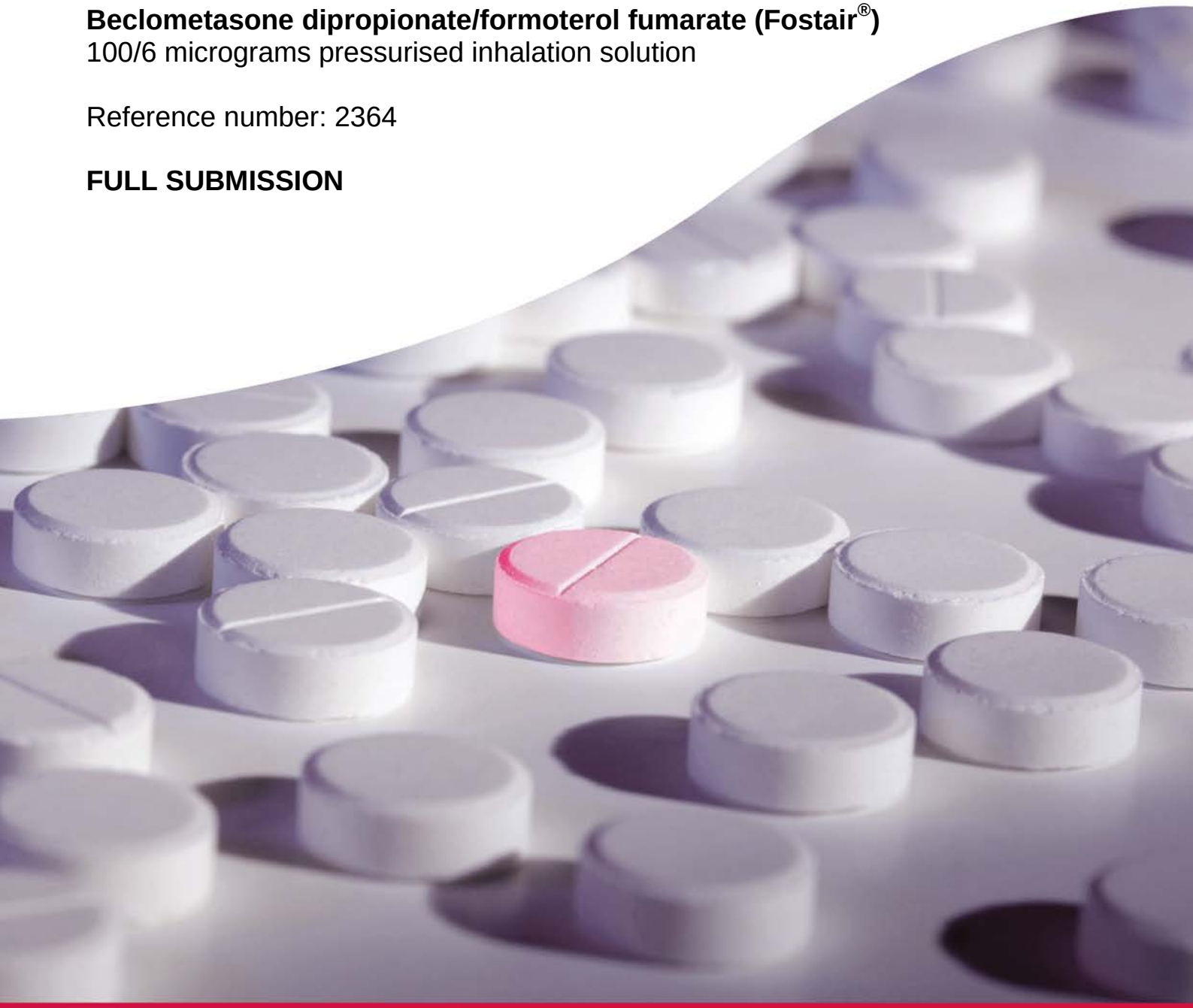
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Beclometasone dipropionate/formoterol fumarate (Fostair®)
100/6 micrograms pressurised inhalation solution

Reference number: 2364

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. Beclometasone dipropionate/formoterol fumarate (Fostair®) 100/6 micrograms pressurised inhalation solution. Reference number: 2364. April 2015.

AWMSG Secretariat Assessment Report
Beclometasone dipropionate/formoterol fumarate (Fostair®) 100/6 micrograms pressurised inhalation solution

This assessment report is based on evidence submitted by Chiesi Ltd on 7 April 2015[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Beclometasone dipropionate/formoterol fumarate (Fostair®) for the symptomatic treatment of patients with chronic obstructive pulmonary disease, with a FEV_1 < 50% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators[2].
Dosing	The recommended dose for adults 18 years and above is two inhalations of 100 micrograms of beclometasone dipropionate and 6 micrograms of formoterol fumarate twice daily[2].
Marketing authorisation date	7 April 2014 (first authorised 15 November 2007 for regular treatment of asthma where use of a combination product [inhaled corticosteroid and long-acting $beta_2$-agonist] is appropriate)[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[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 2013–2014 was 68,419[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. 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]. The National Institute for Health and Care Excellence (NICE) guidelines state a combination inhaler containing an ICS and a LABA should be offered if the forced expired volume in one second (FEV_1: see Glossary) is less than 50% predicted in people with COPD[5]. An ICS/LABA may also be considered in people with stable COPD and an FEV_1 of 50% or more of predicted who remain breathless or have exacerbations despite maintenance therapy with a LABA. Beclometasone dipropionate/formoterol fumarate (100/6 micrograms: BDP/FF–100/6) is an ICS/LABA fixed combination product in a pressurised metered dose inhaler (pMDI), licensed to treat symptoms of COPD in adults[1,2].

2.2 Comparators

The comparators included in the company submission were:

- Fluticasone propionate/salmeterol 500 micrograms/50 micrograms inhalation powder (Seretide® Accuhaler®: FP/S–500/50)
- Budesonide/formoterol fumarate 200 micrograms/6 micrograms inhalation powder (Symbicort® Turbohaler®: BUD/FF–200/6)
- Budesonide/formoterol fumarate 400 micrograms/12 micrograms inhalation powder (Symbicort® Turbohaler®: BUD/FF–400/12)
- Budesonide/formoterol fumarate 200 micrograms/6 micrograms inhalation powder (DuoResp® Spiromax®: BUD/FF–200/6)
- Budesonide/formoterol fumarate 400 micrograms/12 micrograms inhalation powder (DuoResp® Spiromax®: BUD/FF–400/12)
- Fluticasone propionate/salmeterol 250 micrograms/25 micrograms inhalation powder (Seretide® Evohaler®: FP/S–250/25): currently not licensed

2.3 Guidance and related advice

- NICE. Evidence summary ESNM47. Chronic obstructive pulmonary disease: beclometasone/formoterol (Fostair®) (2014)[8].
- NICE. NICE Pathways. Inhaled therapy in COPD (2014)[9].
- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease (2014)[7].
- NICE. Chronic obstructive pulmonary disease. Clinical Guideline 101 (2010)[5].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes details of three randomised, double-blind studies, which provide evidence comparing the use of BDP/FF–100/6 (Fostair® 100/6 micrograms) with the established ICS/LABA combinations for the treatment of COPD.

The first study evaluates BDP/FF–100/6 compared to BUD/FF–200/6 (Symbicort® 200/6 micrograms) and also FF–12 (formoterol fumarate 12 micrograms)[10]. The second study evaluates the efficacy of BDP/FF–100/6 versus FP/S–500/50 (Seretide® 500/50 micrograms)[11] and the remaining study compares the efficacy and safety of BDP/FF–100/6 with FF–12 alone[10,12].

3.1 Calverley et al (2010) study[10]

This was a 48-week, phase III, double-blind, double-dummy, randomised, active controlled, 3-arm parallel group, multicentre study, which investigated the efficacy and safety of BDP/FF–100/6 (fixed combination) pMDI compared to BUD/FF–200/6 (fixed combination), and FF–12 alone[1,10]. A total of 718 patients (≥ 40 years old) with COPD were randomised 1:1:1 to receive either BDP/FF–100/6; two puffs twice daily, BUD/FF–200/6; two puffs twice daily, or FF–12; one puff twice daily.

The two co-primary endpoints were the mean change in pre-dose morning FEV_1 from baseline to 48 weeks, and the mean rate of COPD exacerbations per patient per year[1,10]. Pre-dose morning FEV_1 increased from baseline to 48 weeks in all three treatment groups, with significant differences in the BDP/FF–100/6 and BUD/FF–200/6 groups (0.08 litres) versus the FF–12 (0.03 litres) group ($p < 0.05$)[1,10]. BDP/FF–100/6 was shown to be non-inferior to BUD/FF–200/6 with a difference of 0.002 litres (lower limit of 97.5% confidence interval [CI] was −0.052 litres). The number and rate of exacerbations were not significantly different between treatment groups. The mean exacerbation rate per person per year in the BDP/FF–100/6, BUD/FF–200/6 and FF–12 treatment groups was 0.414, 0.423 and 0.431, respectively. The number of exacerbations leading to hospitalisation was greater in the BDP/FF–100/6 group than in the other two groups (see Appendix 1, Table 1A for full results).

A post-hoc analysis carried out in patients with COPD exacerbations requiring oral corticosteroids and/or antibiotics who were managed in a hospital setting showed a similar mean rate of exacerbations per patient per year in all three groups[1,10].

Health-related quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ: see Glossary). The decrease in the SGRQ mean total scores at Week 48, compared with baseline, were similar for all three groups[1,10].

3.2 Wedzicha et al (2014) study[12]

This was a 48-week, phase III, double-blind, randomised, 2-arm parallel-group study which compared the efficacy of BDP/FF–100/6 with FF–12 in patients (≥ 40 years) with severe COPD and a documented history of at least one exacerbation in the previous year. Patients (n = 1,199) were randomised 1:1 to receive either BDP/FF–100/6; two puffs twice daily, or FF–12; one puff twice daily[1,12].

The two co-primary endpoints were COPD exacerbation rate over the entire treatment period and change in pre-dose morning FEV_1 from baseline, namely the randomisation visit, to week 12. Secondary endpoints included time to first COPD exacerbation, change from baseline in pre-dose morning FEV_1 at other visits, and health status as assessed by SGRQ total score at the end of treatment[1,12].

The percentage of patients with exacerbations was lower in the BDP/FF–100/6 group than in the FF–12 group[1,12]. The adjusted rate of exacerbations per patient per year was also lower in the BDP/FF–100/6 group, which resulted in a statistically significant adjusted rate ratio between the two treatment groups ($p < 0.001$). The adjusted mean change from baseline in pre-dose morning FEV_1 at week 12 was significantly greater in the BDP/FF–100/6 group than the FF–12 group ($p < 0.001$), as well as at all post-randomisation visits ($p < 0.05$ for all visits)[1,12] (see Appendix 1, Table 1A for results).

The improvement in SGRQ total score from baseline to the end of treatment was only statistically significant in the BDP/FF–100/6 group. This group also showed a significantly lower even risk for time to first COPD exacerbation when compared with those receiving FF-12[12].

3.3 Singh et al (2014) study[11]

This study was a 12-week, phase III, randomised, double-blind, double-dummy, 2-arm parallel group study, which compared the use of BDP/FF–100/6 with FP/S–500/50 in patients (≥ 40 years) with moderate to severe COPD. Patients (n = 419) were randomised 1:1 to receive either BDP/FF–100/6; two puffs twice daily, or FP/S–500/50; one puff twice daily[1,11].

The two co-primary endpoints were the equivalence between treatments in terms of transition dyspnoea index (TDI score: see Glossary) at the end of the study and the superiority of BDP/FF–100/6 in terms of the area under the curve ($AUC_{0\text{-}30min}$). The $AUC_{0\text{-}30min}$ was standardised by time of change from pre-dose in FEV_1 after inhalation of either treatment during the morning of the baseline visit. Secondary endpoints included pre-dose morning FEV_1 at week 12, post-dose FEV_1 at week 12, COPD total symptom score, SGRQ total score and occurrence of COPD exacerbations[1,11].

A similar percentage of patients in the BDP/FF–100/6 and the FP/S–500/50 groups had a change in TDI score ≥ 1 (1.32 and 1.15, respectively; $p = 0.56$). The $AUC_{0\text{-}30min}$ was statistically significantly different between the two groups: FEV_1 improved at 5, 15 and 30 minutes post-dose ($p < 0.001$ for all time points). These improvements were significantly greater in the BDP/FF–100/6 groups versus the FP/S–500/50 group at all time points ($p < 0.001$)[1,11] (see Appendix 1, Table 1A for results).

Secondary endpoints which showed significant improvement were post-dose FEV_1 at Week 12, COPD symptom score and SGRQ total score. However only the results for post-dose FEV_1 at Week 12 showed a significantly greater improvement between treatments; for BDP/FF–100/6 compared to FP/S–500/50 ($p < 0.001$ at each time point)[11].

3.4 Comparative safety

As Fostair® contains beclometasone dipropionate and formoterol fumarate, the type and severity of adverse events (AEs) associated with each of the compounds may be expected[1,2]. There is no incidence of additional AEs following concurrent administration of the two compounds[1,2]. In the Calverley et al (2010) study, the incidence of AEs, serious AEs (SAEs), adverse drug reactions (ADRs), and withdrawals due to AEs were not significantly different between treatment groups[1,10]. The most commonly reported AE was exacerbation or worsening of COPD, which was reported in 27–28% of patients. In the Wedzicha et al (2014) study, the incidence of AEs, SAEs, ADRs, and withdrawals due to AEs were also similar in both groups[1,12]. Study treatment emergent SAEs in the Singh et al (2014) study were statistically significantly lower in the BDP/FF–100/6 group compared with the FP/S–500/50 group (4 patients [1.9%] versus 13 patients [6.3%], respectively: $p = 0.024$,)[1,11]. NICE comment that this may be due to the higher BDP equivalent dose of ICS in the FP/S–500/50 inhaler[8]. Pneumonia was reported in zero patients in the BDP/FF–100/6 group and in three patients (1.4%) in the FP/S–500/50 group. Worsening of COPD was reported in zero patients treated with BDP/FF–100/6 and in two patients (1.0%) receiving FP/S–500/50. Other safety evaluations were similar for both groups[1,11].

3.5 AWTTC critique

- In the three studies, the changes in pre-dose morning FEV_1 were less than the improvement that the NICE guidelines on COPD considers to be clinically important (i.e. 0.100 litres or more)[5].
- The NICE clinical guideline on COPD recommends that the choice of treatment should take in to account the person's symptomatic response and preference, and the medicines' potential to reduce exacerbations, side effects and costs[5].
- BDP/FF–100/6 is administered using a pMDI; BUD/FF is administered using a Turbohaler®; FF is administered using an Accuhaler®; and fluticasone/vilanterol is administered using an Ellipta® device. Apart from fluticasone/vilanterol, which is administered once daily, these treatments are administered twice daily. The type of inhaler device may therefore affect the choice of treatment for an individual person[8].
- 100 micrograms of beclometasone dipropionate extrafine in Fostair® is equivalent to 250 micrograms of beclometasone dipropionate in a non-extrafine formulation. This should be taken into consideration when a patient is transferred from a beclometasone dipropionate non-extrafine formulation to Fostair®[2].

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 BDP/FF–100/6 compared against FP/S–500/50, FP/S–250/25, BUD/FF–200/6 and –400/12 (both strengths as Symbicort® Turbohaler® and also DuoResp® Spiromax®)[1]. It is assumed that BDP/F 100/6 is therapeutically equivalent to all four comparators. Direct comparative data are limited to a 12-week study for BDP/FF–100/6 versus FP/S-500/50 demonstrating equivalence in terms of the TDI score and superiority in terms of change from pre-dose in the first 30 minutes in FEV_1[11].

In addition, direct comparative data versus BUD/FF–200/6 from a 48-week study demonstrating non-inferiority in terms of lung function and exacerbations as previously described[10].

There is assumed equivalence between FP/S–500/50 and FP/S–250/25, and also between BUD/FF–200/6 (Symbicort® Turbohaler®) and the alternative product BUD/FF–200/6 (DuoResp® Spiromax®), including the higher strengths.

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. No annual discount rate has been applied[1].

4.1.2 Results

Prescribing data estimates obtained by the company suggest the market share of the comparators to be 35.1%, 31.5%, 13.0% and 5%, respectively. Presentations of fluticasone propionate/formoterol (Flutiform®: FP/F[13]) and fluticasone furoate/vilanterol (Relvar® Ellipta®: FF/V[14,15]) are estimated to each have market shares of less than 0.5% and so have not been included in the analysis[1]. A 5-year time horizon was chosen to align with budgetary planning timelines often used within the NHS[1]. The results of the analysis are presented in Table 1.

Table 1. Cost estimates over one to five years[1]

ICS/LABA	Year 1	Year 2	Year 3	Year 4	Year 5
BDP/FF–100/6 (Fostair® pMDI)	£356.73	£713.45	£1,070.18	£1,426.91	£1,783.63
FP/S–500/50 (Seretide® Accuhaler®)	£497.86	£995.72	£1,493.58	£1,991.44	£2,489.30
FP/S–250/25 (Seretide® Evohaler®)	£723.67	£1,447.35	£2,171.02	£2,894.69	£3,618.37
BUD/FF–200/6 or 400/12 (Symbicort® Turbohaler®)	£462.33	£924.67	£1,387.00	£1,849.33	£2,311.67
BUD/FF–200/6 or 400/12 (DuoResp® Spiromax®)	£364.64	£729.27	£1,093.91	£1,458.54	£1,823.18
BDP/FF–100/6 vs. FP/S–500/50	**–£141.13**	**–£282.27**	**–£423.40**	**–£564.53**	**–£705.67**
BDP/FF–100/6 vs. FP/S–250/25	**–£366.95**	**–£733.89**	**–£1,100.84**	**–£1,467.79**	**–£1,834.73**
BDP/FF–100/6 vs. BUD/FF–200/6 or 400/12 (Symbicort® Turbohaler®)	**–£105.61**	**–£211.21**	**–£316.82**	**–£422.43**	**–£528.03**
BDP/FF–100/6 vs. BUD/FF–200/6 or 400/12 (DuoResp® Spiromax®)	**–£7.91**	**–£15.82**	**–£23.72**	**–£31.63**	**–£39.54**

BDP/FF–100/6 is reported to be the least costly of the ICS/LABAs considered, leading to cost savings (over 5 years) of £706 over FP/S–500/50, £1,835 over FP/S–250/25 and £528 over BUD/FF–200/6 or 400/12 (Symbicort® Turbohaler®) and £40 over the alternative product of BUD/FF–200/6 or 400/12 (DuoResp® Spiromax®).

4.1.3 AWTTC critique

The CMA reflects the use of ICS/LABA combinations recommended within the treatment algorithm of the NICE guidelines (CG101) regarding the management of COPD in adults in primary and secondary care. BDP/FF–100/6 is therefore considered as an option for severe patients with an FEV_1 < 50% who remain symptomatic despite regular therapy with a long acting bronchodilator; this positioning is consistent with the licensed indication.

Although COPD is a chronic condition, the applicant company highlight in their submission that the CMA does not contain a mortality component or suggest differential survival effects between alternative treatments[1]. It assumes that BDP/FF–100/6 is equivalent to all treatments included in the analysis in terms of outcomes.

The reliability of the CMA presented by the applicant company is dependent upon the extent to which BDP/FF–100/6 is considered to be therapeutically equivalent to the current available ICS/LABA combination products in use in Wales.

As equivalence is assumed 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 the All Wales Therapeutics and Toxicology Centre (AWTTC) have not identified any published evidence on the cost-effectiveness of BDP/FF–100/6 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

The budget impact evidence presented by the company included a comparison of the costs associated with the use of BDP/FF–100/6, FP/S–500/50, BUD/FF–200/6, BUD/FF–400/12 and FP/S–250/25 to treat the symptoms of COPD in adults[1].

There are an estimated 68,419 patients with COPD in Wales, based on 2013–2014 data[6]. Using dispensing data, the company estimate that 40,447 patients are currently receiving inhaled ICS/LABA for COPD: the total number of units of ICS/LABA dispensed for COPD between October 2013 and September 2014 was 492,241, and with each unit equalling a 30-day supply, the total number of patients receiving ICS/LABA for COPD is 40,447[1]. The company estimate the number of people likely to be prescribed BDP/FF–100/6 (Fostair®) is 11,856. This figure is derived from the number of FP/S–250/25 (Seretide® Evohaler®) dispensed for COPD between October 2013 and September 2014 (144,287) and makes the assumption that all people currently receiving unlicensed FP/S–250/25 for COPD will be switched to BDP/FF–100/6[1].

The company state that there are no other predicted resources or direct costs associated with any of the treatment options[1].

5.1.2 Results

Table 2. Company budget impact estimates[1].

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	11,856	12,910	13,964	15,018	16,072
Uptake (%)	50%	75%	95%	100%	100%
Treated patients	5,928	9,683	13,266	15,018	16,072
Overall net cost of BDP/FF–100/6*	£2,115,255	£3,455,131	£4,733,632	£5,358,788	£5,734,812
Overall net cost of displaced FP/S*	£3,851,755	£6,291,590	£8,619,667	£9,758,040	£10,442,883
Overall net savings with BDP/FF–100/6 versus FP/S*	£1,736,500	£2,836,459	£3,886,035	£4,399,252	£4,708,071

*The data used for these calculations are taken from dispensing data obtained by the company. The number of dispensed units of all formulations of fluticasone propionate/salmeterol (Seretide® Evohaler®: i.e. 25/50 micrograms, 25/125 micrograms and 25/250 micrograms) have been used in these calculations with an average unit cost of £53.39. There may be some patients who will not be eligible to swap to BDP/FF–100/6.
BDP/FF–100/6: beclometasone dipropionate/formoterol fumarate (100/6 micrograms, respectively); FP/S: fluticasone propionate/salmeterol.

5.1.3 AWTTC critique

- Calculation of the number of patients eligible for BDP/FF–100/6 treatment in Wales, is based on dispensing data obtained by Chiesi Ltd[1].
- In estimating the number of patients likely to be prescribed BDP/FF–100/6, the company make the assumption that all patients currently receiving unlicensed FP/S–250/25 for COPD will be switched to BDP/FF–100/6[1]. There will be other patients that are also eligible to receive BDP/FF–100/6; therefore the calculations may be subject to some uncertainty based only on those patients currently receiving FP/S–250/25.
- The company also make the assumption that adherence is 100% (which may be a slight overestimate) and therefore there may be more patients eligible for BDP/FF–100/6[1].
- BDP/FF–100/6 is licensed for patients with FEV_1 < 50% predicted normal; however, the company acknowledge that patients with FEV_1 < 60% predicted normal may be included[1].

5.2 Comparative unit costs

Table 3 provides information on comparative treatment acquisition costs of FP/S–500/50, BUD/FF–200/6, BUD/FF–400/12, FP/S–250/25 and BDP/FF–100/6. These costs assume that each unit contains enough treatment for a 30-day period at the indicated dose and that patients will receive continuous treatment at the indicated dose throughout the year with 100% adherence[1].

Table 3. Cost and savings associated with BDP/FF–100/6 and comparators[1].

Treatment	Example dose	Annual cost per patient†	Annual savings per patient (BDP/FF–100/6 versus comparator)
FP/S–500/50 (Seretide® Accuhaler®)	One puff twice daily	£497.99	£141.17
BUD/FF–200/6 (Symbicort® Turbohaler®)	Two puffs twice daily	£462.46	£105.64
BUD/FF–400/12 (Symbicort® Turbohaler®)	One puff twice daily	£462.46	£105.64
BUD/FF–200/6 (DuoResp® Spiromax®)	Two puffs twice daily	£364.73	£7.91
BUD/FF–400/12 (DuoResp® Spiromax®)	One puff twice daily	£364.73	£7.91
FP/S–250/25 (Seretide® Evohaler®)	Two puffs twice daily	£723.87	£367.05
BDP/FF–100/6 (Fostair® pMDI)	Two puffs twice daily	£356.82	–

*These costs assume that each unit contains enough treatment for a 30-day period at the indicated dose and that patients will receive continuous treatment at the indicated dose throughout the year with 100% adherence.
†All costs per unit are based on the Monthly Index of Medical Specialities (MIMS) list prices as of January 2015[16].
BDP/FF–100/6: beclometasone dipropionate/formoterol fumarate (100/6 micrograms, respectively)[2]; BUD/FF–200/6: budesonide/formoterol fumarate (200/6 micrograms, respectively)[17,18]; BUD/FF–400/12: budesonide/formoterol fumarate (400/12 micrograms, respectively)[19,20]; FP/S–500/50: fluticasone propionate/salmeterol (500/50 micrograms, respectively)[21]; FP/S–250/25: fluticasone propionate/salmeterol (250/25 micrograms, respectively)[22]; pMDI: pressurised metered dose inhaler.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, beclometasone dipropionate/formoterol fumarate (Fostair®) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

The company do not anticipate that beclometasone dipropionate/formoterol fumarate (Fostair®) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no 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: 9 and 11 December 2014.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Forced expired volume in one second (FEV_1)

FEV_1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration, expressed in litres at body temperature and ambient pressure saturated with water vapour[23].

St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item questionnaire developed to measure health status (i.e. quality of life) in patients with diseases of airway obstruction, such as COPD. The total score is calculated from the scores in the three domains: Symptoms, Activity and Impacts (psycho-social). Psychometric testing has demonstrated its repeatability, reliability and validity; sensitivity has been demonstrated in clinical studies[24].

Transition Dyspnoea Index (TDI)

To rate their change from baseline or the previous visit, patients report their impression of change which is recorded as a score from -3 to +3 for each of the three components of the TDI (intensity of breathlessness, magnitude of task, magnitude of effort), as described in Table 3; the scores for each component are then added to give an overall focal score from -9 to +9[25]. A change of ≥ 1 unit is the minimally important difference[26].

Table 4. TDI scoring: change from previous visit[25].

-3	-2	-1	0	+1	+2	+3
major deterioration	moderate deterioration	minor deterioration	no change	minor improvement	moderate improvement	major improvement

REFERENCES

1 Chiesi Ltd. Form B: Detailed appraisal submission. Beclometasone dipropionate/formoterol fumarate (Fostair®). Apr 2015.

2 Chiesi Ltd. Fostair®. Summary of Product Characteristics. Apr 2014. Available at: http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1397196436455.pdf. Accessed Dec 2014.

3 National Institute for Health and Care Excellence. Quality Standards 10. Chronic obstructive pulmonary disease quality standard. Jul 2011. Available at: http://publications.nice.org.uk/chronic-obstructive-pulmonary-disease-quality-standard-qs10. Accessed Dec 2014.

4 Health and Safety Executive. Chronic Obstructive Pulmonary Disease (COPD) in Great Britain in 2014. Oct 2014. Available at: http://www.hse.gov.uk/statistics/causdis/copd/copd.pdf. Accessed Dec 2014.

5 National Institute for Health and Care Excellence. Clinical Guideline 101. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). Jun 2010. Available at: http://guidance.nice.org.uk/CG101. Accessed Dec 2014.

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

7 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Jan 2014. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Report2014_Feb07.pdf. Accessed Dec 2014.

8 National Institute for Health and Care Excellence. Evidence Summary ESNM47. Chronic obstructive pulmonary disease: beclometasone/formoterol (Fostair). Sep 2014. Available at: http://www.nice.org.uk/advice/esnm47. Accessed Dec 2014.

9 National Institute for Health and Care Excellence. NICE Pathways. Inhaled therapy in COPD. Dec 2014. Available at: http://pathways.nice.org.uk/pathways/chronic-obstructive-pulmonary-disease/inhaled-therapy-in-copd. Accessed Dec 2014.

10 Calverley PMA, Kuna P, Monsó E et al. Beclomethasone/formoterol in the managment of COPD: a randomised controlled trial. *Respiratory Medicine* 2010; 104 (12): 1858-68.

11 Singh D, Nicolini G, Bindi E et al. Extrafine beclomethasone/formoterol compared to fluticasone/salmeterol combination therapy in COPD. *BioMed Central Pulmonary Medicine* 2014; 14 (43): 1-9.

12 Wedzicha JA, Singh D, Vestbo J et al. Extrafine beclomethasone/formoterol in severe COPD patients with history of exacerbations. *Respiratory Medicine* 2014; 108 (8): 1153-62.

13 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 Apr 2015.

14 GlaxoSmithKline. Relvar® Ellipta®▼ 92 micrograms/22 micrograms. Summary of Product Characteristics. Jan 2015. Available at: http://www.medicines.org.uk/emc/medicine/28496/SPC/Relvar+Ellipta+92+micrograms+22+micrograms+inhalation+powder%2c+pre-dispensed/. Accessed Apr 2015.
15 GlaxoSmithKline. Relvar® Ellipta®▼ 184 micrograms/22 micrograms. Summary of Product Characteristics. Jan 2015. Available at: http://www.medicines.org.uk/emc/medicine/28495/SPC/Relvar+Ellipta+184+micrograms+22+micrograms+inhalation+powder%2c+pre-dispensed/. Accessed Apr 2015.
16 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Jan 2015. Available at: http://www.mims.co.uk/. Accessed Jan 2015.
17 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. Accessed Jan 2015.
18 Teva Pharma B.V. Duoresp® Spiromax® 160 micrograms/4.5 micrograms inhalation powder. Summary of Product Characteristics. Sep 2014. Available at: http://www.medicines.org.uk/emc/medicine/29186. Accessed Apr 2015.
19 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. Accessed Jan 2015.
20 Teva Pharma B.V. Duoresp® Spiromax® 320 micrograms/9 micrograms inhalation powder. Summary of Product Characteristics. Sep 2014. Available at: http://www.medicines.org.uk/emc/medicine/29187. Accessed Apr 2015.
21 Allen & Hanburys Ltd. Seretide® Accuhaler®. Summary of Product Characteristics. Dec 2014. Available at: http://www.medicines.org.uk/emc/medicine/2317. Accessed Jan 2015.
22 Allen & Hanburys Ltd. Seretide® Evohaler®. Summary of Product Characteristics. Dec 2014. Available at: http://www.medicines.org.uk/emc/medicine/2914. Accessed Jan 2015.
23 Miller MR, Hankinson J, Brusasco V et al. Standardisation of spirometry. *European Respiratory Journal* 2005; 26 (2): 319-38.
24 Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respiratory Medicine* 1991; Suppl B: 25-31.
25 Mahler DA, Weinber DH, Wells CK et al. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984; 85 (6): 751-8.
26 American Thoracic Society. Baseline dyspnea index (BDI) & transition dyspnea index (TDI). Feb 2015. Available at: http://www.thoracic.org/assemblies/srn/questionaires/bdi-tdi.php. Accessed Feb 2015.

Appendix 1. Additional clinical information

Table 1A. Overview of endpoints from Calverley et al (2010)[10], Wedzicha et al (2014)[12] and Singh et al (2014)[11] studies (intention-to-treat population).

Calverley et al (2010) study			
	BDP/FF–100/6 (N = 232)	**BUD/FF–200/6 (N = 238)**	**FF–12 (N = 233)**
Mean change (SD) in pre-dose morning FEV_1 (l) from baseline to week 48*	0.08 (± 0.28)[†] [§]	0.08 (± 0.28)[†]	0.03 (± 0.28)
Mean change (SD) in three hours post-dose (l) from baseline to week 48	0.20 (± 0.26)[†] [§]	0.20 (± 0.29)[†]	0.14 (± 0.29)[†]
Mean change (SD) in peak from baseline to week 48	0.29 (± 0.34) [†§]	0.26 (± 0.32)[†]	0.22 (± 0.31)[†]
Number (%) of patients with at least one exacerbation during the study	64 (27.6)	64 (26.9)	66 (28.3)
Mean exacerbation rate per patient per year*	0.414[†]	0.423[†]	0.431[†]
Number (%) of patients with exacerbations leading to hospitalisation	13 (5.6)	7 (2.9) [¶]	8 (3.4)
Mean rate of patients with exacerbations leading to hospitalisation per patient per year	0.074	0.033	0.040

Wedzicha et al (2014) study		
	BDP/FF–100/6 (N = 595)	**FF–12 (N = 591)**
Number (%) of patients with at least one exacerbation during the study	264 (44.4)	294 (49.7)
Adjusted exacerbation rate per patient per year (95% CI)*	0.804 (0.713 to 0.907)	1.118 (1.006 to 1.242)
Adjusted exacerbation rate ratio BDP/FF–100/6 versus FF–12 (95% CI)	0.719 (0.619 to 0.837), p < 0.001	
Adjusted mean change in pre-dose morning FEV_1 (l) from baseline to week 12 (95% CI)*	0.081 (0.062 to 0.100)	0.012 (−0.007 to 0.030)
Adjusted mean difference BDP/FF–100/6 versus FF–12 (95% CI) from baseline to week 12*	0.069 (0.043 to 0.095), p < 0.001	

Singh et al (2014) study		
	BDP/FF–100/6 (N = 211)	**FP/S–500/50 (N = 207)**
Adjusted mean TDI score at week 12 (95% CI)*	1.32 (0.87 to 1.77)	1.15 (0.70 to 1.60)
Mean difference in TDI scores between treatments at week 12 (95% CI)*	0.17 (−0.39 to 0.72), p = 0.56	
Percentage of patients with TDI ≥ 1 at week 12*	44.1	43.0
Adjusted mean (95% CI) $AUC_{0\text{-}30min}$ (l)*	0.18 (0.16 to 0.19)	0.11 (0.09 to 0.12)
Mean difference in $AUC_{0\text{-}30min}$ between treatments (95% CI)*	0.07 (0.05 to 0.10), p < 0.001	
Change (SD) in pre-dose morning FEV_1 (l) from baseline to week 12	0.07 (0.23) p < 0.001	0.06 (0.21) p < 0.001

*Primary endpoint
[†]Statistically significant versus baseline: p < 0.001
[§]Statistically significant versus FF–12: p < 0.05
[¶]statistically significant versus BDP/FF–100/6: p < 0.001

$AUC_{0\text{-}30min}$: area under the curve; BDP/FF–100/6: beclometasone dipropionate/formoterol fumarate (100/6 micrograms, respectively); BUD/FF–200/6: budesonide/formoterol fumarate (200/6 micrograms, respectively); CI: confidence interval; FEV_1: forced expiratory volume in one second; FF–12: formoterol fumarate (12 micrograms); FPS–500/50: fluticasone propionate/salmeterol (500/50 micrograms, respectively); l: litre; N: number of patients; SD: standard deviation; TDI: transition dyspnoea index.