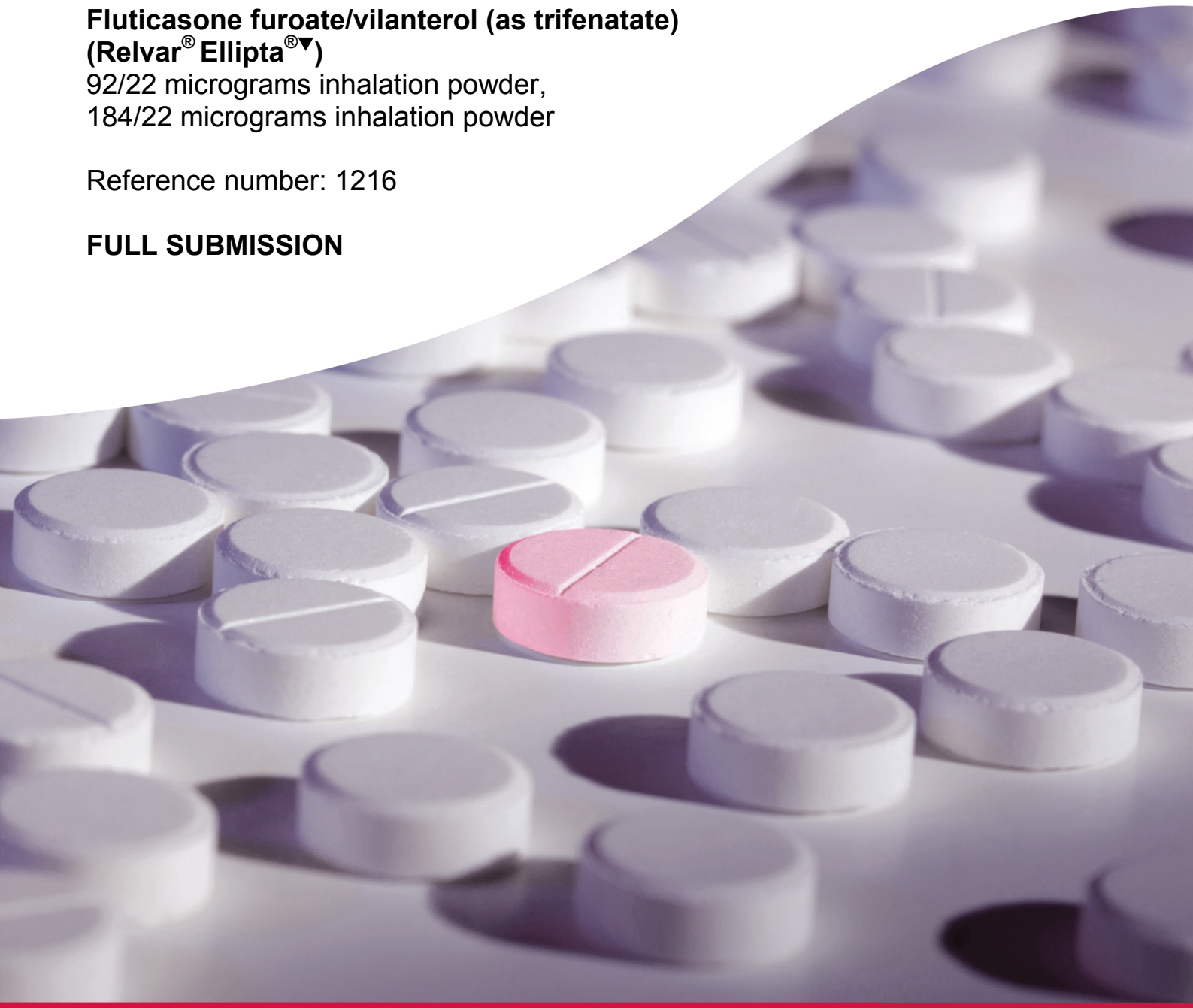
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Fluticasone furoate/vilanterol (as trifenatate) (Relvar® Ellipta®▼)
92/22 micrograms inhalation powder,
184/22 micrograms inhalation powder

Reference number: 1216

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Fluticasone furoate/vilanterol (Relvar® Ellipta®▼)
92/22 micrograms inhalation powder, 184/22 micrograms inhalation powder.
Reference number: 1216. July 2014.

AWMSG Secretariat Assessment Report
Fluticasone furoate/vilanterol (as trifenatate) (Relvar® Ellipta®▼) 92/22 micrograms inhalation powder, 184/22 micrograms inhalation powder

This assessment report is based on evidence submitted by GlaxoSmithKline on 26 February 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Fluticasone furoate/vilanterol (Relvar® Ellipta®▼) is indicated 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 and inhaled corticosteroid) is appropriate: • patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta$_2$-agonists[2,3].
Dosing	The recommended dose is a single inhalation of either 92 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate) or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate) once daily using the Ellipta® inhaler[2,3].
Marketing authorisation date	13 November 2013[2,3].

2.0 DECISION CONTEXT

2.1 Background

Asthma is a chronic long-term lung disorder affecting people of all ages, in which inflammation and narrowing of the bronchial tubes leads to breathing difficulties, tightness in the chest, coughing and wheezing[4,5]. The disorder is diagnosed by symptoms and lung function tests, which measure peak expiratory flow rate (PEF: see Glossary) or the forced expired volume in one second[6] (FEV_1: see Glossary). Asthma episodes can be a consequence of viral respiratory infections, exercise, smoke, cold or allergens such as pollen, mould, fur or dust mites[6]. Exacerbations, acute periods of increased breathlessness or coughing, can be life threatening in severe cases[6]. In 2012–2013 there were 221,356 patients in Wales with asthma[7]. The condition is responsible for a large number of accident and emergency attendances and hospital admissions[5] and results in approximately 60 deaths in Wales each year[8].

Management of asthma follows a stepwise approach with treatment starting at the step most appropriate to initial severity[9]. In patients with asthma symptoms uncontrolled using as-needed short acting beta$_2$-agonists (SABAs) and inhaled corticosteroids (ICS), the combination of a low dose ICS, a long-acting beta$_2$-agonist (LABA) and as needed SABAs can be used in place of the ICS and as needed SABAs. If the symptoms are still not controlled using the low dose ICS/LABA the treatment can be stepped up to a medium-high dose ICS/LABA and as needed SABAs[10,11]. Guidance advises that low doses of ICS are equivalent to 200-800 micrograms daily of beclometasone dipropionate (100–400 micrograms of fluticasone propionate daily) and high doses of ICS are equivalent to 800–2,000 micrograms daily of beclometasone dipropionate (400–1,000 micrograms of fluticasone propionate daily)[6,11]. Fluticasone furoate 100

micrograms once daily (predispensed dose, equivalent to 92 micrograms delivered dose) is approximately equivalent to fluticasone propionate 250 micrograms twice daily and 200 micrograms (predispensed dose, equivalent to 184 micrograms delivered dose) once daily is approximately equivalent to fluticasone propionate 500 micrograms twice daily[2,3]. Fluticasone furoate/vilanterol (Relvar® Ellipta®▼) is an ICS/LABA combination product, licensed to treat symptoms of asthma in adults and adolescents aged 12 years and older where they are not controlled by ICSs and 'as needed' SABAs[1]. It is not licensed for use in patients who are already adequately controlled on both an ICS and a LABA. The National Institute for Health and Care Excellence (NICE) recommends that a decision on whether to prescribe a combination device or separate devices should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence[6].

2.2 Comparators

The comparators included in the company submission were:

- Fluticasone propionate/salmeterol available in a metered dose inhaler (Seretide® Evohaler®)[12] or in a dry powder inhaler (Seretide® Accuhaler®)[13]
- Budesonide/formoterol fumarate, available as a dry powder inhaler (Symbicort® Turbohaler®)[14–16]
- Fluticasone propionate/formoterol fumarate, available as a metered dose inhaler (Flutiform®)[17]
- Beclometasone dipropionate/formoterol fumarate, available as a metered dose inhaler (Fostair®)[18].

2.3 Guidance and related advice

- British guideline on the management of asthma. Clinical Guideline 101. British Thoracic Society, Scottish Intercollegiate Network (2012)[11].
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention (2012)[10].
- NICE Technology Appraisal 138. Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over (2012)[6].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of Fluticasone furoate/vilanterol (as trifenatate):

- Fluticasone furoate/vilanterol (as trifenatate) (Relvar® Ellipta®▼) is recommended as an option for use within NHS Wales for the symptomatic treatment of adults with chronic obstructive pulmonary disease with a FEV_1 < 70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy (2014)

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included a phase III study (HZA113091) comparing the efficacy of fluticasone furoate/vilanterol versus fluticasone propionate/salmeterol in patients with asthma. The applicant company has also provided mixed treatment comparisons (MTCs) evaluating fluticasone furoate/vilanterol against the comparators. In addition, the company submitted evidence from four randomised phase III studies, using fluticasone furoate/vilanterol in patients with asthma; however, these do not provide effectiveness data versus the comparators and so are not discussed further[1].

3.1 HZA113091 study

HZA113091 was a 24-week, multicentre, randomised, double-blind, parallel-group, phase III study to evaluate the clinical superiority of fluticasone furoate/vilanterol 92/22 micrograms delivered via Ellipta® dry powder inhaler, to fluticasone propionate/salmeterol 250/50 micrograms using an Accuhaler® in patients with persistent asthma[1,19,20]. Eligible patients were aged ≥ 12 years, had FEV_1 values between 40% and 85% of FEV_1 predicted (see Glossary) and had asthma symptoms

which were not controlled on a medium dose of ICS fluticasone propionate (250 micrograms twice daily or equivalent). At entry to the study (prior to a four week run-in period on ICS treatment alone), 69% of participants were already using an ICS plus LABA[21]. Patients (n = 806) were randomised (1:1) to one of two treatment arms: fluticasone furoate/vilanterol once daily and a placebo via Accuhaler® twice daily; or fluticasone propionate/salmeterol twice daily with a once daily placebo via Ellipta®. Salbutamol or albuterol were allowed for symptomatic relief during the study, as were other non-asthma medications, providing their use did not affect lung function[1].

The primary endpoint was the change from baseline in weighted-mean 24 hour serial FEV_1 at 24 weeks (see Glossary for endpoint definition). This was determined for the intent-to-treat population as 341 ml in the fluticasone furoate/vilanterol arm (n = 352) and 377 ml in the fluticasone propionate/salmeterol arm (n = 347). The difference between treatments, (37 ml) was not statistically significant (confidence interval [CI], −88 to 15ml; p = 0.162) and therefore the superiority endpoint was not met (see Table 1). A post-hoc Bayesian analysis of the weighted mean FEV_1 at 12 weeks suggested that fluticasone furoate/vilanterol was as effective as fluticasone propionate/salmeterol, with a 93% probability that the difference between the treatments was ≤ 75 ml[1].

Secondary endpoints included individual serial FEV_1 analyses at selected time intervals, time to onset of bronchodilatory effect and change from baseline in asthma quality of life questionnaire (AQLQ) scores (see Table 1). Statistical significance was not achieved for the primary endpoint and therefore no statistical significance could be inferred for the secondary endpoints. Mean differences between fluticasone furoate/vilanterol and fluticasone propionate/salmeterol in serial FEV_1 measurements at 24 weeks which ranged from 2–58 ml, were small with the exception of the 14 and 16 hour assessments, which were in favour of fluticasone propionate/salmeterol[1]. The median time to onset of bronchodilatory effect, defined as the time at which FEV_1 first exceeded a 12% and 200 ml increase over the baseline value, was similar for both treatments, although fewer patients (118 [29%] versus 140 [35%]) failed to achieve a bronchodilatory effect in the fluticasone propionate/salmeterol arm compared to those in the fluticasone furoate/vilanterol arm. The changes from baseline in adjusted mean AQLQ scores at week 24 were not different between the two treatment arms (see Table 1)[1,19,20].

Table 1. Results of the HZA113091 phase III study.

	Treatments (mean ± SE)		Treatment difference
	FF/VI (n = 352)	FP/Sal (n = 347)	
Primary endpoint			
Change from baseline in weighted-mean 24 hour serial FEV_1 at 24 weeks	341 ml ± 18 ml	377 ml ± 19 ml	−37 ml (CI: −88 ml to 15 ml) p = 0.162
Secondary endpoints			
Median time to onset of bronchodilatory effect	61 minutes	59 minutes	2 minutes p = 0.264
LS mean change in AQLQ score at 24 weeks.	0.46 (0.043)	0.37 (0.043)	0.09 (CI: −0.03 to 0.21) p = 0.130
FF/VI: fluticasone furoate/vilanterol; FP/Sal: fluticasone propionate/salmeterol; CI: 95% confidence interval; LS: least square;			

3.2 Mixed treatment comparison

In the absence of studies directly comparing fluticasone furoate/vilanterol with comparators, except fluticasone propionate/salmeterol 250/50 micrograms, the company conducted a systematic review to identify evidence of the clinical effect of fluticasone furoate/vilanterol versus other ICS/LABA combination products in patients with asthma[1]. The systematic review identified randomised controlled studies that compared any combination ICS/LABA product in patients aged ≥ 12 years with asthma. Studies must have reported a relevant outcome, which included: change from baseline in morning PEF, change from baseline FEV_1 and health related quality of life. Safety aspects and study duration > 8 weeks was required[1].

This systematic review was used to inform a set of Bayesian MTC analyses, which were included in the company submission, to examine the probability that fluticasone furoate/vilanterol treatments were noninferior to comparators for the endpoints of PEF, FEV_1, mean rates of moderate/severe exacerbations and AQLQ score. The following medium dose treatments were compared in the MTC analyses:

- fluticasone furoate/vilanterol 92/22 micrograms once daily;
- fluticasone propionate/salmeterol 250/50 micrograms twice daily;
- budesonide/formoterol fumarate 400/12 micrograms twice daily;
- beclometasone dipropionate/formoterol fumarate 200/12 micrograms twice daily;
- fluticasone propionate/formoterol fumarate 250/10 micrograms twice daily.

High dose treatments compared were:

- fluticasone furoate/vilanterol 184/22 micrograms once daily;
- fluticasone propionate/salmeterol 500/50 micrograms twice daily;
- budesonide/formoterol fumarate 800/24 micrograms twice daily;
- fluticasone propionate/formoterol fumarate 500/20 micrograms twice daily.

The probability of superiority and noninferiority resulting from the MTC for fluticasone furoate/vilanterol versus comparator treatments for mean PEF are displayed in Table 2. No comparisons were available for fluticasone furoate/vilanterol 92/22 micrograms versus either beclometasone dipropionate/formoterol fumarate 200/12 micrograms or fluticasone propionate/formoterol fumarate 250/10 micrograms and no comparison between fluticasone furoate/vilanterol 184/22 micrograms versus fluticasone propionate/formoterol fumarate 500/20 micrograms was available.

Table 2. Probabilities of superiority and noninferiority for fluticasone furoate/vilanterol treatments versus comparators for PEF[1].

Treatment	Comparator	Mean difference (litres/minute) (95% credible limit)	Probability of superiority	Probability of noninferiority†
FF/VI 92/22 micrograms	FP/Sal 250/50 micrograms	2.832 (−12.867 to 18.531)	64%	97%
FF/VI 92/22 micrograms	Bud/F 400/12 micrograms	0.579 (−15.155 to 16.312)	53%	94%
FF/VI 184/22 micrograms	FP/Sal 500/50 micrograms	11.323 (0.289 to 22.357)	98%	> 99%
FF/VI 184/22 micrograms	Bud/F 800/24 micrograms	15.136 (−0.943 to 31.215)	97%	> 99%

FF/VI: fluticasone furoate/vilanterol; FP/Sal: fluticasone propionate/salmeterol;
Bud/F: budesonide /formoterol fumarate .
† probability that treatment is noninferior to comparator as defined by a margin of 12 litres/minute.

The probability of superiority and noninferiority resulting from the MTC for fluticasone furoate/vilanterol versus comparator treatments for FEV_1 are displayed in Table 3. The comparison of fluticasone furoate/vilanterol 184/22 micrograms versus fluticasone propionate/formoterol fumarate 500/20 micrograms was not available[1].

Table 3. Probabilities of superiority and noninferiority for fluticasone furoate/vilanterol treatments versus comparators for FEV_1[1].

Treatment	Comparator	Mean difference (litres) (95% credible limit)	Probability of superiority	Probability of noninferiority†
FF/VI 92/22 micrograms	FP/Sal 250/50 micrograms	−0.036 (−0.092 to 0.019)	10%	99%
FF/VI 92/22 micrograms	Bud/F 400/12 micrograms	−0.027 (−0.098 to 0.045)	23%	98%
FF/VI 92/22 micrograms	Bec/F 200/12 micrograms	−0.053 (−0.154 to 0.048)	15%	82%
FF/VI 92/22 micrograms	FP/F 250/10 micrograms	0.000 (−0.123 to 0.123)	50%	95%
FF/VI 184/22 micrograms	FP/Sal 500/50 micrograms	0.147 (0.048 to 0.247)	> 99%	> 99%
FF/VI 184/22 micrograms	Bud/F 800/24 micrograms	0.118 (−0.019 to 0.255)	95%	> 99%

FF/VI: fluticasone furoate/vilanterol; FP/Sal: fluticasone propionate/salmeterol;
Bud/F: budesonide/formoterol fumarate; FP/F: fluticasone propionate/formoterol fumarate;
Bec/F: beclometasone dipropionate/formoterol fumarate.
† probability that treatment is noninferior to comparator as defined by a margin of 100 ml.

MTC results for the probabilities of superiority and noninferiority for event rates of annual moderate-to-severe exacerbations are given in Table 4 for fluticasone furoate/vilanterol 92/22 micrograms versus fluticasone propionate/salmeterol 250/50 micrograms and budesonide/formoterol fumarate 400/12 micrograms only. Relative event rate probabilities were not available versus either beclometasone dipropionate/formoterol fumarate 200/12 micrograms or fluticasone

propionate/formoterol fumarate 250/10 micrograms or for fluticasone furoate/vilanterol 184/22 micrograms versus high dose comparators.

Table 4. Probabilities of superiority and noninferiority for fluticasone furoate/vilanterol versus comparators for event rates of moderate-to-severe annual exacerbation rates[1].

Treatment	Comparator	Event rate ratio (95% credible interval)	Probability of superiority	Probability of noninferiority[†]
FF/VI 92/22 micrograms	FP/Sal 250/50 micrograms	1.164 (0.428 to 3.333)	67%	74%
FF/VI 92/22 micrograms	Bud/F 400/12 micrograms	0.985 (0.336 to 2.574)	76%	82%

FF/VI: fluticasone furoate/vilanterol; FP/Sal: fluticasone propionate/salmeterol;
Bud/F: budesonide/formoterol fumarate .
[†] probability that treatment is noninferior to comparator as defined by a margin of 0.10.

Table 5 lists the probabilities of superiority and noninferiority for AQLQ scores. The MTC network was not available to calculate comparison between either fluticasone furoate/vilanterol 92/22 micrograms versus beclometasone dipropionate/formoterol fumarate 200/12 micrograms and comparative data were not available for the higher dose treatments.

Table 5. Probabilities of superiority and noninferiority for fluticasone furoate/vilanterol versus comparators for AQLQ[1].

Treatment	Comparator	Mean difference (95% credible limit)	Probability of superiority	Probability of noninferiority[†]
FF/VI 92/22 micrograms	FP/Sal 250/50 micrograms	0.060 (−0.104 to 0.224)	76%	> 99%
FF/VI 92/22 micrograms	Bud/F 400/12 micrograms	0.203 (−0.461 to 0.867)	76%	90%
FF/VI 92/22 micrograms	FP/F 250/10 micrograms	0.253 (−0.254 to 0.759)	86%	97%

FF/VI: fluticasone furoate/vilanterol; FP/Sal: fluticasone propionate/salmeterol;
Bud/F: budesonide/formoterol fumarate ; FP/F: fluticasone propionate/formoterol fumarate.
[†] probability that treatment is noninferior to comparator as defined by a margin of 0.25.

3.3 Comparative safety

The number of adverse events (AEs) in the two arms of study HZA113091 was similar although no statistical analysis was provided[21]. Adverse events were reported in 213/403 patients (53%) in the fluticasone furoate/vilanterol arm and in 198/403 (49%) patients in the fluticasone propionate/salmeterol arm, and of these 19 (5%) and 15 (4%) were considered to be treatment-related[19]. The most frequent AEs in both arms were nasopharyngitis which occurred in 46 patients (11%) in each arm and headache which occurred in 34 patients (8%) receiving fluticasone furoate/vilanterol and in 41 patients (11%) receiving fluticasone propionate/salmeterol. Serious adverse events (SAEs) occurred in four patients in the fluticasone furoate/vilanterol arm and in five patients in the fluticasone propionate/salmeterol arm. No SAEs were considered to be treatment-related and no deaths were reported in the study. Urinary corticosteroid excretion measurements at 24 hours post-treatment inhalation increased from baseline to 24 weeks in both arms (ratio to baseline, 1.11 for fluticasone furoate/vilanterol and 1.21 for fluticasone propionate/salmeterol) but was not statistically different between treatments[19]. The number of patients withdrawing from the study due to adverse

events was six (1%) in the fluticasone furoate/vilanterol arm and eight (1%) in the fluticasone propionate/salmeterol arm. Treatment-related AEs, each leading to the withdrawal of one patient in the fluticasone furoate/vilanterol arm were cough, loss of consciousness, chest discomfort and rash. In the fluticasone propionate/salmeterol arm treatment-related AEs leading to study withdrawal were gastritis (in one patient), abnormal liver function test (in one patient), hyperhidrosis and hot flush (both AEs in one patient), chest discomfort and Wolf-Parkinson-White syndrome (both AEs in one patient)[1].

3.4 AWTTC critique

- In clinical study HZA113091, no statistically significant difference in change from baseline in weighted-mean 24 hour serial FEV_1 at 24 weeks was found between patients treated with fluticasone furoate/vilanterol versus those treated with fluticasone propionate/salmeterol; the primary superiority endpoint was not met[1,19].
- The Committee for Medicinal Products for Human Use commented that the duration of the study and sample size were not designed to determine the affect of fluticasone furoate/vilanterol on the rate of exacerbations[19,20].
- Direct comparative evidence is limited to a 24-week study of fluticasone furoate/vilanterol 92/22 micrograms versus fluticasone propionate/salmeterol 250/50 micrograms. There is limited evidence for use of fluticasone furoate/vilanterol 184/22 micrograms and no direct comparisons are available for this higher dose[21].
- In the absence of studies directly comparing fluticasone furoate/vilanterol with other therapies, the applicant company has followed a common approach and conducted a systematic review of available studies and provided MTCs. The results of the MTCs should be interpreted with some caution due to differences in study protocols. The inclusion criteria differed across the studies; pre-treatment requirements, exacerbation history and symptoms at baseline varied. Endpoints were not always determined in an identical manner[1].
- The lower strength formulation delivers 92 micrograms fluticasone furoate, approximately equivalent to 250 micrograms fluticasone propionate twice daily. The absence of a lower strength than fluticasone furoate/vilanterol 92/22 limits the ability of patients to step down[21].
- The recommended dose of fluticasone furoate/vilanterol is a single daily inhalation and patients receiving the comparators require two doses daily. The company suggest fluticasone furoate/vilanterol may be considered a more convenient treatment[2,3,12–18].
- A UK Medicines Information safety assessment report expressed concern that Relvar® Ellipta®▼, a preventer inhaler, may be mistaken by patients, for a reliever inhaler. The name "Relvar®" was considered to look and sound similar to "reliever" and the use of blue colouring on the device was a further concern[22].
- Fluticasone furoate/vilanterol (Relvar® Ellipta®) is licensed in patients aged ≥ 12 years[2]. Fluticasone propionate/salmeterol 50/25 micrograms (Seretide® 50 Evohaler®)[12] and fluticasone propionate/salmeterol 100/50 micrograms (Seretide® 100 Accuhaler®)[13] are licensed in children ≥ 4 years and budesonide/formoterol fumarate 100/6 micrograms (Symbicort® Turbohaler® 100/6) is licensed in children ≥ 6 years[14].
- Fluticasone furoate/vilanterol, unlike other ICS/LABA combination inhalers (Seretide®, Flutiform®, Symbicort® and Fostair®) is not licensed for patients whose asthma is already controlled by an ICS and a LABAs [2,3,12–16,18].

4.0 ASSESSMENT OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company has submitted a cost minimisation analysis (CMA) of fluticasone furoate/vilanterol (Relvar® Ellipta®▼) combination inhaler (92/22 micrograms and 184/22 micrograms) for the treatment for adults and adolescents aged 12 years and over for whom the use of a combination inhaled corticosteroid (ICS) and long acting beta$_2$-agonist (LABA) is appropriate i.e. patients who are not adequately controlled with an ICS and as needed short acting beta$_2$-agonist[1]. The company considered the comparators to be other ICS/LABA combinations consisting of fluticasone propionate/ salmeterol (Seretide® Accuhaler® and Seretide® Evohaler®), budesonide/formoterol fumarate (Symbicort® Turbohaler®) fluticasone propionate/formoterol fumarate (Flutiform®), and beclometasone dipropionate/formoterol fumarate (Fostair®).

The company report the predominant treatment used in the UK is fluticasone propionate/salmeterol (Seretide®), with 66.7% market share based on UK prescription data, assumed by the company to be representative for Wales[1].

The CMA is based on an assumption of broadly comparable efficacy derived from HZA113091, a head-to-head study of fluticasone furoate/vilanterol 92/22 micrograms versus fluticasone propionate/salmeterol 250/50 micrograms, and Bayesian MTCs. The clinical study showed no significant differences in AQLQ score between fluticasone furoate/vilanterol and fluticasone propionate/salmeterol treatment arms (see section 3.1), and a similar incidence of AEs between the treatment groups[1,19]. The MTCs found fluticasone furoate/vilanterol (92/22 micrograms and 184/22 micrograms) had a high probability of noninferiority when compared to selected medium dose and high dose ICS/LABA combinations across the range of outcomes considered.

Only medicine acquisition costs were included in the economic analysis[1,23]. The cost of fluticasone furoate/vilanterol 92/22 micrograms was compared to those of low to medium ICS dose ICS/LABA comparator combinations. The cost of fluticasone furoate/vilanterol 184/22 micrograms was compared to those of high ICS dose ICS/LABA comparator combinations. Within each category the costs are weighted by the estimated relative use in clinical practice of each comparator ICS/LABA dose, based on UK prescription data. In addition, a comparison of costs was performed for all doses based on the proportion of patients estimated to be receiving low, medium and high doses, based on UK prescription data. For all analyses a five-year horizon was adopted, with costs after year 1 discounted at 3.5%. Scenario analysis was performed on the discount rate, and assumptions that adherence is less than 100% for the comparator ICS/LABA combinations (due to these requiring twice daily administration compared to once daily administration with fluticasone furoate/vilanterol).

4.1.2 Results

The results for year 1 of the base case analyses are presented in Tables 6–8 (costs for years 2–5 are simply year 1 costs discounted). The CMA indicates fluticasone furoate/vilanterol 92/22 micrograms to be associated with lower annual medicine costs compared to low-medium dose fluticasone propionate/salmeterol and budesonide/formoterol fumarate, but with higher costs than fluticasone propionate/formoterol fumarate, and beclometasone/formoterol fumarate (Table 6). Higher dose fluticasone furoate/vilanterol 184/22 micrograms has a lower annual cost than the weighted cost of the high dose comparator products (Table 6). From the analysis weighted for estimated utilisation across all doses, fluticasone furoate/vilanterol demonstrated cost savings compared to fluticasone propionate/salmeterol and budesonide/formoterol fumarate but higher costs versus fluticasone propionate/formoterol fumarate and beclometasone dipropionate/formoterol fumarate (Table 6).

Sensitivity analysis showed that applying a 0% or 6% discount rate did not significantly impact the results. Applying adherence rates of 90%, 80% and 70% for the comparator combinations reduced the cost savings or increased the incremental costs of fluticasone furoate/vilanterol versus each comparator. The results for 80% adherence, presented in Table 7, are assumed to be the threshold for patients to be considered adequately adherent[24]. A probabilistic sensitivity analysis was not performed.

Table 6. Base case analysis results[1].

	Low-medium dose ICS/LABA		High dose ICS/LABA		Weighted utilisation all doses		Plausibility
ICS/LABA	Weighted year 1 costs	Cost difference vs. FF/VI 92/22	Weighted year 1 costs	Cost difference vs. FF/VI 184/22	Weighted year 1 costs	Cost difference vs. FF/VI	
FF/VI	£338	-	£473	-	£384	-	The cost estimates seem plausible, although the weighted cost estimates are dependent on the estimates applied for proportionate use of the low-medium, and high doses. The comparison of costs is dependent on the assumption of equivalent outcomes from the MTC, which has inherent limitations .
FP/Sal (Accuhaler®)	£356	−£18	£498	−£25	£404	−£20	
FP/Sal (Evohaler®)	£360	−£22	£724	−£251	£494	−£110	
Bud/F	£435	−£96	£925	−£452	£472	−£88	
FP/F	£307	£31	£554	−£81	£362	£22	
Bec/F	£320	£18	£713	−£241	£323	£61	

FF/VI: fluticasone furoate/vilanterol; FP/Sal: fluticasone propionate/salmeterol; Bud/F: budesonide/formoterol fumarate ; FP/F: fluticasone propionate/formoterol fumarate ; Bec/F: beclometasone dipropionate/formoterol fumarate

Table 7: Sensitivity analysis assuming 80% adherence for comparator ICS/LABA combinations[1].

	Low-medium dose ICS/LABA		High dose ICS/LABA		Weighted utilisation all doses		Plausibility
	Weighted year 1 costs	Cost difference vs. FF/VI 92/22	Weighted year 1 costs	Cost difference vs. FF/VI 184/22	Weighted year 1 costs	Cost difference vs. FF/VI	
FF/VI	£338		£473		£384		The cost estimates seem plausible although the weighted cost estimates are dependent on the estimates for the proportionate use of the low-medium, and high doses. However, the usefulness of the adherence sensitivity analysis is limited, as patient outcomes have not been adjusted. Sensitivity analysis varying the proportionate use of low-medium, high dose use may have been more useful.
FP/Sal (Accuhaler®)	£285	£53	£398	£75	£323	£61	
FP/Sal (Evohaler®)	£288	£50	£579	−£106	£395	−£12	
Bud/F	£348	−£9	£740	−£267	£378	£6	
FP/F	£245	£93	£443	£29	£289	£95	
Bec/F	£256	£82	£571	−£98	£258	£125	

FF/VI: fluticasone furoate/vilanterol; FP /Sal: fluticasone propionate/salmeterol; Bud/F: budesonide/formoterol fumarate ; FP/F: fluticasone propionate/formoterol fumarate ; Bec/F: beclometasone dipropionate/formoterol fumarate

4.1.3 AWTTC critique

The company has concluded that despite some limitations, the MTC has demonstrated broadly comparable efficacy across a range of comparisons of fluticasone furoate/vilanterol 92/22 micrograms and 184/22 micrograms versus a range of ICS/LABA comparators and doses used in clinical practice. This has been used to support a CMA which, based on weighted costs shows fluticasone furoate/vilanterol has a lower cost than some ICS/LABA combinations, and a higher cost than other combinations. The ICS/LABAs that were less costly than fluticasone furoate/vilanterol (i.e. fluticasone propionate/formoterol fumarate and beclometasone/ formoterol fumarate) are claimed to have the smallest market share.

However, it should be noted that against individual ICS/LABA doses (i.e. analysis not weighted by prescriptions dispensed), fluticasone furoate/vilanterol 92/22 micrograms has a higher drug acquisition cost than each low dose ICS/LABA comparator, but lower cost than medium dose ICS/LABA combinations (see Table 9). This difference is confirmed by sensitivity analysis. Fluticasone furoate/vilanterol 184/22 micrograms is less expensive than each comparator high dose combination used (see Table 9).

Strengths of the economic evaluation include:

- A range of comparators used in clinical practice have been considered (although it should be noted that there are differences in the licensed indications for fluticasone furoate/vilanterol and the other ICS/LABA combinations).
- A number of approaches to compare the costs of the combination ICS/LABAs have been used, producing similar findings.

Limitations of the economic evidence include:

- The validity of the CMA submitted by the company is dependent on the critical assumption of equivalence in clinical effectiveness and safety outcomes from the MTC as well as equivalence in patient preferences and adherence that might impinge on these parameters.
- Broadly comparable efficacy has been demonstrated through the analysis of noninferiority across a range of efficacy/effectiveness outcomes. However, there were limitations in the MTC in that comparisons were not possible for fluticasone furoate/vilanterol against some comparators due to insufficient study data. There were no comparisons with low dose ICS/LABA combinations. The MTC results were also relatively less robust for the rate of moderate/severe exacerbations outcome. There is evidence of between-study heterogeneity, and safety outcomes have not been included.
- No probabilistic sensitivity analysis has been performed to assess the probability of fluticasone furoate/vilanterol being less costly and more or less efficacious versus comparator ICS/LABAs.
- The use of the weighted cost approach is dependent on the estimated proportions of each dose used for the ICS/LABAs considered. These are based on UK prescription data which was assumed to be relevant for Wales. Whilst this may be the case, sensitivity analysis was not performed for variations in relative use of each dose.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost effectiveness of fluticasone furoate/vilanterol within its current licensed indication for patients with asthma.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on published prevalence in Wales (6.7%)[25], incidence estimates from England (5.2/1000)[26] and mortality estimates from Asthma UK[27] the company has estimated that the number of people with asthma in Wales in year 1 is 221,894, rising to 285,612 in year 5. The company assumed all these patients will receive treatment, with 63% receiving an ICS/LABA combination (based on UK prescription data[28]). A company estimate of 2% uptake in year 1 rising to 15% in year 5 produced an estimated number of patients treated with fluticasone furoate/vilanterol of 2,796 in year 1 rising to 26,990 in year 5.

5.1.2 Results

The company has assumed fluticasone furoate/vilanterol uptake will be shared evenly through displacement of 20% of each of the five comparator ICS/LABA products: fluticasone propionate/salmeterol (Seretide® Accuhaler® and Seretide® Evohaler®) budesonide/formoterol (Symbicort® Turbohaler®), fluticasone propionate/formoterol fumarate (Flutiform®), and beclometasone dipropionate/formoterol fumarate (Fostair®), resulting in an overall net cost saving from the uptake of fluticasone furoate/vilanterol of £75,488 in 2014, rising to £728,740 in 2018. The results of this base case analysis are presented in Table 8.

The company also reported the results of a scenario analysis based on the displacement being proportionate to the estimated market share in Wales of each comparator ICS/LABA, estimated to be 16.4% fluticasone propionate/salmeterol (Seretide® Accuhaler®), 41.5% fluticasone propionate/salmeterol (Seretide® Evohaler®), 33.5% budesonide/formoterol fumarate (Symbicort® Turbohaler®), 7.7% fluticasone propionate/formoterol fumarate (Flutiform®), and 0.9% beclometasone/formoterol fumarate (Fostair®). This scenario resulted in a net cost saving of £221,894 in 2014 rising to a cost saving in 2018 of £1,997,288[1].

Table 8. Company budget impact estimates[1].

	Year 1 (2014)	Year 2 (2015)	Year 3 (2016)	Year 4 (2017)	Year 5 (2018)
Number of eligible patients	139,793	149,829	159,865	169,900	179,936
Uptake (%)	2%	6%	10%	15%	15%
Treated patients	2,796	8,990	15,986	25,485	26,990
Net costs based on 20% displacement of each comparator (base case)					
Net cost per patient (medicine costs)	−£27	−£27	−£27	−£27	−£27
Overall net cost	**−£75,488**	**−£242,723**	**−£431,634**	**−£688,096**	**−£728,740**
Net costs based on displacement according to market share of comparators (scenario analysis)					
Net cost per patient (medicine costs)	−£74	−£74	−£74	−£74	−£74
Overall net cost	**−£221,894**	**−£665,241**	**−£1,182,998**	**−£1,885,892**	**−£1,997,288**

5.1.3 AWTTC critique of the budget impact analysis

- The company has made reasonable effort to characterise the epidemiology of asthma using a combination of Welsh specific and UK data.
- It seems unlikely that all patients with asthma in Wales will be receiving treatment, hence the drug cost savings maybe overestimated.
- It is not clear how the uptake of fluticasone furoate/vilanterol has been estimated, but the figures appear plausible.
- The budget impact assessment based on fluticasone furoate/vilanterol uptake being shared evenly between the five comparator ICS/LABAs seems improbable, given the low relative use of some inhalers. The assessment based on market share is more realistic although this approach assumes that the UK prescription data is representative of Wales.
- The budget impact assessment may also be constrained by uncertainties over dose equivalence between fluticasone furoate/vilanterol and the comparators.
- The company submission did not include any sensitivity analysis for the budget impact assessment.

5.2 Comparative unit costs

Acquisition costs for fluticasone furoate/vilanterol and comparators are shown in Table 9.

Table 9. Acquisition costs for ICS/LABAs combination inhalers.

Treatment	Maintenance Dose	Cost per patient per year
Low-medium doses:		
FF/VI (Relvar® Ellipta®▼)[9] 92/22 micrograms	1 puff once daily	£338.23
FP/Sal (Seretide® Accuhaler®) 100/50 micrograms	1 puff twice daily	£219.00
FP/Sal (Seretide® Accuhaler®) 250/50 micrograms	1 puff twice daily	£425.83
FP/Sal (Seretide® Evohaler®) 50/25 micrograms	2 puffs twice daily	£219.00
FP/Sal (Seretide® Evohaler®) 125/25 micrograms	2 puffs twice daily	£425.83
Bud/F (Symbicort® Turbohaler® 100/6 micrograms	2 puffs twice daily§	£401.50
Bud/F (Symbicort® Turbohaler®) 200/6 micrograms	1 puff twice daily§	£231.17
FP/F (Flutiform®) 50/5 micrograms	2 puffs twice daily	£219.00
FP/F (Flutiform®) 125/5 micrograms	2 puffs twice daily	£356.00
Bec/F (Fostair®) 100/6 micrograms	1–2 puffs twice daily	£178.36–£356.73*
High doses:		
FF/VI (Relvar® Ellipta®▼)[9] 184/22 micrograms	1 puff once daily	£472.91
FP/Sal (Seretide® Accuhaler®) 500/50 micrograms	1 puff twice daily	£497.86
FP/Sal (Seretide® Evohaler®) 250/25 micrograms	2 puffs twice daily	£723.67
Bud/F (Symbicort® Turbohaler®) 200/6 micrograms	2 puffs twice daily§	£462.33
Bud/F (Symbicort® Turbohaler®) 400/12 micrograms	1–2 puffs twice daily§	£462.33–£924.67
FP/F (Flutiform®) 250/10 micrograms	2 puffs twice daily	£554.31

FF/VI: fluticasone furoate/vilanterol; FP/Sal: fluticasone propionate/salmeterol;
Bud/F: budesonide/formoterol fumarate ; FP/F: fluticasone propionate/formoterol fumarate ;
Bec/F: beclometasone dipropionate/formoterol fumarate.
Costs of comparators obtained from www.drugtariff.co.uk[23].

* Cost range based on 1-2 puffs twice daily.
§ some patients may require up to 4 inhalations twice daily[14,15].
This table does not imply therapeutic equivalence of drugs or the stated doses.
See relevant Summaries of Product Characteristics for full dosing details[2,3,12–18].
Half the dose of fluticasone propionate in micrograms is equivalent to the given dose of budesonide or beclometasone dipropionate[6]. 100 micrograms (predispensed dose, equivalent to 92 micrograms delivered dose) of fluticasone furoate given once daily is approximately equivalent to 250 micrograms of fluticasone propionate given twice daily and 200 micrograms (predispensed dose) of fluticasone furoate is approximately equivalent to 500 micrograms of fluticasone propionate given twice daily[2,3].

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, fluticasone furoate/vilanterol 92/22 micrograms and 184/22 micrograms (Relvar® Ellipta®▼) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

The company do not anticipate that Relvar® Ellipta®▼ will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company did not identify any ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 7 March 2014.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Forced expired volume in one second (FEV_1)
The forced expired volume in one second is the volume of air that can be expelled from maximum inspiration in the first second[6].

FEV_1% predicted
The forced expiratory volume in one second (FEV_1) expressed as a percentage of a predicted value, which depends on the individual's age, height and sex, obtained using a reference population[6].

Change from baseline in weighted-mean 24 hour serial FEV_1
The weighted-mean serial FEV_1 was calculated in the HZA113091 study from the pre-dose FEV_1 and the post-dose FEV_1 measurements at 5, 15, 30 and 60 minutes and at 2, 3, 4, 11, 12, 12.5, 13, 14, 16, 20, 23 and 24 hours after 24 weeks. The weighted-mean change was the area under the curve of FEV_1 versus time divided by the time interval[1].

Peak Expiratory Flow (PEF)
Patient's maximum speed of expiration, measured with a peak flow meter[29].

REFERENCES

1 GlaxoSmithKline. Form B: Detailed appraisal submission. Fluticasone furoate and vilanterol (Relvar® Ellipta®▼). Mar 2014.

2 GlaxoSmithKline. Relvar® Ellipta®▼ 92 micrograms/22 micrograms. Summary of Product Characteristics. Jan 2014. Available at: http://www.medicines.org.uk/emc/medicine/28496/SPC/Relvar+Ellipta+92+micrograms+22+micrograms+inhalation+powder%2c+pre-dispensed/. Accessed Mar 2014.

3 GlaxoSmithKline. Relvar® Ellipta®▼ 184 micrograms/22 micrograms. Summary of Product Characteristics. Jan 2014. Available at: http://www.medicines.org.uk/emc/medicine/28495/SPC/Relvar+Ellipta+184+micrograms+22+micrograms+inhalation+powder%2c+pre-dispensed/. Accessed Apr 2014.

4 British Lung Foundation. Asthma. 2014. Available at: http://www.blf.org.uk/conditions/detail/asthma. Accessed Mar 2014.

5 National Institute for Health and Care Excellence. Quality standard for asthma. Feb 2013. Available at: http://publications.nice.org.uk/quality-standard-for-asthma-qs25/introduction-and-overview. Accessed Mar 2014.

6 National Institute for Health and Care Excellence. Technology Appraisal 138. Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over. Nov 2012. Available at: http://www.nice.org.uk/nicemedia/live/11945/40099/40099.pdf. Accessed Mar 2014.

7 Welsh Government. Quality and Outcomes Framework Disease Registers. Oct 2013. Available at: https://statswales.wales.gov.uk/Catalogue/Health-and-Social-Care/NHS-Primary-and-Community-Activity/GMS-Contract/PatientsOnQualityAndOutcomesFramework-by-LocalHealthBoard-DiseaseRegister. Accessed Apr 2014.

8 Asthma UK. Compare your care. How asthma care in Wales matches up to standards. 2013. Available at: http://www.asthma.org.uk/compareyourcare-reports. Accessed Mar 2014.

9 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. Apr 2014. Available at: http://www.bnf.org/bnf/index.htm. Accessed May 2014.

10 Global Initiative for Asthma. Global strategy for asthma management and prevention. 2012. Available at: http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf. Accessed Mar 2014.

11 British Thoracic Society, Scottish Intercollegiate Network. British Guideline on the Management of Asthma. National Clinical Guideline 101. Jan 2012. Available at: http://www.sign.ac.uk/guidelines/fulltext/101/. Accessed Mar 2014.

12 Allen and Hanburys Ltd. Seretide® 50, 125, 250 Evohaler® . Summary of Product Characteristics. May 2013. Available at: http://www.medicines.org.uk/emc/medicine/2914/SPC/Seretide+50%2c+125%2c+250+Evohaler/. Accessed May 2014.

13 Allen and Hanburys Ltd. Seretide® 100, 250, 500 Accuhaler® . Summary of Product Characteristics. Sep 2013. Available at: http://www.medicines.org.uk/emc/medicine/2317/SPC/Seretide+100%2c+250%2c+500+Accuhaler/. Accessed Mar 2014.

14 AstraZeneca UK Ltd. Symbicort® Turbohaler® 100/6 inhalation powder. Summary of Product Characteristics. Mar 2013. Available at: http://www.medicines.org.uk/emc/medicine/4820/SPC/Symbicort+Turbohaler+100+6%2c+Inhalation+powder./. Accessed Mar 2014.

15 AstraZeneca UK Ltd. Symbicort® Turbohaler® 200/6 inhalation powder. Summary of Product Characteristics. Mar 2013. Available at:

http://www.medicines.org.uk/emc/medicine/4821/SPC/Symbicort+Turbohaler+200+6+Inhalation+powder/. Accessed Mar 2014.
16 AstraZeneca UK Ltd. Symbicort® Turbohaler® 400/12 inhalation powder. Summary of Product Characteristics. Mar 2013. Available at: http://www.medicines.org.uk/emc/medicine/11882/SPC/Symbicort+Turbohaler+400+12%2c+Inhalation+powder./. Accessed Mar 2014.
17 Napp Pharmaceutical Ltd. Flutiform® 50 microgram/5 microgram, 125 microgram/5 microgram, 250 microgram/10 microgram inhalation suspension. Summary of Product Characteristics. Nov 2013. Available at: http://www.medicines.org.uk/emc/medicine/26954/SPC/flutiform+50+microgram+5+microgram%2c+125+microgram+5+microgram+and+250+microgram+10+microgram+per+actuation+pressurised+inhalation%2c+suspension/. Accessed Mar 2014.
18 Chiesi Ltd. Fostair® 100/6 inhalation solution. Summary of Product Characteristics. Jan 2013. Available at: http://www.medicines.org.uk/emc/medicine/21006/SPC/Fostair+100+6+inhalation+solution/. Accessed Mar 2014.
19 Woodcock A, Bleecker ER, 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. *Chest* 2013; 144 (4): 1222-9.
20 European Medicines Agency. Assessment Report for Relvar® Ellipta®▼. Procedure No.: EMEA/H/C/002673. Sep 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002673/WC500157635.pdf. Accessed May 2014.
21 National Institute for Health and Care Excellence. Evidence summary ESNM34 asthma : fluticasone furoate/vilanterol (Relvar® Ellipta®▼) combination inhaler. Mar 2014. Available at: http://publications.nice.org.uk/esnm34-asthma-fluticasone-furoatevilanterol-relvar-ellipta-combination-inhaler-esnm34/key-points-from-the-evidence. Accessed Apr 2014.
22 UK Medicines Information. In use product safety assessment report for Relvar® Ellipta®▼ (fluticasone furoate/vilanterol inhalation powder). Apr 2014. Available at: http://www.ukmi.nhs.uk/filestore/ukmianp/FluticasonevilanterolRelvar_Mar-2014.pdf. Accessed Apr 2014.
23 Prescribing Services Ltd. drugtariff.co.uk. Apr 2014. Available at: https://www.drugtariff.co.uk/. Accessed Apr 2014.
24 York Health Economics Consortium, School of Pharmacy University of London. Evaluation of the scale, causes and costs of waste medicines. 2010. Available at: http://discovery.ucl.ac.uk/1350234/. Accessed Apr 2014.
25 NHS Wales. Health in Wales: Asthma. May 2014. Available at: http://www.wales.nhs.uk/ourservices/unscheduledcareconditions/asthma. Accessed May 2014.
26 Simpson CR, Sheikh A. Trends in the epidemiology of asthma in England: a national study of 333,294 patients. *J R Soc Med* 2010; 103: 98-106.
27 Asthma UK. 9 out of 10 people in Wales may be getting substandard care. 2014. Available at: http://www.asthma.org.uk/News/9-out-of-10-people-with-asthma-in-wales-may-be-getting-substandard-care. Accessed Apr 2014.
28 GlaxoSmithKline. Company marketing data on file. Feb 2013.
29 Healthline. Peak expiratory flow rate. 2014. Accessed Apr 2014.