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Budesonide/Formoterol Pressurized Metered-Dose Inhaler

In Chronic Obstructive Pulmonary Disease

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Abstract

▲ The corticosteroid budesonide and the rapid-onset, long-acting β_2-adrenoceptor agonist formoterol have been combined into a single pressurized metered-dose inhaler (pMDI) for use in patients with chronic obstructive pulmonary disease (COPD).

▲ Well designed 6- and 12-month clinical trials, twice-daily budesonide/formoterol pMDI 320 μg/9 μg effectively improved lung function in patients with moderate to very severe COPD.

▲ The co-primary endpoints of adjusted mean morning predose forced expiratory volume in 1 second (FEV_1) and 1-hour post-dose FEV_1 improved from baseline to a significantly greater extent with twice-daily budesonide/formoterol pMDI 320 μg/9 μg than with twice-daily placebo, budesonide pMDI 320 μg and formoterol dry powder inhaler 9 μg.

▲ Budesonide/formoterol pMDI was also associated with improvements from baseline in other measures of lung function, COPD control (including the time to first COPD exacerbation in the 12-month trial), symptoms and health status. These improvements were significantly greater than those observed with placebo and, for some endpoints, monotherapy with the individual components.

▲ Budesonide/formoterol pMDI was well tolerated in clinical trials in patients with COPD. Its overall adverse event profile is consistent with the known tolerability profiles of formoterol and budesonide, and is generally similar to that with placebo.

Features and properties of budesonide/formoterol in a pressurized metered-dose inhaler (pMDI) [Symbicort®] in chronic obstructive pulmonary disease (COPD)	
Featured indication	
Maintenance treatment of airway obstruction in patients with COPD, including those with chronic bronchitis and emphysema	
Mechanism of action	
Budesonide	Anti-inflammatory activity
Formoterol	Bronchodilation
Dosage and administration	
Route of administration	Inhalation
Dose (budesonide/formoterol)	320 μg/9 μg (i.e. two inhalations of 160 μg/4.5 μg)
Frequency of administration	Twice daily
Pharmacokinetic profile (geometric mean values in 26 patients with COPD receiving a single dose of budesonide/formoterol pMDI 960 μg/54 μg)	
Peak plasma concentration (C_{max})	Budesonide: 3.3 nmol/L Formoterol: 167 pmol/L
Time to C_{max}	Budesonide: 30 min Formoterol: 15 min
Area under the plasma concentration-time curve from time zero to infinity	Budesonide: 14.08 nmol • h/L Formoterol: 945 pmol • h/L
Elimination half-life	Budesonide: 5.3 h Formoterol: 9.2 h
Most common adverse events	
Reported in ≥3% of patients and more commonly than with placebo in pooled data from two 6- and 12-mo clinical trials	Nasopharyngitis, oral candidiasis, bronchitis, sinusitis, viral upper respiratory tract infection

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in adults throughout the world, contributing to a substantial social and economic burden.[1] In the US, COPD is estimated to affect ≈24 million adults, has been associated with direct medical costs of $US26.7 billion and total economic costs of $US42.6 billion in 2007,[2] and, together with allied conditions (i.e. chronic lower respiratory diseases), is the fourth leading cause of death.[2]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD),[1] COPD is a preventable and treatable disease, has both pulmonary and extra-pulmonary effects, and is associated with important co-morbidities. The pulmonary component of COPD is characterized by the presence of airflow limitation that is not fully reversible, generally progressive and usually accompanied by an abnormal inflammatory response of the lung to noxious particles or gases.[1] The risk factor most commonly associated with the development of COPD is cigarette smoking; other risk factors include environmental pollution, occupational exposure and severe hereditary deficiency of α_1-antitrypsin.[1]

The aims of treatment for patients with COPD are to relieve symptoms, prevent disease progression, prevent and treat complications and exacerbations, improve health status and exercise tolerance, and reduce mortality.[1] Although the progressive development of airflow limitation is slowed only by smoking cessation,[1] benefits have been shown with other interventions, including the use of long-term oxygen therapy, bronchodilators and inhaled corticosteroids (ICSs).[1,3] Bronchodilation with inhaled long-acting β_2-adrenoceptor agonist (LABAs) and/or anticholinergics has been associated with improvements in lung function, symptoms, exercise tolerance and health status.[1,3,4] ICSs have a broad range of clinically relevant anti-inflammatory effects, leading to reductions in exacerbations and improvements in health status.[1,3,5-7] Relative to treatment with the individual agents, treatment with an ICS plus a LABA is more effective in reducing exacerbations and improving lung function and health status.[1,3,8,9]

Current GOLD guidelines for the pharmacological treatment of stable COPD recommend a step-up approach based on the individual's disease severity and treatment response.[1] Regular treatment with bronchodilators (preferably long-acting agents) is the central component of COPD therapy, with a step-up to additional regular treatment with an ICS in symptomatic COPD patients with a forced expiratory volume in 1 second (FEV_1) of <50% predicted values (classified as stage III [severe] or stage IV [very severe] COPD) and repeated exacerbations.[1] The combination of a LABA and an ICS into a single inhaler simplifies the dosing regimen and may have beneficial effects on treatment adherence in patients for whom combination therapy is appropriate.[10]

In the US, the combination of budesonide (a synthetic corticosteroid) plus formoterol (a rapid-onset LABA) in a single hydrofluoroalkane-propelled pressurized metered-dose inhaler (pMDI),[11] hereafter referred to as budesonide/formoterol pMDI (Symbicort®), has recently been approved as a maintenance treatment for COPD.[11] This profile reviews the pharmacological and clinical properties of budesonide/formoterol pMDI in this new indication. The approved use of budesonide/formoterol pMDI as a maintenance treatment for asthma[11] has been previously reviewed,[12] and is beyond the scope of this review.

Medical literature on the use of budesonide/formoterol pMDI were identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

This section reviews the pharmacodynamic properties of budesonide and formoterol, with a focus on recent data relevant to the pMDI formulation in patients with COPD. Some data are from a randomized, double-blind, crossover trial in 90 patients with moderate to severe COPD and reversible airway obstruction,[13] and subsets of patients with moderate to very severe COPD in whom various

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pharmacodynamic parameters were evaluated in the pivotal 6-[14] or 12-month,[15] randomized, double-blind, multicentre clinical trials (see section 3 for trial design details and a discussion of clinical endpoint results).

- Budesonide, a potent and topically active corticosteroid, has a high affinity for the glucocorticoid receptor and a high ratio of topical to systemic activity.[16,17] The efficacy of budesonide in the treatment of COPD may be related to its anti-inflammatory activity, because it has a wide range of inhibitory activities against multiple cell types and mediators involved in inflammation.[11]
- The potent and selective β_2-adrenoceptor agonist formoterol is associated with a rapid onset of local bronchodilatory activity when inhaled.[11] It displays full agonist activity at β_2-adrenoceptors (the predominant adrenergic receptors in bronchial smooth muscle), but has low affinity for β_1-adrenoceptors (the predominant receptors in the heart).[18]
- Budesonide and formoterol have different mechanisms of action[16] and, therefore, each agent targets different aspects of COPD pathology. The two agents display complementary and additive effects when administered concomitantly.[16,19,20]
- In a rat model of COPD, the combination of budesonide and formoterol generally reduced levels of inflammation markers (bronchoalvelor lavage neutrophilia, plasma tumour necrosis factor-α and plasma fibrinogen) more effectively than monotherapy with either of the individual components.[20]
- Budesonide/formoterol provides a rapid bronchodilatory response in patients with COPD.[13-15] In subsets of patients receiving 12-hour serial spirometry in the 6-[14] and 12-month[15] trials ($n = 618$[14] and 491[15]), patients receiving budesonide/formoterol pMDI 320 μg/9 μg had a clinically significant improvement in FEV_1 of ≈15–18% at 5 minutes after administration on the day of randomization.
- The rapid bronchodilatory effect of budesonide/formoterol did not diminish over the 12-hour serial spirometry testing period.[14,15] Twice-daily budesonide/formoterol pMDI 320 μg/9 μg was associated with significantly ($p \leq 0.03$) greater mean improvements from baseline in mean FEV_1 at 12 hours and baseline-adjusted mean 12-hour FEV_1 than twice-daily placebo[14,15] or budesonide pMDI 320 μg (not available commercially; comparator in 6-month trial only)[14] on the day of randomization and at the end of treatment (i.e. the last assessment during randomized treatment), and twice-daily formoterol dry powder inhaler (DPI) 9 μg on the day of randomization in the 12-month trial[15] and at the end of treatment in both trials.[14,15]
- Budesonide/formoterol pMDI has a more rapid onset of a bronchodilatory action than salmeterol/fluticasone propionate pMDI.[13] In the crossover trial,[13] improvements from baseline in FEV_1 at 5 minutes (primary endpoint) were significantly ($p \leq 0.0001$) greater with single-dose budesonide/formoterol pMDI 320 μg/9 μg than with single-dose salmeterol/fluticasone propionate pMDI 50 μg/500 μg and placebo (adjusted ratios 105% [95% CI 103, 108] and 116% [95% CI 113, 119]).
- Budesonide/formoterol pMDI 320 μg/9 μg also had other beneficial effects on pulmonary function assessed by serial spirometry.[13-15] In the crossover trial, single-dose budesonide/formoterol pMDI 320 μg/9 μg was associated with significantly ($p < 0.0001$) greater improvements from baseline than placebo in inspiratory capacity (IC) at 15 minutes, FEV_1 and IC at 180 minutes, maximal increase in FEV_1 and IC, and average FEV_1 and IC over 180 minutes.[13] Budesonide/formoterol pMDI 320 μg/9 μg was associated with a significantly ($p = 0.02$) higher maximal increase in IC than salmeterol/fluticasone propionate pMDI 50 μg/500 μg.[13]
- In the 6-month trial,[14] mean adjusted improvements in maximum FEV_1 were also significantly ($p < 0.01$) greater with twice-daily budesonide/formoterol pMDI 320 μg/9 μg than with twice-daily placebo and budesonide pMDI 320 μg on the day of randomization and over the treatment period.
- Although there were no significant between-group differences in the adjusted mean change from baseline in pre-dose IC in the long-term trials,[14,15] twice-daily budesonide/formoterol pMDI 320 μg/9 μg was generally associated with significantly greater improvements from baseline in the adjusted mean change in 1-hour post-dose IC over the treat-

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ment period than twice-daily placebo ($p < 0.001$),[14,15] budesonide pMDI 320 μg ($p < 0.001$)[14] and formoterol DPI 9 μg ($p \leq 0.02$ in the 12-month study only).[15]

- Treatment with β_2-adrenoceptor agonists, such as formoterol, have been associated with cardiovascular effects through their activity on extrapulmonary β_2-adrenoceptors.[18,21] In the 6-[14] and 12-month[15] trials, there were no clinically meaningful differences between the groups receiving budesonide/formoterol pMDI and those receiving placebo or budesonide or formoterol monotherapy with regard to mean changes from baseline in pulse rate, BP, or serum glucose and potassium levels.
- Moreover, ECG monitoring did not show any clinically meaningful between-group differences in heart rate, PR interval, QRS duration, signs of cardiac ischaemia or arrhythmias.[14,15] Budesonide/formoterol pMDI, in common with other products containing β_2-adrenoceptor agonists, should be used with caution in patients with concomitant cardiovascular disease that could be adversely affected by such therapy.[11]
- Long-term treatment with ICSs, including budesonide, have been associated with hypercorticism and adrenal suppression in patients with COPD.[22] In subsets of patients who underwent 24-hour urinary cortisol measurements in the 6-[14] and 12-month[15] trials (n = 437[14] and 175[15]), clinically significant changes from baseline in 24-hour urinary cortisol were rare across the treatment groups, and between-group differences were not considered clinically important.
- Reductions in bone mineral density (BMD) and the development of increased intraocular pressure, glaucoma and cataracts have also been associated with long-term treatment with ICSs.[22] In subsets of patients in the 12-month trial in whom measurements of BMD (n = 320) or intraocular pressure and lenticular opacity (n = 461) were assessed,[15] BMD remained stable and clinically significant changes in ophthalmological assessment were infrequent across all groups.

2. Pharmacokinetic Profile

This section briefly reviews the pharmacokinetic properties of budesonide and formoterol, focusing on data relevant to the combination pMDI formulation in patients with COPD. Data are primarily derived from a randomized, open-label, crossover, single-dose study of budesonide/formoterol pMDI 960 μg/54 μg versus the same doses of individual components administered via separate inhalers (budesonide pMDI and formoterol DPI) in patients with COPD or asthma (both n = 26),[23] and a steady-state pharmacokinetic study in a subset (number of patients not provided) of patients with COPD in the pivotal 6-month clinical trial[14] and other studies that are reported the manufacturer's prescribing information.[11] The doses in the single-dose study were higher than therapeutic doses, in order to reliably estimate pharmacokinetic parameters.[23] The statistical significance of between-group differences was not reported.

- Budesonide and formoterol are rapidly absorbed after oral inhalation.[11] Following a single dose of budesonide/formoterol pMDI 960 μg/54 μg in patients with COPD, geometric mean values for maximum plasma concentration (C_{max}) for budesonide and formoterol were 3.3 nmol/L and 167 pmol/L;[23] the corresponding values for time to C_{max} were 30 and 15 minutes.[11]
- Systemic exposure to budesonide administered via the budesonide/formoterol pMDI was nearly identical to that of the same nominal dose of budesonide administered alone[11] or in combination with formoterol via separate inhalers in patients with COPD.[11,23] In the single-dose study,[23] mean budesonide area under the plasma concentration-time curve (AUC) and C_{max} values were respectively 3% lower and 4% higher with budesonide/formoterol 960 μg/54 μg administered via the combination pMDI than via separate inhalers.[23]
- At steady state, C_{max} and AUC values for budesonide were proportional to the increases in budesonide dosage from 160 μg to 320 μg twice daily in patients with COPD receiving twice-daily budesonide/formoterol pMDI 160 μg/9 μg or 320 μg/9 μg, budesonide pMDI 320 μg or budeso-

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nide pMDI 320 μg plus formoterol DPI 9 μg.[11] Exposure to budesonide was generally similar in the three treatment groups receiving budesonide 320 μg twice daily as monotherapy or in combination with formoterol in the same or separate inhalers.[11]

- In patients with COPD, systemic exposure to formoterol was somewhat higher when budesonide/formoterol was administered via the combination pMDI than via separate inhalers[11,23] and as formoterol alone.[11] Single-dose budesonide/formoterol pMDI 960 μg/54 μg had a mean formoterol AUC value that was 18% higher than that of the components administered via separate inhalers.[11,23] During steady-state administration of twice-daily budesonide/formoterol pMDI 320 μg/9 μg, AUC values for formoterol were about 16% and 30% higher than with twice-daily budesonide pMDI 320 μg plus formoterol DPI 9 μg and twice-daily formoterol DPI 9 μg monotherapy, respectively.[11]
- As expected, overall systemic exposure to budesonide and formoterol after administration of a single dose of budesonide/formoterol pMDI 960 μg/54 μg was similar in COPD and asthma patients.[23] Relative to asthma patients, COPD patients had budesonide and formoterol mean AUC values that were 12% and 15% higher and mean C_{max} values that were 10% lower and 12% higher.[23]
- Budesonide has a volume of distribution of ≈3 L/kg and is 85–90% bound to plasma proteins.[11] Plasma protein binding of formoterol is ≈50%.[11]
- Budesonide is rapidly and extensively metabolized by the cytochrome P450 (CYP) isoenzyme 3A4 to two essentially inactive metabolites.[11] Formoterol is metabolized primarily by direct glucuronidation, and by *O*-demethylation by CYP2D6 and CYP2C, followed by conjugation to inactive metabolites.[11]
- Budesonide and formoterol are both excreted primarily in the urine.[11] Approximately 60% of a radiolabelled dose of budesonide was excreted via the urine and the rest in the faeces.[11] In a study in four healthy volunteers, 62% of radiolabelled formoterol (administered orally and intravenously, simultaneously) was excreted in the urine and 24% in the faeces.[11]
- In the single-dose study of budesonide/formoterol pMDI 960 μg/54 μg,[23] the geometric mean elimination half-life ($t_{½}$) values for budesonide and formoterol were 5.3 and 9.2 hours in patients with COPD, which were similar to those following administration of the same nominal doses of each component via separate inhalers.[23] Mean $t_{½}$ values for budesonide and formoterol administered as budesonide/formoterol pMDI 960 μg/54 μg were 15% and 6% longer in COPD patients than in asthma patients.[23]
- There was no evidence of pharmacokinetic interactions between the two components of budesonide/formoterol pMDI in a single-dose, crossover study of budesonide pMDI 1280 μg, formoterol DPI 36 μg and budesonide pMDI 1280 μg plus formoterol DPI 36 μg in 28 healthy volunteers.[10]
- Although there are no reported data regarding pharmacokinetic interactions between inhaled budesonide/formoterol and other drugs, budesonide plasma concentrations may increase when potent inhibitors of CYP3A4 (e.g. ketoconazole, clarithromycin, nefazodone, telithromycin and ritonavir) are coadministered with budesonide.[11] Concomitant use of budesonide/formoterol pMDI and potent CYP3A4 inhibitors, therefore, requires caution.[11]
- The pharmacokinetics of budesonide and formoterol have not been studied in patients with renal or hepatic dysfunction.[11] Because both drugs are eliminated primarily by metabolism in the liver, patients with hepatic disease who are receiving budesonide/formoterol pMDI should be closely monitored.[11]

3. Therapeutic Efficacy

The efficacy of twice-daily budesonide/formoterol pMDI in adults with moderate to very severe COPD has been investigated in two similarly designed, 6-[14] or 12-month,[15] randomized, double-blind, double-dummy, multicentre trials (n = 1704[14] and 1964[15]).

Patients received twice-daily treatment with budesonide/formoterol pMDI 160 μg/9 μg (n = 281[14] and 494[15]) or 320 μg/9 μg (n = 277[14] and 494[15]), formoterol 9 μg DPI monotherapy

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(n = 284[14] and 495[15]) or placebo (n = 300[14] and 481[15]); the 6-month trial[14] also included treatment arms in which patients received twice-daily treatment with budesonide 320 μg pMDI monotherapy (n = 275) or budesonide 320 μg pMDI plus formoterol 9 μg DPI (n = 287). Results for budesonide/formoterol pMDI are presented only for the treatment arm receiving the dosage approved for the treatment of COPD in the US (i.e. twice-daily budesonide/formoterol pMDI 320 μg/9 μg).[11] For all treatment arms, the reported dose is the total metered dose of the two inhalations administered at the same time (i.e. two inhalations of budesonide/formoterol pMDI 160 μg/4.5 μg is reported as budesonide/formoterol pMDI 320 μg/9 μg).

Patients with moderate to very severe COPD (i.e. suitable candidates for combination therapy with an ICS plus a LABA) were enrolled in the trials.[14,15] Key inclusion criteria included age ≥40 years, diagnosis of symptomatic COPD for ≥2 years, ≥10 pack-year smoking history, prebronchodilator FEV_1 ≤50% of predicted normal, prebronchodilator FEV_1 : forced vital capacity (FVC) ratio <70%, Modified Medical Research Council dyspnoea scale score ≥2, and a history of at least one COPD exacerbation within 1–12 months before screening.[14,15] Exclusion criteria included a history of asthma, a history of allergic rhinitis before 40 years of age, significant/unstable cardiovascular disorders, homozygous α_1-antitrypsin deficiency or clinically significant respiratory tract disorder other than COPD.[14,15] Patients with worsening COPD symptoms within the 30 days before screening or during the run-in period were also excluded.[14,15]

Patients were randomized to one of the treatment arms after a run-in period of 2 weeks, during which patients received their prestudy stable dose of an ICS (whether it had been used alone or in combination with a LABA), stable doses of ipratropium bromide (to replace any previous use of anticholinergic therapies) plus rescue therapy with a short-acting β_2-adrenoceptor agonist (SABA) as required.[14,15] After randomization, patients were allowed to receive a number of concomitant medications (e.g. salbutamol [albuterol] pMDI as study rescue medication [not be used within 6 hours of each clinic visit], stable doses of non-nebulized ipratropium bromide [not be used within 8 hours of each clinic visit], bronchodilator-free antitussives and mucolytics, nasal corticosteroids and various medications to treat acute exacerbations), but were not allowed to use a number of other medications (e.g. long-acting anticholinergics, ephedrine-containing medications, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, disodium cromoglicates, and inhaled LABAs, SABAs and corticosteroids [other than study medications]).

Demographic and baseline disease characteristics were generally similar across treatment groups.[14,15] Across all treatment groups in both trials, mean patient age was 62.9–63.7 years, 92–95% of patients were White, 39–45% of patients were current smokers, and patients had a mean time since first COPD symptoms of 117–135 months, a median smoking history of 40–42 pack-years, a mean prebronchodilator FEV_1 of 1.0–1.1 L at baseline, and a post-bronchodilator FEV_1 of 38.6–41.3% of predicted normal at screening.[14,15] Co-morbid conditions were common in the overall populations of the 6-[14] and 12-month[15] trials; 42%[14,15] of patients in both trials had hypertension, 24%[14] and 22%[15] had lipid profile abnormalities, 18%[14,15] in both trials had cardiac disease, 10%[14] and 11%[15] had diabetes mellitus, 8%[14] and 11%[15] had osteoporosis, and 5%[14,15] in both trials had cataracts.

The co-primary endpoints were the mean change from baseline over the treatment period in morning predose FEV_1 (primary comparison for budesonide/formoterol pMDI vs formoterol DPI,[14,15] to assess the contribution of budesonide) and 1-hour post-dose FEV_1 (primary comparison for budesonide/formoterol pMDI vs budesonide pMDI[14] or placebo,[15] to assess the contribution of formoterol). A number of secondary clinical efficacy endpoints relating to lung function, COPD exacerbations (defined as worsening of COPD requiring treatment with an oral corticosteroid and/or hospitalization), COPD symptoms and health status (assessed using the St George's Respiratory Questionnaire [SGRQ]) were also evaluated.[14,15] In the 12-month trial,[15]

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the COPD exacerbation rate was analysed using a Poisson regression model, and the time to first COPD exacerbation was described via Kaplan-Meier plot and analysed using the log-rank test.

Analyses in both studies were conducted in the intent-to-treat populations (defined as all randomized patients who received at least one dose of study medication and contributed sufficient data for at least one co-primary or secondary endpoint during the randomization period).[14,15] In the 6-[14] and 12-month[15] studies, a total of 19%[14] and 31%[15] of patients discontinued treatment; the most common reasons for treatment discontinuation were adverse events (8%[14] and 13%[15] of patients in the overall population; see section 4 for further details) and withdrawal of consent (5%[14] and 11%[15]). In the 6-month trial,[14] discontinuation rates were significantly ($p \leq 0.018$) lower in the twice-daily budesonide/formoterol pMDI 320 μg/9 μg group than in the placebo, twice-daily budesonide pMDI 320 μg and twice-daily formoterol DPI 9 μg groups (14% vs 26%, 23% and 22%, respectively). In the 12-month trial,[15] the overall discontinuation rates was numerically lower in the twice-daily budesonide/formoterol pMDI 320 μg/9 μg than in the placebo and twice-daily formoterol DPI 9 μg groups (27% vs 36% vs 32%; significance not reported), and the time to discontinuation was significantly ($p \leq 0.004$) longer in the budesonide/formoterol pMDI groups than in the placebo group. In both trials, the differences in discontinuation rates are driven by the lower proportion of patients who withdrew consent in the twice-daily budesonide/formoterol pMDI 320 μg/9 μg groups than in the monotherapy or placebo groups (2% vs 4–9%[14] and 8% vs 11–16%[15]).

Effect on Pulmonary Function

- Lung function improved to a significantly greater extent with long-term treatment with twice-daily budesonide/formoterol pMDI 320 μg/9 μg than with placebo[14,15] or the same nominal twice-daily dosage of one of the individual components (budesonide pMDI[14] and formoterol DPI[14,15]) in patients with moderate to very severe COPD.
- Over the treatment period of the 6-[14] and 12-month[15] trials, adjusted mean morning predose FEV_1 improved from baseline to a significantly greater extent with twice-daily budesonide/formoterol pMDI 320 μg/9 μg than with twice-daily formoterol DPI 9 μg (primary comparison in both trials; $p \leq 0.03$),[14,15] budesonide pMDI 320 μg ($p < 0.001$)[14] and placebo ($p < 0.001$)[14] [figure 1a].
- Twice-daily budesonide/formoterol pMDI 320 μg/9 μg was also associated with significantly greater adjusted mean increases in 1-hour post-dose FEV_1 over the treatment period than twice-daily budesonide pMDI 320 μg (primary comparison in the 6-month trial;[14] $p < 0.001$),[14] placebo (primary comparison in the 12-month trial;[15] $p < 0.001$)[14,15] and formoterol DPI 9 μg ($p \leq 0.04$)[14,15] [figure 1b].
- Improvements from baseline in the co-primary endpoints with twice-daily budesonide/formoterol pMDI 320 μg/9 μg were apparent at the first assessment (end of month 1 for mean morning predose FEV_1 and day of randomization for 1-hour post-dose FEV_1) and were generally maintained at each monthly visit.[14,15]
- In addition, twice-daily budesonide/formoterol pMDI 320 μg/9 μg improved many secondary assessments of pulmonary function from baseline to a significantly greater extent than the comparators.[14,15]
- Over the 6-[14] and 12-month[15] treatment periods, mean improvements from baseline in morning and evening peak expiratory flow were significantly ($p \leq 0.02$) greater with twice-daily budesonide/formoterol pMDI 320 μg/9 μg than with twice-daily placebo,[14,15] budesonide pMDI 320 μg[14] and formoterol DPI 9 μg.[14,15]
- Twice-daily budesonide/formoterol pMDI 320 μg/9 μg also improved pre-dose and 1-hour post-dose FVC to a significantly ($p < 0.05$) greater extent than placebo over the 12-month treatment period.[15]
- In the 6-month trial,[14] the twice-daily administration of budesonide 320 μg plus formoterol 9 μg in a single pMDI did not affect its therapeutic efficacy (with regard to any of the primary or secondary endpoints) relative to twice-daily administration of

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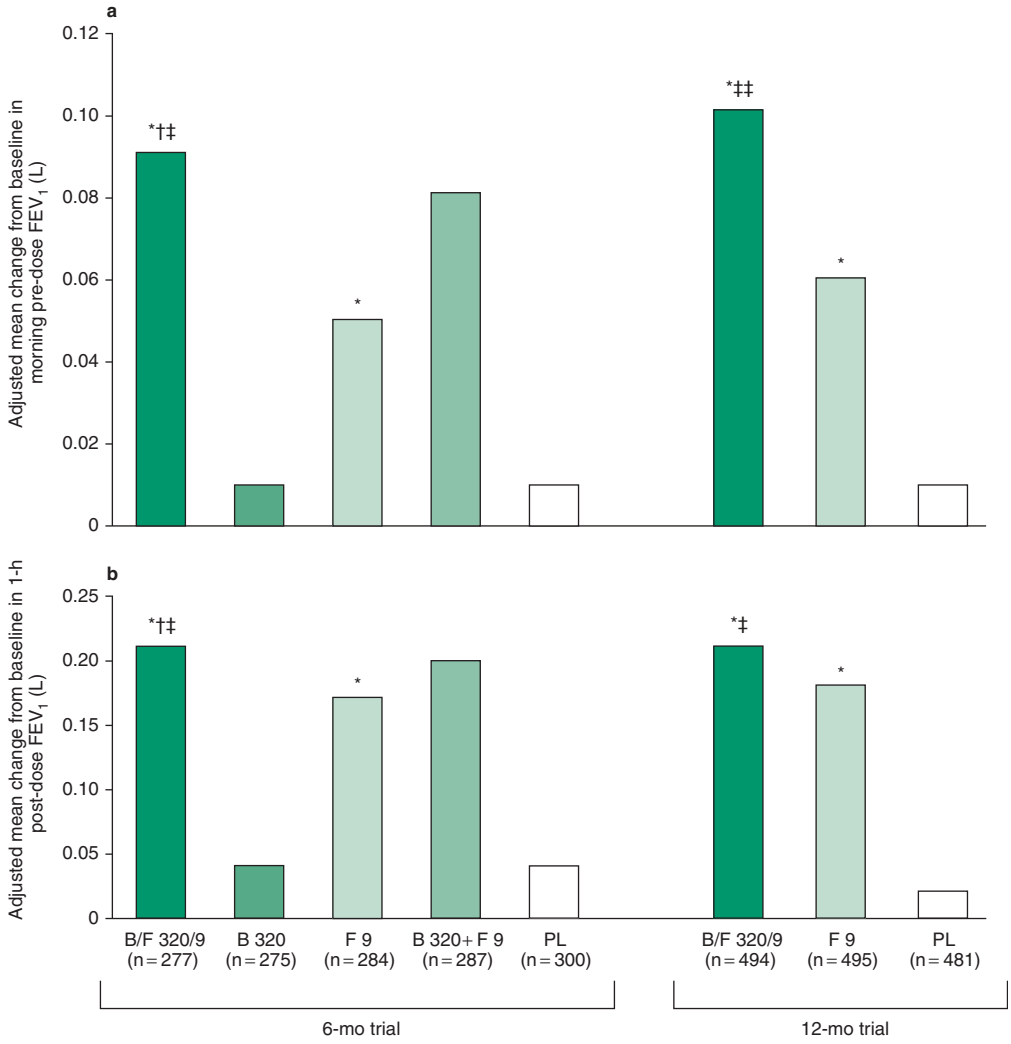

Fig. 1. Effect of twice-daily budesonide/formoterol (B/F) pressurized metered-dose inhaler (pMDI) on pulmonary function in patients with moderate to very severe chronic obstructive pulmonary disease. Adjusted mean changes from baseline over the treatment period in (**a**) morning pre-dose forced expiratory volume in 1 second (FEV_1) and (**b**) 1-h post-dose FEV_1 in two similarly designed, 6-[14] or 12-mo,[15] randomized, double-blind, multicentre trials. Results are shown for the twice-daily B/F pMDI 320 μg/9 μg,[14,15] budesonide (B) pMDI 320 μg,[14] formoterol (F) dry powder inhaler (DPI) 9 μg,[14,15] B pMDI 160 μg plus F DPI 9 μg[14] or placebo (PL)[14,15] treatment arms. Values for the 12-mo trial[15] were estimated from a figure. * $p < 0.001$ vs PL; † $p < 0.001$ vs B; ‡ $p < 0.05$, ‡‡ $p = 0.008$ vs F.

the same nominal doses of the individual components via two separate inhalers.

Effect on Exacerbations and Symptoms

• Secondary COPD symptom and control outcomes improved to a greater extent in patients receiving twice-daily budesonide/formoterol pMDI 320 μg/9 μg than in those receiving placebo and, for some outcomes, those receiving twice-daily treatment with its individual components.[14,15]

• Twice-daily budesonide/formoterol pMDI 320 μg/9 μg significantly prolonged the time to first COPD exacerbation relative to twice-daily placebo ($p \leq 0.004$) and formoterol DPI 9 μg ($p = 0.03$)

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according to Kaplan-Meier probability curves based on data from the 12-month trial.[15]

- In the 12-month trial, budesonide/formoterol pMDI 320 μg/9 μg reduced the overall number of exacerbations per treatment-year by 37% relative to placebo ($p < 0.001$) and by 25% relative to formoterol ($p \leq 0.004$).[15]
- The number of COPD exacerbations per treatment-year with budesonide/formoterol pMDI 320 μg/9 μg was 20–25% lower than those with twice-daily placebo or formoterol DPI 9 μg (0.88 vs 1.11 and 1.10 exacerbations per treatment year) in the 6-month trial.[14] Although the differences were not statistically significantly different ($p \geq 0.06$), the trial was not powered to show between-group differences in this endpoint.[14]
- Total breathlessness, cough and sputum scores (BCSS), as well as individual scores for dyspnoea, cough and sputum, improved from baseline to a significantly ($p < 0.05$) greater extent in patients receiving twice-daily budesonide/formoterol pMDI 320 μg/9 μg than in patients receiving placebo over the 6-[14] and 12-month[15] treatment periods, with the exception of sputum scores in the 6-month trial.[14]
- Twice-daily budesonide/formoterol pMDI 320 μg/9 μg also improved mean total BCSS scores and individual scores for dyspnoea and cough from baseline to a significantly ($p < 0.05$) greater extent than twice-daily formoterol DPI 9 μg in the 12-month trial,[15] and mean dyspnoea scores to a significantly ($p < 0.05$) greater extent than budesonide pMDI 320 μg or formoterol DPI 9 μg in the 6-month trial.[14]
- Improvements from baseline in dyspnoea scores were clinically significant in patients receiving budesonide/formoterol pMDI 320 μg/9 μg (i.e. the change from baseline was ≥0.2 points on the 5-point scale of the Breathlessness Diary component of the BCSS). The difference between twice-daily budesonide/formoterol pMDI 320 μg/9 μg and placebo in the mean change from baseline in dyspnoea scores was clinically relevant only in the 12-month trial.[15]
- The mean improvement from baseline in sleep score and the percentage of awakening-free nights was significantly ($p \leq 0.003$) greater with twice-daily budesonide/formoterol pMDI 320 μg/9 μg than with placebo over the treatment period of both trials.[14,15] Mean sleep scores also improved to a significantly ($p < 0.05$) greater extent with twice-daily budesonide/formoterol pMDI 320 μg/9 μg than with formoterol DPI 9 μg.[14,15]
- Patients receiving twice-daily budesonide/formoterol pMDI 320 μg/9 μg used significantly ($p < 0.01$) less rescue medication (salbutamol) than those receiving placebo[14,15] or twice-daily budesonide pMDI 320 μg,[14] as assessed by the number of inhalations of rescue medication per day[14,15] and/or the proportion of rescue medication-free days.[14]

Effect on Health Status

- Twice-daily budesonide/formoterol pMDI 320 μg/9 μg was associated with clinically meaningful improvements in adjusted mean SGRQ total scores (i.e. ≥4-point reduction from baseline on a scale of 0–100) at all assessment timepoints (months 1, 2 and 6) in the 6-month trial, as well as at the end of treatment.[14] In the 12-month trial,[15] the mean change from baseline to the end of treatment with budesonide/formoterol pMDI 320 μg/9 μg was −3.9, which did not meet prespecified clinical relevance criteria.
- Adjusted mean SGRQ total and individual domain (symptoms, activity and impacts) scores improved from baseline to a statistically significant ($p < 0.05$) greater extent with twice-daily budesonide/formoterol pMDI 320 μg/9 μg than with placebo in both trials,[14,15] with the exception of the impacts domain score in the 6-month trial.[14]
- In addition, twice-daily budesonide/formoterol pMDI 320 μg/9 μg was associated with statistically significant ($p < 0.05$) greater improvements from baseline in mean SGRQ total, symptoms domain and activity domains scores than twice-daily budesonide pMDI 320 μg and formoterol DPI 9 μg in the 6-month trial,[14] and SGRQ symptoms domain scores than twice-daily formoterol DPI 9 μg in the 12-month trial.[15]
- From baseline to the end of treatment in the 6-month trial, the proportion of patients who experi-

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enced a clinically meaningful improvement in SGRQ total score was significantly greater with budesonide/formoterol pMDI 320 μg/9 μg than with placebo (45.5% vs 35.0%; $p \leq 0.02$), whereas the proportion with a clinically meaningful worsening in SGRQ total score was significantly lower with budesonide pMDI 320 μg/9 μg than with placebo (22.5% vs 31.1%; $p \leq 0.05$).[14]

4. Tolerability

Descriptive tolerability data for twice-daily budesonide/formoterol pMDI 320 μg/9 μg in patients with COPD are primarily derived from the 6-[14] and 12-month[15] trials discussed in section 3, including pooled trial data reported in the manufacturer's prescribing information.[11] Reported results are for the treatment groups receiving budesonide/formoterol 320 μg/9 μg combination therapy via a single pMDI[14,15] or separate inhalers,[14] budesonide pMDI 320 μg[14] or formoterol DPI 9 μg[14,15] monotherapy, or placebo.[14,15]

- Inhalation therapy with twice-daily budesonide/formoterol pMDI 320 μg/9 μg was generally well tolerated.[14,15] Across treatment groups, the incidence of drug-related adverse events was 5.9–8.7%[14] and 6.2–12.8%[15] in the 6-[14] and 12-month[15] trials, respectively. No clinically important differences in the incidence of drug-related adverse events was observed between treatment groups.[14,15]
- Adverse events were mostly of mild or moderate severity and were consistent with the known tolerability profiles of β_2-adrenoceptor agonist and ICS therapy.[14,15]
- In pooled 6- and 12-month trial data,[11] some adverse events (regardless of causality) occurred numerically more frequently with twice-daily budesonide/formoterol pMDI 320 μg/9 μg (n = 771) than with placebo (n = 781). Of note, incidences were not adjusted for the longer mean duration of therapy with budesonide/formoterol pMDI 320 μg/9 μg than with placebo (255 vs 224 days).[11]
- Adverse events that occurred at an incidence of ≥3% with twice-daily budesonide/formoterol pMDI 320 μg /9 μg and at a numerically greater incidence than with placebo were nasopharyngitis (7.3% vs 4.9% of patients), oral candidiasis (6.0% vs 1.8%), bronchitis (5.4% vs 3.5%), sinusitis (3.5% vs 1.8%) and viral upper respiratory tract infection (3.5% vs 2.7%).[11]
- In the 6-[14] and 12-month[15] trials, adverse events led to study withdrawal by 6.9%[14] and of 11.3%[15] of patients receiving twice-daily budesonide/formoterol 320 μg/9 μg. Adverse event-related discontinuation rates in the other treatment arms were 4.5–11.3%[14] and 12.3–12.5%.[15] The most common reason for treatment discontinuation was COPD (2.9–4.0% of patients in any of the budesonide plus formoterol combination therapy groups, and 5–7.4% of patients in the monotherapy and placebo groups).[14,15]
- Non-fatal treatment-emergent serious adverse events were reported in 11.2%[14] and 15.6%[15] of patients receiving twice-daily budesonide/formoterol pMDI 320 μg/9 μg in the 6-[14] and 12-month[15] trials. The incidences across the other treatment groups were 8.3–9.5%[14] and 12.1–17.8%[15] (values not adjusted for between-group differences in treatment exposure time).
- None of the deaths that occurred during the randomized treatment period of the two trials were considered to be related to study medications.[14,15]
- Treatment with corticosteroids has been associated with pneumonia and lower respiratory tract infections.[5,24] However, no increase in the incidence of pneumonia in the active treatment groups relative to the placebo groups was shown in the 6-[14] and 12-month[15] trials. Pneumonia occurred in 1.1% of twice-daily budesonide/formoterol pMDI 320 μg/9 μg and 1.3% of placebo recipients in the 6-month trial;[14] the corresponding proportions in the 12-month trial were 4.0% and 5.0%.[15]
- The active treatment groups had a slightly higher incidence of lung infections other than pneumonia than the placebo groups, largely because of a higher incidence of bronchitis.[11,14,15] Lung infections other than pneumonia occurred in 7.6%[14] and 8.1%[15] of twice-daily budesonide/formoterol pMDI 320 μg/9 μg recipients, and 3.3%[14] and 6.2%[15] of placebo

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recipients in the 6-[14] and 12-month[15] trials, respectively.

5. Dosage and Administration

As maintenance treatment of airflow obstruction in patients with COPD, the only recommended dosage of budesonide/formoterol pMDI is two inhalations of 160 μg/4.5 μg twice daily (i.e. 320 μg/9 μg administered twice daily).[11] An inhaled SABA should be used for immediate relief if shortness of breath occurs in the between-dose period.[11] No dosage adjustments of budesonide/formoterol pMDI are required in elderly patients.[11]

Local prescribing information should be consulted for detailed information on the use of budesonide/formoterol pMDI 160 μg/4.5 μg in the treatment of COPD.

6. Budesonide/Formoterol Pressurized Metered-Dose Inhaler: Current Status in Chronic Obstructive Pulmonary Disease

In the US, two inhalations twice daily of the budesonide/formoterol pMDI delivering 160 μg/4.5 μg per inhalation is approved for use as maintenance treatment of airway obstruction in patients with COPD, including those with chronic bronchitis and emphysema.

In well designed clinical trials in patients with COPD, twice-daily budesonide/formoterol pMDI demonstrated rapid and durable improvements in lung function that were greater than those with placebo or monotherapy with the same nominal dosage of its individual components, and were similar to its components administered via separate inhalers. It was generally well tolerated, with a low overall incidence of adverse events.

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