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Beclometasone Dipropionate/ Formoterol

In an HFA-Propelled Pressurised Metered-Dose Inhaler

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Abstract

▲ A hydrofluoroalkane (HFA)-propelled pressurised metered-dose inhaler (pMDI) has been developed (using Modulite® technology) for a new fixed combination of beclometasone dipropionate/formoterol fumarate (BDP/formoterol) 100μg/6μg. Each actuation of the BDP/formoterol HFA pMDI 100μg/6μg delivers 86.4μg of BDP and 5μg of formoterol.

▲ BDP/formoterol HFA pMDI was associated with significantly higher morning peak expiratory flow (PEF) values than BDP administered alone via a chlorofluorocarbon (CFC) pMDI (including when BDP was administered at a higher dosage) in well designed trials in adults with mild to moderate or moderate to severe asthma.

▲ In terms of morning PEF values, BDP/formoterol HFA pMDI was noninferior to BDP plus formoterol administered via separate inhalers in well designed trials in adults with moderate to severe asthma.

▲ BDP/formoterol HFA pMDI was noninferior to fixed-combination budesonide/formoterol (the daily dosage of BDP was half that of budesonide) in terms of lung function, asthma symptoms and use of rescue medications in adults with moderate to severe asthma. BDP/formoterol HFA pMDI was also noninferior to, and had a faster onset of bronchodilation than, fixed-combination fluticasone propionate/salmeterol.

▲ BDP/formoterol 200μg/12μg per day or 400μg/24μg per day administered by the HFA pMDI was generally well tolerated. Moreover, a single high dose of BDP/formoterol (1000μg/60μg) was generally well tolerated in patients with asthma.

Features and properties of BDP/formoterol (Foster™, Formodual®)	
Featured indication	
Treatment of asthma where use of a combination of inhaled corticosteroid and a long-acting β_2-agonist is appropriate	
Mechanism of action	
BDP: corticosteroid	
Formoterol: long-acting β_2-agonist	
Dosage and administration	
Dose	200μg/12μg per day or 400μg/24μg per day
Frequency of administration	Twice daily
Route of administration	Inhalation (via HFA-propelled pressurised metered-dose inhaler)
Pharmacokinetic profile (twice-daily 200μg/12μg for 7 days) [values reported are for the BDP active metabolite B-17-MP and formoterol] in patients with asthma	
Mean peak plasma concentration (C_{max})	B-17-MP: 545 pg/mL
	Formoterol: 14.9 pg/mL
Mean time to C_{max}	B-17-MP: 0.25h
	Formoterol: 0.25h
Mean area under the plasma concentration-time curve from time 0–12h	B-17-MP: 1940 pg • h/mL
	Formoterol: 72.2 pg • h/mL
Most commonly occurring treatment related adverse events	
Headache, hoarseness, pharyngitis	

Asthma is one of the most common chronic diseases and is associated with considerable social burden and costs to healthcare systems.[1] It has been described as a chronic inflammatory disorder of the airways associated with increased airway hyperresponsiveness, airflow limitation and respiratory symptoms that include wheezing, breathlessness, chest tightness and coughing, especially during the night or early morning.[1,2] Symptoms tend to be variable, intermittent, become worse at night and may be prompted by stimuli such as exercise.[2]

Inhaled corticosteroids (e.g. beclometasone dipropionate [BDP], budesonide, fluticasone propionate) play an important role in maintaining long-term disease control in patients with asthma.[3] The addition of a long-acting inhaled β_2-agonist (e.g. formoterol fumarate [formoterol], salmeterol) is an option for patients who do not achieve optimal control with inhaled corticosteroids alone.[4] For example, studies have shown that adding formoterol to BDP is an alternative to increasing the BDP dosage in patients whose asthma symptoms are inadequately controlled with an inhaled corticosteroid alone.[5,6]

The phasing out of chlorofluorocarbons (CFCs) led to the development of pressurised metered-dose inhalers (pMDIs) that use hydrofluoroalkane (HFA) propellants. More recently, using Modulite® [1] technology, new pMDIs have been developed which use active compounds reformulated into solutions based on the propellant HFA 134a.[7] The advantages of Modulite® technology include stable and uniform dose delivery as well as the flexibility to tailor the quality of the aerosol cloud (by modulating particle size) and the quantity of drug particles that reach the lungs.[7] HFA pMDIs using the Modulite® platform that deliver BDP, budesonide or formoterol are available in various European countries.[8] A Modulite® HFA pMDI (Foster™, Formodual®) that delivers fixed-combination BDP/formoterol 100μg/6μg has also been developed (hereafter referred to as BDP/formoterol HFA pMDI). This article briefly summarises the design characteristics of the Modulite® HFA pMDI, as well as reviewing the pharmacodynamic properties of BDP and formoterol. Also reviewed are the pharmacokinetic properties of BDP/formoterol delivered via the HFA pMDI and the clinical profile of BDP/formoterol HFA pMDI in adults with asthma. Each actuation of the BDP/formoterol HFA pMDI 100μg/6μg delivers 86.4μg of BDP and 5μg of formoterol.

1. Inhaler Design and Delivery Characteristics

This section summarises the main characteristics of the Modulite® HFA pMDI. In addition, data concerning drug delivery from the HFA pMDI are available from *in vitro* and *in vivo* studies using a formoterol Modulite® HFA pMDI (Atimos®; Forair®)[9] and an *in vitro* study that assessed the BDP/formoterol combination.[10] The *in vivo* study, which is the first to examine high lung deposition using Modulite® technology in HFA pMDI solutions rich in extra-fine particles, included healthy volunteers, patients with moderate to severe persistent asthma (FEV_1 30–80%) or patients with severe chronic obstructive pulmonary disease (COPD) [n = 6 per group] who received radiolabelled formoterol 24μg via the HFA pMDI.[9] One study is available as an abstract and poster;[9] additional data have been provided by the manufacturer.[11]

- Using Modulite® technology, the characteristics of the aerosol cloud generated may be modulated by modifying the quantity of non-volatile components within the solution and the size of the actuator orifice diameter.[12,13] Both the particle size (mass median aerodynamic diameter [MMAD]) and amount of drug reaching the lung (fine particle dose [FPD]) can be tailored by manipulating these parameters.[12,13]
- In Modulite® HFA pMDIs, the drug is dissolved in the HFA 134a propellant with the aid of a co-solvent.[12,14] In addition, a non-volatile component may be added to the formulation in order to modulate particle size; the higher the amount of the non-volatile component, the higher the MMAD of the particles and vice versa.[15]

1 The use of trade names is for product identification only and does not imply endorsement.

• In practice, the particle size selected for drugs formulated in Modulite® HFA pMDIs is usually very small, with MMAD values of 0.8–1.2μm;[12] this allows homogeneous and uniform distribution throughout the entire bronchial tree.[9] As an example, the MMAD of formoterol was 0.8μm in an *in vitro* study examining particle size distribution with formoterol HFA Modulite® pMDI.[9]

• With the Modulite® HFA pMDIs, it is possible to tailor the amount of drug that may reach the lungs after inhalation, defined as FPD, by modulating the actuator orifice diameter (i.e. the lower the actuator orifice diameter, the higher the FPD and vice versa).[12,16]

• In the new extra-fine fixed-combination BDP/formoterol Modulite® HFA pMDI, both beclometasone and formoterol are formulated with small MMADs (1.4 and 1.5μm),[10] suitable for homogeneous distribution throughout the bronchial tree.

• Furthermore, in an *in vitro* study, the FPD of formoterol was 1.9μg, which corresponds to 38.6% of the delivered dose (fine particle fraction), and that of BDP was 34.5μg, corresponding to 39.7% of the delivered dose, indicating a high amount of active medication suitable for lung availability.[10] In addition, the ratio of the two drugs (mean ratio 17.6) was maintained at each stage of the Anderson Cascade Impactor, suggesting the likelihood of their co-deposition in the lungs.[10] Co-deposition, in turn, may lead to a synergistic interaction between the two drugs (section 2), similar to that demonstrated previously for other drugs.[17]

• Because of the extra-fine formulation, the nominal dose of BDP was reduced from 250μg (the BDP dose in the CFC pMDI) to 100μg, while maintaining a similar FPD,[11] resulting in similar lung deposition but a reduction in the quantity of corticosteroid available for systemic absorption.[18] BDP extra-fine HFA Modulite® 100 μg/actuation, developed as a single agent, was shown to be clinically equivalent to BDP CFC pMDI 250 μg/actuation, when the two drugs were compared at a dosage of 400 μg/day versus 1000 μg/day in patients with asthma.[19]

• On the other hand, because of the extra-fine formulation generated by the Modulite® technology, the FPD of formoterol was similar to that of the reference product.[11] Studies in patients with asthma have shown a clinical equivalence between formoterol HFA extra-fine Modulite® (two puffs of 6μg each) and formoterol DPI Aerolizer™ (one puff of 12μg).[11]

• With Modulite®, the use of fine orifices generates slow-moving clouds over a much longer period.[12] The reduced plume velocity minimises unwanted oropharyngeal impaction.[12] In addition, its long duration may improve the patient's hand-breath coordination allowing more time for inhalation.[12] The small particle size and reduced plume velocity mean that Modulite® HFA pMDIs can deliver drugs to the lungs independent of underlying airway obstruction.[9] Indeed, lung deposition of formoterol obtained with the HFA pMDI was 31%, 34% and 35% of the nominal dose (24μg as two puffs) in healthy volunteers, patients with asthma and patients with COPD, respectively.[9] Deposition in the oropharynx, stomach and actuator was ≈40%, 7–17% and ≈10%, respectively.[9]

2. Pharmacodynamic Profile

This section provides a brief overview of the pharmacodynamic properties of BDP and formoterol, administered alone and in combination. The systemic effects of BDP/formoterol administered by HFA pMDI in healthy volunteers are also discussed briefly in this section.[20]

• The anti-inflammatory activity of inhaled corticosteroids such as BDP is mediated by activation of the glucocorticoid receptor.[21] In the airways of asthmatic patients, inhaled corticosteroids suppress the influx of eosinophils, T cells and mast cells (reviewed by Chung and Adcock).[21] In addition, inhaled corticosteroid therapy reduces airway secretions, mucous production, airway microvascular leakage and reduces exhaled nitric oxide.[21]

• The therapeutic effect of BDP is largely attributable to its active metabolite beclometasone-17-monopropionate (B-17-MP), especially the fraction retained in lung tissue (section 3).[22] B-17-MP has

affinity for the glucocorticoid receptor ≈25-fold higher than that of BDP.[22] In terms of potency, B-17-MP has an anti-inflammatory effect similar to that of budesonide.[23]

- The long-acting β_2-agonist formoterol binds to β_2-adrenergic receptors resulting in activation of intracellular adenyl cyclase, which in turn catalyses the conversion of adenosine triphosphate to cyclic adenosine monophosphate (cAMP).[24] Increased cAMP levels lead to relaxation of airway smooth muscle and consequent bronchodilation.[24] Formoterol is moderately lipophilic and has a faster onset of action than salmeterol.[25-27]

- Interactions between inhaled corticosteroids and β_2-agonists at a molecular level may lead to complementary or synergistic effects.[21] An *ex vivo* study showed that incubation with BDP significantly ($p < 0.0001$) increased β_2-adrenergic receptor expression on induced sputum cells from patients with mild to moderate asthma,[28] although this finding needs to be confirmed by additional *in vivo* studies.[21] Moreover, β_2-agonists have been shown to activate the glucocorticoid receptor *in vitro*.[29]

- *In vitro*, treating human airway smooth muscle cells with both a β_2-agonist and a corticosteroid potentiated the corticosteroid-induced inhibition of tumour necrosis factor-α-mediated interleukin-8 (IL-8) release.[30]

- In induced sputum cells from patients with mild to moderate asthma, the release of granulocyte-macrophage colony-stimulating factor, IL-8 and RANTES (released on activation normal T cells expressed and secreted) was reduced to a significantly ($p < 0.0001$) greater extent by incubation with BDP plus formoterol than with either of the drugs alone.[28] Moreover, the nuclear translocation of glucocorticoid receptors was significantly ($p < 0.0001$) greater with BDP plus formoterol than with BDP or formoterol alone, in particular in macrophages and eosinophils.[28]

- In terms of systemic effects, serum cortisol was inhibited to a significantly ($p = 0.01$) lesser extent in healthy volunteers (n = 12) receiving a single dose of BDP/formoterol HFA pMDI 400μg/24μg than in those receiving BDP CFC pMDI 1000μg and formoterol 24μg administered by separate inhalers in an open-label, crossover, placebo-controlled study (study available as an abstract).[20] This reflects the smaller amount of corticosteroid available for systemic absorption with the extra-fine BDP/formoterol HFA pMDI.

3. Pharmacokinetic Profile

The pharmacokinetics of BDP/formoterol administered by the HFA pMDI were assessed in the open-label phase of a randomised, double-blind study in adult patients (n = 18) with moderate to severe asthma (see also section 5),[31] and in an open-label study in healthy volunteers (n = 12).[20] Patients in one study received twice-daily BDP/formoterol 200μg/12μg administered by the HFA pMDI for 7 days.[31] Healthy volunteers received a single administration of BDP/formoterol HFA pMDI 400μg/24μg (four puffs), BDP CFC 1000μg plus formoterol 24μg via separate MDIs (four puffs each) or placebo.[20] Both studies are available as abstracts;[20,31] quantitative results for one study[31] are data on file.[11]

- In a randomised, double-blind, placebo-controlled trial in patients with moderate to severe asthma,[11,31] BDP was rapidly absorbed and metabolised after repeat administration via the HFA pMDI in patients with moderate to severe asthma.[11] A mean plasma concentration of 387 pg/mL was reached 5 minutes post-dose; the mean plasma concentration decreased to 40.4 pg/mL within 15 minutes and was below the level of quantification after 30 minutes.[11]

- Mean peak plasma concentrations (C_{max}) of B-17-MP and formoterol were 545 and 14.9 pg/mL, both reached after a mean time (t_{max}) of 0.25 hours.[11] The mean area under the plasma concentration-time curve values from time zero to 12 hours (AUC_{12}) were 1940 and 72.2 pg • h/mL.[11]

- In the other study, healthy volunteers receiving a single dose of BDP/formoterol HFA 400μg/24μg had significantly ($p = 0.001$) lower systemic exposure to B-17-MP than those receiving BDP CFC plus formoterol in separate MDIs (see section 2 for results pertaining to systemic effects).[11,20]

- BDP is metabolised by esterase enzymes that are found in most tissues including the lung.[22] The main product of metabolism is the active metabolite B-17-MP and several minor less active metabolites.[22] Pulmonary metabolism of BDP to B-17-MP is essential for the topical anti-inflammatory activity of the drug.[32] Formoterol is metabolised in the liver via direct conjugation at the phenolic hydroxyl group, and *O*-methylation then glucuronide conjugation at the phenolic 2′-hydroxyl group.[24]
- Following repeat administration of BDP/formoterol HFA in the randomised, double-blind trial in patients with moderate to severe asthma,[11,31] the B-17-MP metabolite was rapidly eliminated from the body with a mean terminal half-life ($t_{1/2}$) of 3.74 hours ($t_{1/2}$ for formoterol not calculated as a clear elimination phase was not identified).[11]
- Furthermore, no pharmacokinetic interaction (i.e. no increase in systemic exposure) or pharmacodynamic interaction between BDP and formoterol was observed in these patients (see section 5 for further information regarding the lack of pharmacodynamic interaction between the two drugs).[31]

4. Therapeutic Efficacy

The efficacy of the fixed-combination BDP/formoterol HFA pMDI was evaluated in four randomised, double-blind, multicentre trials in adults with mild to moderate[33] or moderate to severe[34-36] asthma. One study compared BDP/formoterol HFA pMDI 100μg/6μg twice daily with BDP 500μg twice daily administered via a CFC pMDI for 12 weeks.[33] Another study compared BDP/formoterol HFA pMDI 200μg/12μg twice daily with BDP 500μg twice daily administered via a CFC pMDI either alone or in combination with formoterol 12μg twice daily administered via a dry powder inhaler for 24 weeks.[36] A third study compared BDP/formoterol HFA pMDI 200μg/12μg twice daily with fluticasone propionate/salmeterol 250μg/50μg twice daily administered via pMDI for 12 weeks[34] and a fourth study compared BDP/formoterol HFA pMDI 200μg/12μg twice daily with budesonide/formoterol 400μg/12μg twice daily administered via dry powder inhaler for 12 weeks.[35] All of the trials included a 2-week run-in period and all are available as abstracts,[33-36] supplemented by additional data provided by the manufacturer.[11]

Two studies included patients who were symptomatic despite prior inhaled corticosteroid therapy[33,36] with an FEV_1 of 60–85% and 40–80% of predicted.[11,33,36] Mean patient age was 40 and 47 years.[11,33,36]

The primary endpoint in all four studies was the mean morning pre-dose peak expiratory flow (PEF) assessed over the last 14 days of treatment.[33-36] Three studies assessed BDP/formoterol HFA for noninferiority versus the comparator.[34-36] Noninferiority was shown if the lower margin of the 95% CI for the between-group difference in morning PEF was higher than −20 L/min.[11,34-36] The intent-to-treat population comprised 227,[34] 216,[35] 395[33] and 643[11,36] patients.

Compared with Beclometasone Dipropionate Alone

- The morning PEF was significantly ($p < 0.001$) higher with BDP/formoterol HFA pMDI 200μg/12μg per day than with a double corresponding dosage of BDP CFC pMDI 1000 μg/day in adults with mild to moderate asthma[11,33] (monotherapy with BDP 400 μg/day administered via a Modulite® HFA pMDI has previously been shown to be clinically equivalent to BDP 1000 μg/day administered via a CFC pMDI [Becloforte®] in patients with moderate asthma[19]). The between-group difference of 22.8 L/min (95% CI 12.5, 33.2) favoured BDP/formoterol HFA.[33]
- Ninety-two asthma exacerbations occurred in BDP/formoterol HFA pMDI recipients, compared with 111 in BDP CFC pMDI monotherapy recipients.[33]
- The morning PEF was significantly ($p < 0.001$) higher with BDP/formoterol HFA pMDI 400μg/24μg per day than BDP CFC pMDI 1000 μg/day in adults with moderate to severe asthma.[11,36] The between-group difference in morning PEF of 30.22 L/min (95% CI 16.22, 44.23) favoured BDP/formoterol HFA.[36]

• Among patients reporting severe asthma exacerbations, at least one asthma exacerbation requiring oral corticosteroids occurred in 6.0% of BDP/formoterol HFA recipients and in 14.1% of BDP monotherapy recipients.[36]

Compared with Beclometasone Dipropionate plus Formoterol Administered Separately

• BDP/formoterol HFA pMDI 400μg/24μg per day was noninferior to BDP 1000 μg/day plus formoterol 24 μg/day administered via a CFC pMDI and dry powder inhaler in adults with moderate to severe asthma.[36] The between-group difference in morning PEF was 7.27 L/min (95% CI −6.29, 20.1), meeting the criterion for noninferiority.[36]

• Among patients reporting severe asthma exacerbations, at least one asthma exacerbation requiring oral corticosteroids occurred in 6.0% of patients receiving BDP/formoterol HFA pMDI and in 12.1% of patients receiving BDP plus formoterol via separate inhalers.[36]

Compared with Other Fixed-Combination Therapies

• BDP/formoterol HFA pMDI 400μg/24μg per day was noninferior to fluticasone propionate/salmeterol pMDI 500μg/100μg per day,[34] and to budesonide/formoterol 800μg/24μg per day administered via dry powder inhaler[11,35] in terms of the morning PEF in patients with moderate to severe asthma. Mean morning PEF values for the final 14 days of both studies are shown in figure 1.

• Lung function, asthma symptoms and use of rescue medication were significantly ($p < 0.001$) improved from baseline with both fixed combination therapies in both studies; there were no significant between-group differences.[34,35] There were also no significant between-group differences in the exacerbation rate[34,35] or the time to first exacerbation.[35]

• In terms of lung function, BDP/formoterol HFA pMDI was noninferior to budesonide/formoterol (the daily dosage of BDP was half that of budesonide). In addition, BDP/formoterol HFA pMDI had a more rapid onset of bronchodilation compared with fluticasone propionate/salmeterol pMDI in the first hour post-dose (data on file).[11,34,35]

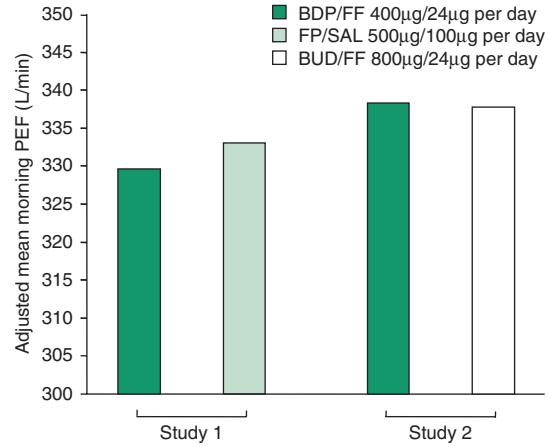

Fig. 1. Morning peak expiratory flow (PEF) in adults with moderate to severe asthma receiving beclometasone dipropionate/formoterol fumarate (BDP/FF) via an HFA pMDI in two randomised, double-blind, multicentre trials. Patients in one study (study 1)[34] received BDP/FF HFA pMDI 400μg/24μg per day or fluticasone propionate/salmeterol (FP/SAL) 500μg/100μg per day administered via pMDI (n = 227), whereas those in the other study (study 2),[35] received BDP/FF HFA pMDI 400μg/24μg per day or budesonide/formoterol (BUD/FF) 800μg/24μg per day administered via DPI (n = 216) for 12 weeks. All study drugs were fixed combination formulations and the daily dosage was administered as a divided dose twice daily. Morning PEF values were averaged over the last 14 days of treatment. **DPI** = dry powder inhaler; **HFA** = hydofluoroalkane; **pMDI** = pressurised metered-dose inhaler.

5. Tolerability

Data concerning the tolerability of BDP/formoterol HFA pMDI were obtained from clinical studies discussed in section 4 and a randomised, double-blind, three-way crossover, placebo-controlled tolerability trial.[31] The latter study examined whether in patients with asthma receiving regular treatment with the combination, doses in excess of the recommended dose of BDP/formoterol are at least as well tolerated as formoterol. In addition, the study examined whether the concomitant administration of BDP would exacerbate the decrease in serum potassium levels seen with high doses of formoterol (previously demonstrated for other fixed combinations of formoterol and inhaled

corticosteroids[37]). In this study, patients (n = 18) with moderate to severe asthma (50–80% predicted FEV_1) undergoing open-label maintenance treatment with twice-daily BDP/formoterol HFA pMDI 200μg/12μg were administered ten doses of BDP/formoterol 100μg/6μg, formoterol 6μg or placebo on each of days 14, 21 and 28 in addition to the morning maintenance dose.[31] The primary endpoint was the serum potassium level assessed over a 12-hour period, while the secondary endpoints included corrected QT (QTc) interval and plasma lactate levels as well as vital signs.[31] Results are available as abstracts and/or posters[31,33-36] and as data on file (including quantitative data).[11]

- In a 24-week study (see section 4 for further study design details), BDP/formoterol HFA/pMDI was generally well tolerated in patients with moderate to severe asthma.[11,36] The incidence of treatment-related adverse events was 12.3% in BDP/formoterol HFA pMDI 400μg/24μg per day recipients, 17.3% in BDP CFC pMDI 1000 μg plus formoterol dry powder inhaler 24 μg/day recipients and 15.0% in BDP CFC pMDI 1000μg/day recipients.[11] Only one serious adverse event (oesophageal candidiasis) in the BDP/formoterol group was considered to be treatment related.[11] Treatment-related adverse events with an incidence of ≥1.0% in any treatment group are summarised in figure 2.[11]

- In a 12-week study, the incidence of treatment-related adverse events was 5.0% in BDP/formoterol HFA pMDI 200μg/12μg per day recipients and 6.1% in those receiving BDP CFC pMDI 1000μg/day monotherapy.[11,33] Treatment-related adverse events with an incidence of ≥1.0% in any treatment group were headache (1.0% vs 2.0% for BDP monotherapy recipients) and pharyngitis (1.0% vs 0.5%).[11]

- The tolerability profile of BDP/formoterol HFA pMDI 400 μg/24μg was similar to that of fluticasone/salmeterol or budesonide/formoterol.[34,35] There were no significant between-group differ-

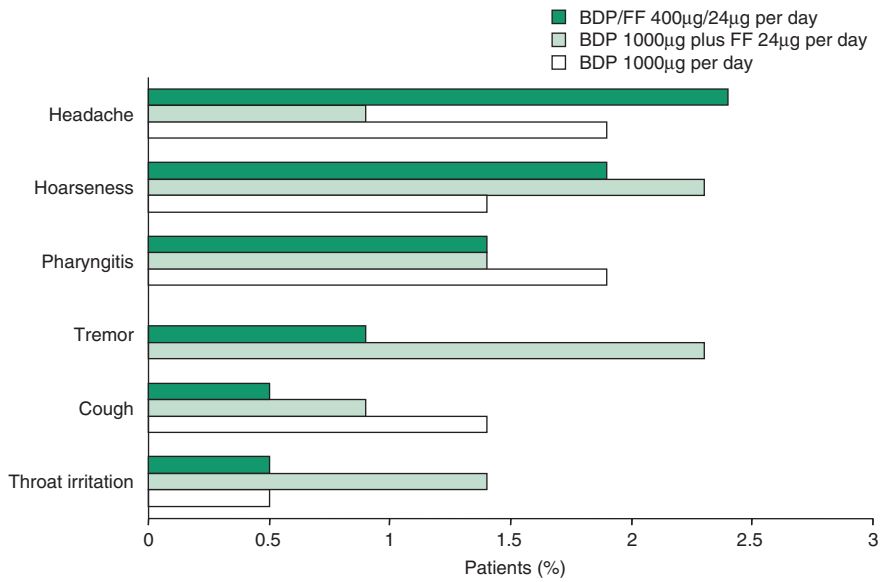

Fig. 2. Tolerability profile of beclometasone dipropionate/formoterol fumarate (BDP/FF) HFA pMDI in the treatment of patients with moderate to severe asthma. Incidence of treatment-related adverse events that occurred in ≥1.0% of BDP/FF HFA pMDI, beclometasone (BDP) plus formoterol (FF) or BDP monotherapy recipients.[11] In a randomised, double-blind, multicentre phase III trial, patients (n = 643) received BDP/FF 400μg/24μg per day administered via pMDI or BDP 1000μg per day administered via a CFC pMDI either alone or in combination with formoterol 24μg per day administered via a DPI for 24 weeks.[11,36] All study drugs were administered as a divided dose twice daily. No recipients of BDP monotherapy reported tremor.[11] **CFC** = chloroflourocarbon; **DPI** = dry powder inhaler; **HFA** = hydofluoroalkane; **pMDI** = pressurised metered-dose inhaler.

ences in terms of the number of patients with adverse events and effects on heart rate or ECG parameters.[11,34,35] There were also no significant between-group differences or differences from baseline in the 12-hour overnight urinary cortisol : creatinine ratio.[11,34]

- In the study assessing the effect of cumulative doses of BDP/formoterol HFA pMDI (1000μg/60μg), a single high dose of the combination was generally well tolerated in patients with moderate to severe asthma.[11,31] There was no significant difference in the decrease in serum potassium levels between patients receiving high-dose BDP/formoterol and those receiving maintenance therapy alone (i.e placebo recipients). However, high-dose formoterol was associated with a significant ($p < 0.02$ vs BDP/formoterol) decrease in the serum potassium level.[11,31]
- Vital signs, the QTc interval and plasma lactate levels were similar in high-dose BDP/formoterol HFA pMDI and high-dose formoterol recipients.[11,31] Although both treatment groups showed some differences from placebo, changes to these parameters were not considered clinically significant.[11,31]

6. Dosage and Administration

In Germany, fixed-combination BDP/formoterol 100μg/6μg HFA pMDI has been approved for use in the management of asthma in adolescents aged ≥12 years and adults.[38] The recommended dose of 1–2 inhalations twice daily is indicated as maintenance treatment in patients when the use of a combination of an inhaled corticosteroid and a long-acting β_2-agonist is appropriate. Each actuation of the BDP/formoterol HFA pMDI 100μg/6μg delivers 86.4μg of BDP and 5μg of formoterol.[38]

7. Beclometasone Dipropionate/Formoterol HFA: Current Status

BDP/formoterol HFA pMDI has been approved for use in Germany[38,39] and is awaiting approval in other European countries. In terms of mean morning PEF, the fixed-combination BDP/formoterol HFA pMDI is more effective than BDP administered alone (including at an increased dosage) in adults with asthma. Moreover, BDP/formoterol HFA pMDI is noninferior to BDP and formoterol administered via separate inhalers. It is also noninferior to fixed-combination budesonide/formoterol (the daily dosage of BDP was half that of budesonide). In addition, BDP/formoterol HFA pMDI had a faster onset of bronchodilation than, and was noninferior to, fixed-combination fluticasone propionate/salmeterol. BDP/formoterol HFA pMDI is generally well tolerated in patients with asthma.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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