risk of pneumonia was not considered to be fully characterised and the company are to undertake studies in asthma and COPD to investigate the risk of pneumonia with fluticasone furoate/vilanterol compared with other ICS/LABA combination products.[3]

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis of fluticasone furoate/vilanterol 92/22 and 184/22 micrograms for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist (LABA) and inhaled corticosteroid) is appropriate in patients not adequately controlled with inhaled corticosteroids (ICS) and 'as needed' inhaled short acting beta2-agonists (SABA). The comparators included fluticasone propionate/salmeterol (Seretide Accuhaler®, Seretide Evohaler®), budesonide/formoterol fumarate (Symbicort®), fluticasone propionate/formoterol fumarate (Flutiform®) and beclometasone dipropionate/formoterol fumarate (Fostair®). SMC clinical experts confirmed the comparators to be appropriate and indicated fluticasone propionate/salmeterol to be the treatment most likely to be displaced by fluticasone furoate/vilanterol. The time horizon was five years and the perspective was NHS Scotland.

The data to support comparable efficacy were based on Bayesian mixed treatment comparisons (MTCs) assessing the probability of non-inferiority of fluticasone furoate/vilanterol compared with each of the comparator ICS/LABAs. A 24 week study directly compared fluticasone furoate/vilanterol with fluticasone propionate/salmeterol; however, the purpose of this was to demonstrate superiority and the primary superiority endpoint was not met.

Only drug costs were included in the analysis. Costs were presented over one to five years with a weighted cost provided for low/medium dose comparator ICS/LABAs. The results (Table 3) estimate the introduction of fluticasone furoate/vilanterol 184/22 micrograms will lead to cost savings of £25-£452 per year (£117-£2,111 over 5 years) when compared to alternative high-dose ICS/LABA preparations (Table 3).

Table 3: Base case results, cost minimisation results in year 1 and year 5 – fluticasone furoate/vilanterol 184/22 micrograms to high dose ICS/LABAs

ICS/LABA (high dose)	Comparator daily dose	Year 1	Year 5	Cost difference fluticasone furoate/vilanterol 184/22 micrograms vs comparator	
				Year 1	Year 5
Fluticasone furoate/ vilanterol (Relvar Ellipta®)		£473	£2,210	NA	NA
Fluticasone propionate/ salmeterol (Seretide Accuhaler®)	1000/100	£498	£2,327	-£25	-£117
Fluticasone propionate/ salmeterol (Seretide Evohaler®)	1000/100	£724	£3,382	-£251	-£1,172
Budesonide/ formoterol fumarate (Symbicort®)	1600/48	£925	£4,321	-£452	-£2,111

Fluticasone propionate/ formoterol fumarate (Flutiform®)	1000/40	£554	£2,590	-£81	-£380
Beclometasone dipropionate/ formoterol fumarate (Fostair®)*	800/48	£713	£3,334	-£241	-£1,124

*The submitting company included a comparison with Fostair® but noted that the high dose is considered outwith licence

For the comparison of fluticasone furoate/vilanterol (92/22 micrograms) to low/medium dose ICS/LABA comparators, the results of the analysis (Table 4) estimate cost savings when compared to fluticasone propionate/salmeterol (Accuhaler® & Evohaler®) and budesonide/formoterol. However, compared with low/medium doses of fluticasone propionate/formoterol fumarate and beclometasone dipropionate/formoterol fumarate, fluticasone furoate/vilanterol 92/22 micrograms is associated with incremental costs of £31 and £18, respectively in year 1 and £147 and £84, respectively in year 5. It is worth noting that these are the comparators with the lowest current market share.

Table 4: Base case results, cost minimisation results in year 1 and year 5 – fluticasone furoate/vilanterol 92/22 micrograms to low/medium dose ICS/LABA comparators

ICS/LABA (low/medium dose)	**Comparator daily dose range used for weighting**	**Year 1**	**Year 5**	**Cost difference. fluticasone furoate/vilanterol 92/22 micrograms vs comparator**	
				Year 1	**Year 5**
Fluticasone furoate/ vilanterol (Relvar Ellipta®)		£338	£1,581	NA	NA
Fluticasone propionate/ salmeterol (Seretide Accuhaler®)	200/100 to 500/100	£356	£1,664	-£18	-£84
Fluticasone propionate/ salmeterol (Seretide Evohaler®)	200/100 to 500/100	£360	£1,684	-£22	-£103
Budesonide/ formoterol fumarate (Symbicort®)	400/24 to 800/24	£435	£2,031	-£96	-£451
Fluticasone propionate/ formoterol fumarate (Flutiform®)	200/20 to 500/20	£307	£1,434	£31	£147
Beclometasone dipropionate/ formoterol fumarate (Fostair®)	200/12 to 400/24	£320	£1,497	£18	£84

When the costs are weighted by the proportions of patients receiving low/medium and high dose ICS/LABA (i.e. the relative use of ICS/LABA comparator treatments in clinical practice), results of the analysis (Table 5) estimate cost savings from introducing fluticasone furoate/vilanterol 92/22 micrograms and 184/22 micrograms versus fluticasone propionate/salmeterol (Accuhaler® & Evohaler®) and budesonide/formoterol.fumarate However, compared with fluticasone propionate/formoterol fumarate and beclometasone dipropionate/formoterol fumarate, fluticasone furoate/vilanterol is associated with incremental costs of £22 and £61, respectively in year one (£105 and £284 in year five). As noted above, these are the comparators with the lowest current market share.

Table 5: Base case weighted results by utilisation of low/medium and high dose over 1 to 5 years

Weighted results by utilisation of low/medium and high dose ICS/LABA comparators	**Year 1**	**Year 5**	**Cost difference fluticasone furoate/vilanterol vs comparator**	
			Year 1	**Year 5**
Fluticasone furoate/ vilanterol (Relvar Ellipta®)	£384	£1,794	NA	NA
Fluticasone propionate/ salmeterol (Seretide Accuhaler®)	£404	£1,889	-£20	-£95
Fluticasone propionate/ salmeterol (Seretide Evohaler®)	£494	£2,310	-£110	-£516
Budesonide/ formoterol fumarate (Symibort®)	£472	£2,205	-£88	-£411
Fluticasone propionate/ formoterol fumarate (Flutiform®)	£362	£1,689	£22	£105
Beclometasone dipropionate/ formoterol fumarate (Fostair®)*	£323	£1,510	£61	£284

*The submitting company included a comparison with Fostair® but noted that the high dose is considered outwith licence.

When the market share of all comparator treatments (across their dose ranges) is taken into consideration, the overall cost saving per patient from introducing fluticasone furoate/vilanterol in year 1 is £74 and £345 in year 5 (Table 6).

Table 6: Overall cost savings per patient per year (weighted)

Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
£73.77	£145.05	£213.91	£280.45	£344.77

The main concerns with the analysis were:

- There are limited direct comparative data and none comparing fluticasone furoate/vilanterol 184/22 micrograms with other ICS/LABA combination inhalers.
- Lack of data to compare fluticasone furoate/vilanterol with all ICS/LABA comparators across all four outcome measures; the evidence networks in the MTC did not allow for all comparator doses to be compared with fluticasone furoate/vilanterol, across all four included outcome measures
- Uncertainty around the appropriateness of the comparator doses, such that dose equivalence has not been demonstrated.

Despite these concerns, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The BTS/SIGN British Guideline on the management of asthma (number 101) was revised in January 2012.[1] The following recommendations relate to step 3 and 4 in children >12 years and adults. In patients not adequately controlled at step 2, adherence and inhaler technique should be rechecked and trigger factors should be eliminated. Add-on therapy should then be considered.

Step 3
In adult patients taking inhaled steroids at doses of 200 to 800 micrograms beclometasone dipropionate/day the following interventions are of value:

- first choice would be the addition of an inhaled LABA, which improves lung function and symptoms, and decreases exacerbations.
- Leukotriene receptor antagonists may provide improvement in lung function, a decrease in exacerbations, and an improvement in symptoms.
- Theophyllines may improve lung function and symptoms, but side effects occur more commonly.
- Slow-release beta$_2$-agonist tablets may also improve lung function and symptoms, but side effects occur more commonly.

The first choice as add-on therapy to inhaled steroids in adults is an inhaled LABA which should be considered before going above a dose of 400 micrograms beclometasone dipropionate or equivalent per day and certainly before going above 800 micrograms of beclometasone dipropionate.

If asthma control remains suboptimal after the addition of an inhaled LABA then the dose of inhaled steroids should be increased to 800 micrograms/day in adults, if not already on these doses.

Step 4
If control remains inadequate on 800 micrograms beclometasone dipropionate daily of an inhaled steroid plus LABA, consider the following interventions:

- increasing inhaled steroids to 2,000 micrograms beclometasone dipropionate /day
- leukotriene receptor antagonists
- theophyllines
- slow release beta$_2$-agonist tablets, though caution needs to be used in patients already on LABA.

Additional information: comparators

Fluticasone propionate/salmeterol (Seretide Accuhaler®, Seretide Evohaler®), budesonide/ formoterol fumarate dihydrate (Symbicort Turbohaler®), beclometasone dipropionate/formoterol fumarate dihydrate (Fostair®) and fluticasone propionate/ formoterol fumarate dihydrate (Flutiform®).

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
fluticasone furoate/vilanterol (Relvar Ellipta®)	**92/22 micrograms once daily to 184/22 micrograms once daily**	**337 to 472**
Beclometasone dipropionate/formoterol fumarate dihydrate (Fostair®)	100/6 micrograms twice daily to 200/12 micrograms twice daily	178 to 356
budesonide/ formoterol fumarate dihydrate (Symbicort Turbohaler®)	100/6 micrograms twice daily to 800/24 micrograms twice daily	200 to 922
fluticasone propionate/salmeterol (Seretide Accuhaler®)	100/50 micrograms twice daily to 500/50 micrograms twice daily	218 to 496
fluticasone propionate/salmeterol (Seretide Evohaler®)	100/50 micrograms twice daily to 500/50 twice daily	218 to 722
fluticasone propionate/ formoterol fumarate dihydrate (Flutiform®)	100/10 micrograms twice daily to 500/20 micrograms twice daily	218 to 553

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 March 2014.Equivalent ICS doses: beclometasone dipropionate 800 micrograms is equivalent to budesonide 800 micrograms or fluticasone propionate 400 micrograms.[1]

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 2,048 in year 1 rising to 19,777 in year 5 based on an assumed market share of 2% in year 1 rising to 15% in year 5.

Base case
The gross impact on the medicines budget was estimated to be £786k, in year 1 and £7.592m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be a savings of £56k, in year 1 and £537k in year 5. These estimates were based on drug costs weighted by usage across the doses and equal displacement (20%) of patients switching from each of the five ICS/LABA comparators.

Weighted
The gross impact on the medicines budget was estimated to be £786k, in year 1 and £7.592m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be a savings of £151k, in year 1 and £1.458m in year 5. These estimates were based on drug costs weighted by usage across the doses and displacement across the five ICS/LABA comparators according to current market share usage.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. British Thoracic Society/Scottish Intercollegiate Guidelines Network. Guidance number 101; British guideline on the management of asthma. Revised January 2012.
2. Woodcock A, Bleecker E, Lotvall J et al. Efficacy and Safety of Fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma, a randomized trial. Chest 2013; 144(4):1222-1229
3. European Medicines Agency. Assessment Report Relvar Ellipta. 2013
4. www.clinicaltrials.gov
5. *Commercial in Confidence*
6. Busse W, O'Byrne P, Bleecker E et al. Safety and tolerability of the novel inhaledcorticosteroid fluticasone furoate in combination with the β2 agonist vilanterol administered once daily for 52 weeks in patients ≥12 years old with asthma: a randomised trial. Thorax 2013;68:513-520.
7. BMJ Group/Pharmaceutical Press. British National Formulary; fluticasone furoate 92 micrograms / vilanterol 22 micrograms (RelvarEllipta®) monograph. February 2014.
8. *Commercial in Confidence*
9. *Commercial in Confidence*
10. GlaxoSmithKline UK. Summary of product characteristics for fluticasone furoate 92 micrograms / vilanterol 22 micrograms (RelvarEllipta®). 13 November 2013.
11. Committee for Proprietary Medicinal Products (CPMP). CPMP/ EWP/ 2922/01: Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Asthma. 2002.

This assessment is based on data submitted by the applicant company up to and including 10 March 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override

the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.