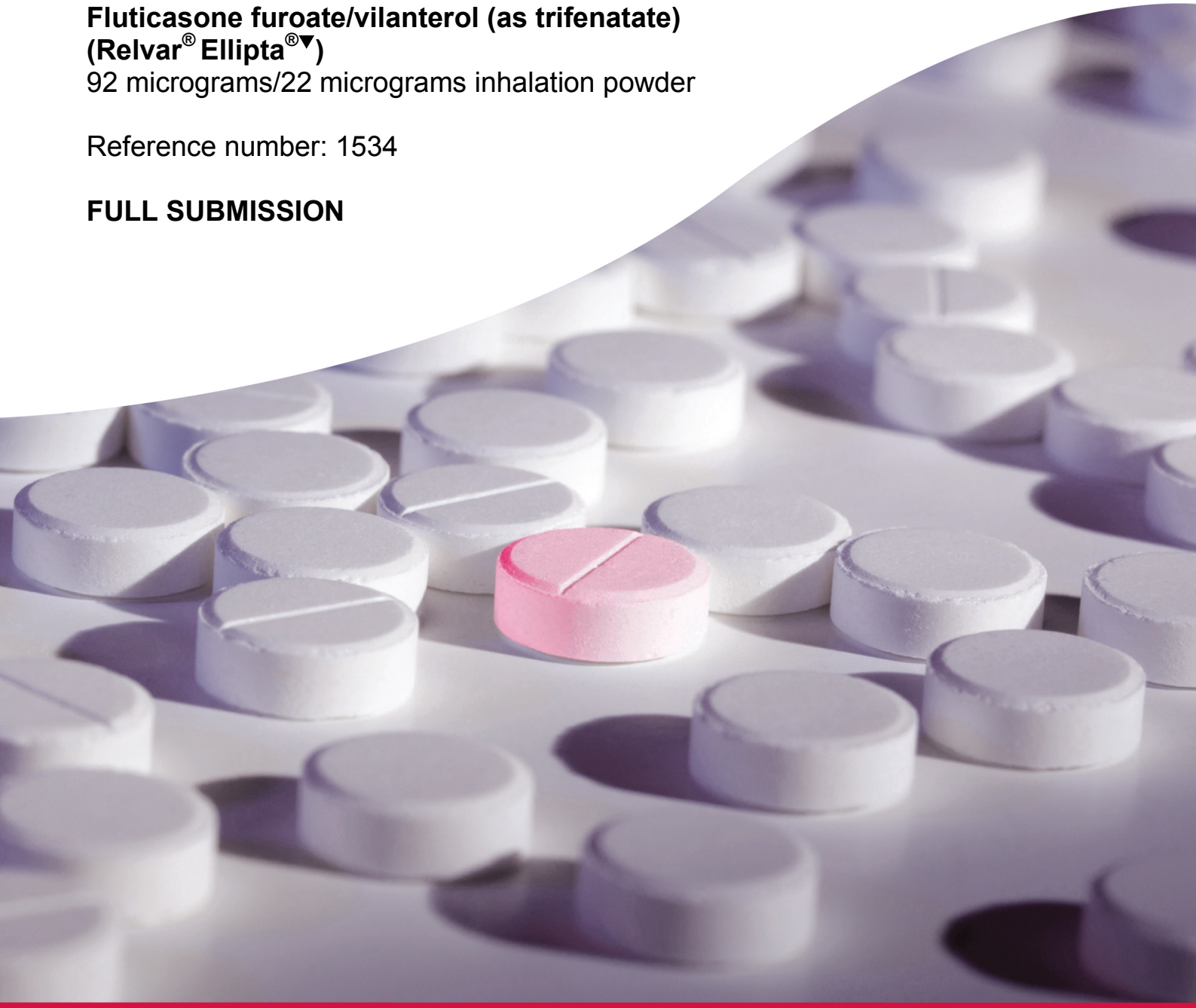
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

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

Reference number: 1534

FULL SUBMISSION



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

This assessment report is based on evidence submitted by GlaxoSmithKline on 5 December 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Fluticasone furoate/vilanterol (Relvar® Ellipta®▼) is indicated for the symptomatic treatment of adults with chronic obstructive pulmonary disease with a forced expiratory volume in one second < 70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy[2].
Dosing	The recommended dose is a single inhalation of 92 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate) once daily using the Ellipta® inhaler[2].
Marketing authorisation date	13 November 2013[2].

2.0 DECISION CONTEXT

2.1 Background

Chronic obstructive pulmonary disease (COPD) is a chronic disorder characterised by consistent airflow obstruction, which is usually progressive and not fully reversible[3]. This is associated with persistent and progressive breathlessness, a chronic productive cough and limited exercise capacity. COPD can be used to describe a number of conditions, such as chronic bronchitis, emphysema, chronic obstructive airways disease and chronic airflow limitation[3]. Smoking is the main cause of COPD, but other factors include exposure to dusts, fumes and certain chemicals[4]. It is estimated that three million people have COPD in the UK, of which approximately 900,000 have been diagnosed[5]. The number of patients with COPD in Wales in 2012–2013 was 67,773[6]. COPD prevalence increases with age and is rarely seen in people under the age of 35 years[3].

COPD treatment aims to reduce symptoms, lower the frequency and severity of exacerbations, improve health status and increase exercise tolerance[7]. Bronchodilators, including beta$_2$-agonist and muscarinic antagonist (anticholinergic) inhalation therapies, are central to the management of COPD symptoms[7]. For patients with stable COPD, a long-acting muscarinic receptor antagonist (LAMA) or the combination of an inhaled corticosteroid (ICS) with a long-acting beta$_2$-agonist (LABA) is recommended[5,7]. Fluticasone furoate/vilanterol (Relvar® Ellipta®▼) is an ICS/LABA combination product, licensed to treat symptoms of COPD in adults[1,2].

2.2 Comparators

The comparators included in the company submission were:

- Fluticasone propionate/salmeterol (Seretide® 500 Accuhaler®) 500 micrograms/ 50 micrograms inhalation powder[8]
- Budesonide/formoterol fumarate (Symbicort® Turbohaler®) 400 micrograms/ 12 micrograms inhalation powder[9]

2.3 Guidance and related advice

- National Institute for Health and Care Excellence (NICE). NICE Pathways (2013)[10].
- Chronic obstructive pulmonary disease (2013)[11].
- NICE. Chronic obstructive pulmonary disease: evidence update (2012)[12].
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD (updated 2014)[7].
- NICE. Chronic obstructive pulmonary disease. Clinical Guideline 101 (2010)[5].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of the LAMAs aclidinium bromide and glycopyrronium bromide:

- Aclidinium bromide (Eklira® Genuair®▼) is recommended as an option for use within NHS Wales as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (2013)[13].
- Glycopyrronium bromide (Seebri® Breezhaler®▼) is recommended as an option for use within NHS Wales as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (2013)[14].

In February 2014, AWMSG will be considering the use of the LABA/LAMA combination product indacaterol/glycopyrronium (Ultibro® Breezhaler®▼) as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD[15].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included a phase III trial (HCZ113107) comparing the efficacy of fluticasone furoate/vilanterol (FF/VI) versus fluticasone propionate/salmeterol (FP/Sal) in patients with COPD[1]. The applicant company have also provided mixed treatment comparisons (MTCs) evaluating FF/VI against FP/Sal and budesonide/formoterol fumarate (Bud/F).

In addition, the applicant company submitted evidence from four placebo-controlled phase III trials, using FF/VI in patients with COPD; however, these trials do not provide effectiveness data versus the comparators and so are not further discussed.

3.1 HCZ113107 study

HCZ113107 was a 12-week, multicentre, randomised, double-blind, parallel-group phase III study to evaluate the clinical superiority of FF/VI 92 micrograms/ 22 micrograms delivered via Ellipta® dry powder inhaler (DPI) to FP/Sal 500 micrograms/50 micrograms using an Accuhaler® DPI in patients (≥ 40 years) with moderate to very severe COPD[1,16,17]. Patients (n = 528) were stratified according to reversibility to salbutamol and randomised (1:1) to one of two treatment arms: FF/VI once-daily and a placebo via Accuhaler® twice-daily; or FP/Sal twice-daily with a once-daily placebo via Ellipta®. Salbutamol was supplied for symptomatic relief during the study, as were other concomitant medicines where dose did not change during the study[17].

The primary endpoint, the change from baseline trough 24-hour weighted-mean forced expiratory volume in one second (FEV_1) at 12 weeks (see Glossary for endpoint definition), determined for the intent-to-treat population, was 130 ml in the FF/VI arm (n = 266) and 108 ml in the FP/Sal arm (n = 262)[1,17]. The difference between treatments was not statistically significant (p = 0.282) and therefore the superiority endpoint was not met[16] (see Table 1). A post-hoc Bayesian re-analysis of the primary endpoint suggested that FF/VI was as effective as FP/Sal, with an 86% probability that the improvement in weighted-mean FEV_1 is numerically in favour of FF/VI (treatment difference > 0 ml) and 20% probability that the treatment difference in favour of FF/VI is > 40 ml[1].

Statistical significance was not achieved for the primary endpoint and therefore no statistical significance could be inferred for the secondary endpoints[17]. The results for time to onset of a FEV_1 increase of 100 ml above baseline on treatment day 1 and change from baseline in trough FEV_1 on day 85 (FEV_1 measured at 24 hours post dose at 12 weeks) are shown in Table 1. The health-related quality-of-life according to the St. George's Respiratory Questionnaire (SGRQ) total score was also measured as a secondary endpoint and showed a clinically meaningful change from baseline in SGRQ score (defined as a reduction of > 4 points) in the FF/VI arm only[17].

Table 1. Results of the HCZ113107 phase III trial[1,17].

	Treatments (mean ± standard deviation)		Treatment difference (with confidence intervals [CI])
	FF/VI (n = 266)	FP/Sal (n = 262)	
Primary endpoint			
Change from baseline in trough weighted-mean FEV_1 at 12 weeks[17]	130 ml ± 222 ml	108 ml ± 221 ml	22 ml (95% CI: −18 to 63) p = 0.282
Secondary endpoints			
Time to onset (≥100ml increase in FEV_1 from baseline on day 1[1]	16 minutes	28 minutes	p = 0.280
Change from baseline in trough FEV_1 on day 85[1,17]	111 ml ± 241 ml	88 ml ± 241 ml	23 ml (95% CI: −20 to 66) p = 0.294
SGRQ total score at week 12[1]	−4.3 ± 11.8	−3.0 ± 11.8	−1.3 (95% CI: −3.5 to 0.8) p = 0.215

3.2 Mixed treatment comparison

In the absence of trials directly comparing FF/VI and Bud/F, the applicant company conducted a systematic review to identify evidence of the clinical effect of FF/VI versus other ICS/LABA combination products in patients with COPD[1]. The systematic review identified all randomised controlled trials that compared any combination ICS/LABA product in patients aged ≥ 12 years with an established diagnosis of COPD (FEV_1 ≤ 80%). Studies must have reported a relevant outcome, which included COPD exacerbations, change from baseline FEV_1 and change from baseline and clinically relevant improvement in patient reported outcome measures, such as SGRQ score.

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 FF/VI 92 micrograms/22 micrograms was noninferior to FP/Sal 500 micrograms/50 micrograms and Bud/F 400 micrograms/12 micrograms for the endpoints of change from baseline in FEV_1, annual rate of moderate/severe exacerbations and change from baseline in SGRQ score. Results of the MTC for change from baseline FEV_1, based on 28 studies demonstrated noninferiority for FF/VI versus FP/Sal and Bud/F, and are displayed in Table 2[1].

Table 2. Differences between treatments from MTC analyses[1].

Treatment	Comparator	Mean difference or hazard ratio (95% credible interval)	Probability of superiority*	Probability of noninferiority
Mean differences in FEV_1				
FF/VI	FP/Sal	0.023 (−0.002 to 0.048)	0.962	>0.999[†]
FF/VI	Bud/F	0.027 (−0.007 to 0.061)	0.939	>0.999[†]
Hazard ratios for exacerbation rates				
FF/VI	FP/Sal	0.961 (0.499 to 1.833)	0.642	0.787[§]
FF/VI	Bud/F	0.887 (0.439 to 1.721)	0.706	0.838[§]
Mean differences in SGRQ scores				
FF/VI	FP/Sal	−1.595 (−4.483 to 1.293)	0.860	0.999[¶]
FF/VI	Bud/F	−1.404 (−4.581 to 1.772)	0.810	0.996[¶]

* probability that treatment is superior to comparator.
[†] probability that treatment is noninferior to comparator as defined by a margin of 50 ml.
[§] probability that treatment is noninferior to comparator as defined by a 20% margin.
[¶] probability of noninferiority as defined by a score difference of 3 points.

An MTC investigating event rates of moderate/severe exacerbations in patients with COPD, did not find a statistical difference between FF/VI, FP/Sal and Bud/F. Health-related quality-of-life (SGRQ scores), analysed via a further MTC, demonstrated noninferiority for FF/VI versus FP/Sal and Bud/F. The probabilities for noninferiority of FF/VI versus the comparators were > 99% for the change from FEV_1 and SGRQ score and > 78% for the rate of exacerbations[1].

3.3 Comparative safety

The number of adverse events (AEs) in the two arms of trial HCZ113107 was similar; AEs occurred in 73/266 patients (27%) in the FF/VI arm and in 68/262 patients (26%) in the FP/Sal arm, and of these 4 (2%) and 9 (3%) were considered to be treatment-related[1,17]. Non-fatal serious AEs (SAEs) were reported in six patients (2%) in the FF/VI arm versus three patients (1%) in the FP/Sal arm but no SAEs were considered by the investigators to be treatment-related. One patient who had received FF/VI died as a result of congestive heart failure during the follow-up period, but this was not considered to be treatment-related. Oral candidiasis, the most frequent treatment-related AE, was recorded in two patients in the FF/VI arm and in four patients in the FP/Sal arm. The number of patients withdrawing from treatment due to AEs was six (2%) for the FF/VI arm and three (1%) for the FP/Sal arm; however, none of these AEs were considered to be treatment-related[1,17].

3.4 AWTTC critique

- During clinical study HCZ113107, no statistically significant difference in change from baseline in trough weighted-mean FEV_1 was found between patients treated with FF/VI versus those treated with FP/Sal; the primary superiority endpoint was not met[17]. Improvements in SGRQ quality-of-life scores were not statistically different between the two treatments; however FF/VI achieved a clinically meaningful mean decrease from baseline in SGRQ score of > 4 points[17].
- In the absence of studies directly comparing FF/VI and Bud/F, the applicant company has followed a common approach and conducted a systematic review of available trials and MTCs. The results of the MTCs should be interpreted with some caution due to differences in the study patient populations, such as prior medication and age. Furthermore, the length of the studies varied from < 20 weeks to > 60 weeks, and the applicant company states that this factor has a significant impact on analysis of outcomes. The doses of the three ICS/LABA combination products being compared varied within the different trials included in the MTCs; additionally, the results of the exacerbations and

SGRQ MTC analyses were subject to uncertainty, due to the relatively large credibility intervals around the hazard ratios and mean differences derived for the comparison of FF/VI with other ICS/LABA combination treatments[1].

- Direct comparative data are limited to a 12-week trial of FF/VI versus FP/Sal[1].
- The incidence of pneumonia in the head-to-head HCZ113107 trial was low and similar in both arms, occurring in one patient receiving FF/VI and two patients receiving FP/Sal[17]. However, the company, as required in the risk management plan, is conducting a post-authorisation safety study to further investigate the risk of pneumonia in patients with COPD receiving FF/VI versus those receiving other ICS/LABA combination products[16].
- The company conducted a head-to-head comparison (study HCZ113107) of FF/VI versus FP/Sal in patients with COPD with a $FEV_1 \leq 70\%$ predicted (post-bronchodilator)[17]; this is consistent with the licensed indication for FF/VI, but differs slightly to that for FP/Sal, which is licensed in COPD patients with a $FEV_1 < 60\%$ predicted (pre-bronchodilator)[2,8]. Bud/F is indicated in COPD patients with $FEV_1 < 50\%$ predicted[9].
- Since the recommended dose of FF/VI for COPD is a single daily inhalation, and patients receiving either FP/Sal or Bud/F require two doses daily, FF/VI may be considered a more convenient treatment[2,8,9].
- FF has different pharmacological properties compared with FP[18] and has demonstrated higher in vitro glucocorticoid receptor affinity than FP and budesonide, although the clinical significance of this factor is unknown[1,16]. FF/VI shows a rapid onset of lung function improvement in COPD patients in clinical studies[17]. The clinical significance of differences in the selectivity profile of the $beta_2$ receptors to VI versus other LABAs is unknown[1,17,19].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-minimisation analysis (CMA) of FF/VI compared against FP/Sal or Bud/F in patients with moderate to very severe COPD[1]. It is assumed that FF/VI and both comparators are therapeutically equivalent. Direct comparative data are limited to a 12-week trial that found a numerically greater, but not statistically significant different, change from baseline in trough weighted-mean FEV_1 or SGRQ (health-related quality-of-life) scores for FF/VI compared with FF/Sal[17]. In the absence of direct evidence on comparative exacerbation rates for FF/VI and FP/Sal, and a lack of any direct comparative trial data for FF/VI versus Bud/F, a systematic literature review was undertaken to identify trials for inclusion in Bayesian network meta-analyses. Based on these adjusted indirect comparisons, the applicant company suggests that FF/VI is at least comparable to FP/Sal and Bud/F for the change from baseline in FEV_1, annual rate of moderate and severe exacerbations, and change from baseline in SGRQ score[1].

The cost analysis is limited to drug acquisition costs, which are estimated over a five-year time horizon and assume 100% adherence to treatment and continuation of therapy. Costs accrued after one year are discounted at 3.5% per annum[1].

4.1.2 Results

The results of the base case analysis are presented in Table 3. FF/VI is reported to be the least costly of the ICS/LABA combination products considered in the analysis, leading to (discounted) cost savings over FP/Sal of £777 and (discounted) cost savings over Bud/F of £604 per patient treated over five years[1].

Table 3. Base case cost estimates over one to five years[1].

ICS/LABA	Year 1	Year 2	Year 3	Year 4	Year 5
FF/VI	£338.23	£665.03	£991.82	£1,318.62	£1,645.42
FP/Sal	£497.86	£978.88	£1,459.91	£1,940.93	£2,421.96
Bud/F	£462.33	£909.03	£1,355.73	£1,802.43	£2,249.13
FF/VI vs. FP/Sal	**−£159.63**	**−£313.86**	**−£468.08**	**−£622.31**	**−£776.54**
FF/VI vs. Bud/F	**−£124.10**	**−£244.00**	**−£363.91**	**−£483.81**	**−£603.71**

Company-obtained market research data suggest 73.14% of patients currently receive FP/Sal 500/50 for COPD versus 26.86% receiving Bud/F 400/12. Based on a cost analysis weighted by these data, the company estimates savings of £150 in year one, rising to £730 over five years per patient treated with FF/VI instead of the current ICS/LABAs combination products[1].

In scenario analyses using discount rates of 0% and 6%, FF/VI continues to be cost saving relative to the comparators. Further analyses, labelled as exploring the impact of reducing adherence to the comparators, have also been provided, but as efficacy is assumed to be maintained, these analyses are, in effect, simply explorations of lower costs of comparators. Threshold analyses indicate that FF/VI remains cost saving while the cost of FP/Sal remains above 68% of its current costs, and Bud/F remains above 73% of its current costs; below these levels of current comparator costs FF/VI is more costly[1].

4.1.3 AWTTC critique

The reliability of the CMA presented by the company is dependent upon the extent to which FF/VI is considered to be therapeutically equivalent to the currently available ICS/LABA combination products in use in Wales. There are limited direct comparative data for FF/VI against FP/Sal, and no direct comparative data against Bud/F. Adjusted indirect comparisons have been made using data appropriately identified via systematic literature reviews, which appear to support comparable effects on FEV_1 and SGRQ score[1]. However, there are significant uncertainties in the assumption of equivalent effects on exacerbation rates, which are clinically and economically important endpoints. Under an assumption of therapeutic equivalence, the acquisition cost of FF/VI is lower than the current costs of FP/Sal and Bud/F.

Strengths of the economic evidence include:

- The applicant company has made significant efforts to address the lack of direct comparative evidence for FF/VI and the comparator products[1]. Bayesian network meta-analyses have been conducted to explore the relative efficacy of FF/VI and other ICS/LABA combination products in improving FEV_1, moderate to severe exacerbations and health-related quality of life. A systematic literature review was appropriately undertaken to identify potentially relevant studies for inclusion in these analyses.

Limitations of the economic evidence include:

- Indirect comparisons of trial data have been necessary to estimate comparative effectiveness[1]. Although these are adjusted comparisons, taking into account potentially important differences in trial design and populations, some limitations exist. The network of trials providing estimates of relative exacerbation rates is weak, being linked by only one trial of FF/VI that precluded assessment of consistency. Three of seven FP/Sal trials, included in the network for analysis of exacerbation rates used a FP dose of 250 micrograms twice-daily, rather than

the recommended 500 micrograms twice-daily. The company acknowledges a great deal of uncertainty in the relative efficacy of FF/VI on exacerbation rates, reflected in the wide credible intervals around the hazard ratio and lack of statistical significance versus placebo. Credible intervals around other endpoints are also wide, and reported probabilities of noninferiority and superiority should be viewed with caution.

- As the CMA framework assumes equivalence in all domains of health outcomes, this precludes exploration of any differences that may exist in important clinical and economic endpoints, such as exacerbation rates. Any potential differences in patient preferences for device and frequency of administration are not considered.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on cost-effectiveness of FF/VI in the symptomatic treatment of COPD.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on Welsh Government statistics, the company estimates a prevalence of COPD of 2.2% in Wales, equivalent to 67,773 patients in 2013[6]. A constant yearly incidence of 84/100,000 population is assumed based on published estimates[20], and an annual death rate of 2.03%–1.91% is assumed based on Office for National Statistics death registrations data[21]. Company-obtained market research data suggest 63% of patients currently receive ICS/LABA combination therapy; the company anticipates that 2% of these COPD patients would receive FF/VI in year one, rising to 15% in years four and five[1].

Annual acquisition costs of FF/VI are estimated at £338.23 for FF/VI, compared with £497.86 for FP/Sal and £462.33 for Bud/F. Assuming 50% displacement of each comparator, the company estimates a mean cost saving of £142 per patient per year[1].

5.1.2 Results

Table 4 presents the net uptake and cost estimates provided by the company[1].

Table 4. Company budget impact estimates[1].

	Year 1 (2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)
Number of COPD patients (receiving ICS/LABAs)	43,390	44,082	44,775	45,467	46,160
Uptake (%)	2%	6%	10%	15%	15%
Treated patients	868	2,645	4,477	6,820	6,924
Net medicines savings	−£142	−£142	−£142	−£142	−£142
Net budget impact	-£123,226	-£375,580	-£635,801	-£968,454	-£983,206

An alternative estimate of the budget impact of FF/VI has been provided by the company, based on market research data, which indicates that 73.14% of patients currently receive FP/Sal for COPD versus 26.86% receiving Bud/F. Using these figures, the weighted cost difference between FF/VI and the comparators is around £150, which would produce a net cost saving of £130,169 in year one, rising to £1,038,598 in year five[1].

5.1.3 AWTTC critique

- The company has adopted a pragmatic approach to estimate COPD patient numbers in Wales.
- Uptake estimates are subject to uncertainty, as in all budget impact exercises.
- Irrespective of actual uptake figures, under an assumption of therapeutic equivalence, FF/VI is less costly than the most commonly prescribed ICS/LABA combination product.

5.2 Table of comparative unit costs

Table 5 provides comparative acquisition costs for FF/VI and alternative licensed ICS/LABA combination products.

Table 5. Examples of acquisition costs.

Treatment	Example regimen	Approximate annual cost
Fluticasone furoate/vilanterol (Relvar® Ellipta®▼) inhalation powder in blister strips (for use with Ellipta® device), 92 micrograms fluticasone furoate/22 micrograms vilanterol	1 puff once daily	£338[22]
Fluticasone propionate/salmeterol (Seretide® 500 Accuhaler®) inhalation powder in blister strips (for use with Accuhaler® device), 500 micrograms fluticasone propionate/50 micrograms salmeterol	1 puff twice daily	£498
Budesonide/formoterol fumarate (Symbicort® 400/12 Turbohaler®) inhalation powder delivered in metered dose (for use with Turbohaler® device), 400 micrograms budesonide/12 micrograms formoterol fumarate	1 puff twice daily	£462
Cost of comparators obtained from drugtariff.co.uk[23]. This table does not imply therapeutic equivalence of the medicines and doses listed. See Summaries of Products Characteristics for full dosing details[2,8,9].		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, fluticasone furoate/vilanterol 92 micrograms/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 fluticasone furoate/vilanterol 92 micrograms/22 micrograms (Relvar® Ellipta®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted two studies that are likely to report in the next 12 months. The Salford Lung Real World Effectiveness Study is an open-label, 52-week phase III trial of FF/VI versus existing COPD maintenance therapies, due to report in the first quarter of 2015[24]. A preference study of FF/VI versus FP/Sal in COPD patients is projected to report in the second quarter of 2014[25].

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: 3 December 2013.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Chronic obstructive pulmonary disease (COPD)

National Institute for Health and Care Excellence use the following working definition of COPD:

- Airflow obstruction is defined as a reduced FEV_1/FVC ratio, such that FEV_1/FVC is less than 0.7.
- If FEV_1 is ≥ 80% FEV_1 predicted, a diagnosis of COPD should only be made in the presence of respiratory symptoms, for example breathlessness or cough[5].

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[26].

FVC

Forced vital capacity is the volume of air that can be forcibly expelled from the lung from the maximum inspiration to the maximum expiration[26].

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[26].

Change from baseline in trough weighted-mean FEV_1

The weighted-mean FEV_1 was calculated in the HCZ113107 study from the pre-dose FEV_1 and the post-dose FEV_1 measurements at 5, 15, 30 and 60 minutes and at 2, 4, 6, 8, 12, 13, 14, 16, 20 and 24 hours after 12 weeks. The weighted-mean was the area under the curve of FEV_1 versus time divided by the time interval. The change from baseline in trough weighted-mean FEV_1 was the weighted-mean FEV_1 at 12 weeks minus the baseline FEV_1[1,17].

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