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Budesonide/Formoterol Pressurized Metered-Dose Inhaler

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Contents

Abstract

▲ The corticosteroid budesonide and the long-acting β_2-adrenoceptor agonist formoterol have been combined into a single pressurized metered-dose inhaler (pMDI) for use in patients aged ≥12 years with asthma.

▲ In well designed 12-week clinical trials in patients with mild to moderate or moderate to severe persistent asthma, lung function improved to a significantly greater extent with twice-daily budesonide/formoterol pMDI 160 μg/9 μg or 320 μg/9 μg than with placebo or the same nominal dosage of either of the components alone.

▲ Budesonide/formoterol pMDI was also associated with improvements from baseline in patient-reported asthma control, asthma symptom and asthma-related quality of life outcomes that were significantly greater than those with placebo and, for many endpoints, monotherapy with the individual components.

▲ In a 52-week safety study, treatment with twice-daily budesonide/formoterol pMDI 320 μg/9 μg was associated with rapid and durable improvements in lung function and asthma control that were significantly greater than those with twice-daily budesonide pMDI 640 μg monotherapy.

▲ Budesonide/formoterol pMDI was well tolerated in clinical trials. Its overall adverse event profile is consistent with the known tolerability profiles of long-acting β_2-adrenoceptor agonist and inhaled corticosteroid therapy, and is similar to that shown with placebo.

Features and properties of budesonide/formoterol in a pressurized metered-dose inhaler (Symbicort®)	
Indication	
Long-term maintenance treatment of asthma in patients aged ≥12 y in whom a combination of inhaled corticosteroid and long-acting β_2-adrenoceptor agonist is considered appropriate	
Mechanism of action	
Budesonide: corticosteroid Formoterol: long-acting β_2-adrenoceptor agonist	
Dosage and administration	
Route of administration	Inhalation
Dose (budesonide/formoterol)	160 μg/9 μg or 320 μg/9 μg (i.e. two inhalations of 80 μg/4.5 μg or 160 μg/4.5 μg)
Frequency of administration	Twice daily
Pharmacokinetic profile (geometric means in 26 adult patients with moderate asthma receiving budesonide/formoterol 320 μg/9 μg twice daily)	
Peak plasma concentration (C_{max})	Budesonide: 1.2 nmol/L Formoterol: 28 pmol/L
Time to C_{max}	Budesonide: 21 min Formoterol: 10 min
Area under the plasma concentration-time curve from time 0 to 12 h	Budesonide: 4.9 nmol • h/L Formoterol: 158 pmol • h/L
Most common adverse events	
Reported in ≥5% of patients and more commonly than with placebo in three 12-week clinical trials	Nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, stomach discomfort

Asthma is a common chronic respiratory disease, which affects more than 22 million individuals in the US and contributes to a substantial social and economic burden.[1] The condition is characterized by chronic inflammation and hyperresponsiveness of the airways.[1]

Current US asthma guidelines for the treatment of adolescents aged ≥12 years and adults with persistent asthma use a stepwise approach to asthma control.[1] Daily long-term anti-inflammatory control medication is recommended, with a low dose of an inhaled corticosteroid (ICS; e.g. budesonide, beclometasone or fluticasone propionate) as the preferred initial option.[1] If asthma is not sufficiently controlled with low-dose ICS therapy alone, the preferred step-up treatment is to either add an inhaled long-acting β_2-adrenoceptor agonist (LABA; e.g. formoterol fumarate dihydrate [formoterol] or salmeterol) to low-dose ICS therapy or increase the ICS dose to the medium-dose range.[1] In patients whose asthma is still not controlled, the preferred option is to step up to medium-dose ICS therapy plus an LABA, with further steps up to high-dose ICS therapy plus an LABA, and finally, if necessary, the addition of oral corticosteroid therapy.[1] The addition of an LABA to an ICS regimen improves lung function and asthma symptoms, and decreases the as-required use of quick-relief medications (i.e. rapid-acting inhaled β_2-adrenoceptor agonists).[1,2]

In the US, the combination of budesonide plus formoterol has recently become available for administration via a single hydrofluoroalkane-propelled pressurized metered-dose inhaler (pMDI),[3] hereafter referred to as budesonide/formoterol pMDI (Symbicort®).[1] This article reviews the pharmacodynamic properties, clinical efficacy and tolerability of budesonide/formoterol pMDI.

1. Pharmacodynamic Profile

The pharmacodynamic properties of budesonide and formoterol are well established;[2,4-8] this section briefly reviews the pharmacodynamic properties of budesonide and formoterol, with a focus on more recent data[9-16] (some of which are available as abstracts[9,12,13]). Some data are from patients enrolled in pivotal clinical trials;[14-16] see section 3 for trial design details.

- The mechanisms of action of budesonide and formoterol are different and, therefore, the agents target different aspects of asthma pathology.[2,8] When administered concomitantly, the two agents display complementary and additive effects.[2,8]
- Budesonide is a potent corticosteroid, with a high affinity for the glucocorticoid receptor and a high ratio of topical to systemic activity.[2,6] Its potent anti-inflammatory activity, particularly on epithelial cells in the airways, is considered to be responsible for its clinical efficacy as an inhalation therapy in asthma.[2,6]
- The dose-response curve of ICSs in patients is relatively flat, with most of the benefit obtained at the lowest doses.[2] Of note, the lowest effective dose varies amongst patients, with some patients, usually those with more severe asthma, requiring higher doses than other patients.
- The bronchodilatory activity of formoterol, a potent, selective β_2-adrenoceptor agonist, has a rapid onset and lasts for at least 12 hours.[4] It displays full agonist activity at β_2-adrenoceptors, which produces relaxation of contracted bronchial smooth muscle.[7] It has low affinity for β_1-adrenoceptors and negligible α-adrenoceptor stimulating properties.[7]
- Adding formoterol to budesonide produces greater improvements in pulmonary function and symptomatology than higher doses of ICSs alone for maintenance therapy in patients with asthma.[2,4,5,8] It is not yet clear whether this represents a synergistic interaction between the two agents or the additive bronchodilatory effects of an LABA to the anti-inflammatory effects of an ICS.[2,8]
- There is growing evidence that the addition of formoterol to budesonide may provide greater anti-inflammatory effects than the use of budesonide alone. Combination therapy was associated with anti-inflammatory effects additional to those of

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

budesonide in pharmacodynamic studies in patients with mild persistent[10] or mild to moderate persistent[9] asthma.

● Budesonide/formoterol pMDI provides a rapid bronchodilatory response in patients with asthma.[11,12] Its onset of action was significantly faster than that of salmeterol/fluticasone dry powder inhaler (DPI) or placebo in two identical randomized, crossover, multicentre, single-dose studies in 109 patients with mild to moderate asthma (figure 1).[11] Moreover, a ≥15% improvement in forced expiratory volume in 1 second (FEV_1) in 15 minutes was achieved in a significantly ($p < 0.001$) greater proportion of budesonide/formoterol pMDI than salmeterol/fluticasone propionate DPI recipients (40% vs 19%).[11]

● The bronchodilatory response with twice-daily budesonide/formoterol pMDI was also significantly faster than that with budesonide pMDI or placebo, and similar to that with formoterol DPI and budesonide pMDI plus formoterol DPI.[12] In an analysis[12] of bronchodilatory response in two 12-week clinical trials conducted in the US,[14,15] the proportion of patients achieving a 15% improvement in FEV_1 in 15 minutes was significantly ($p < 0.001$) greater in twice-daily budesonide/formoterol pMDI 160 μg/9 μg or 320 μg/9 μg recipients (48.8% and 56.5%) than in twice-daily budesonide pMDI 160 or 320 μg (5.8% and 5.5%) or placebo (8.2% and 5.6%) recipients. In the other treatment groups in these two trials, 57.0% and 56.9% of patients receiving formoterol DPI 9 μg (both $p = 0.001$ vs placebo) and 52.2% of those receiving budesonide pMDI 320 μg plus formoterol DPI 9 μg achieved this improvement.[12]

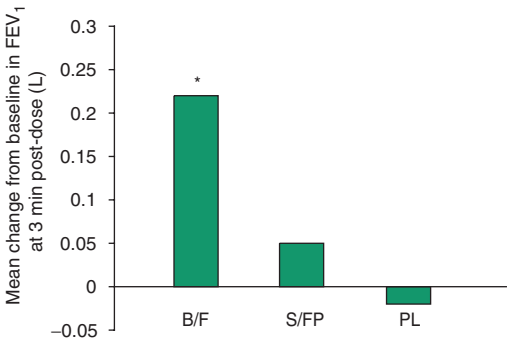

Fig. 1. Onset of action of budesonide/formoterol (B/F) administered via a single pressurized metered-dose inhaler (pMDI). Combined results of two identical randomized, crossover, multicentre, single-dose studies in patients with mild to moderate asthma.[11] Mean change from baseline in mean forced expiratory volume in 1 second (FEV_1) at 3 minutes (primary endpoint) after treatment with B/F pMDI 160 μg/9 μg (n = 92), salmeterol/fluticasone propionate (S/FP) dry powder inhaler 50 μg/250 μg (n = 94) or placebo (PL) pMDI (n = 96). * $p < 0.001$ vs S/FP and PL.

● The use of a full β_2-adrenoceptor agonist, such as formoterol, may maintain optimal bronchial relaxation during periods of increased inflammation.[13] *In vitro*, budesonide prevented the cytokine-induced decrease in the relaxation response of mice tracheal segments to the full β_2-adrenoceptor agonists formoterol and terbutaline, but not to that of the partial β_2-adrenoceptor agonist salmeterol.[13]

● Through their effects on extrapulmonary β_2-adrenoceptors, β_2-adrenoceptor agonists have been associated with increases in heart rate, the QT interval and plasma glucose levels, and decreases in plasma potassium levels.[7] However, clinically meaningful differences in mean changes from baseline in heart rate, the uncorrected and corrected QT intervals, and mean serum glucose and potassium levels were generally small[16] or not shown[14,15] between the groups receiving budesonide/formoterol pMDI and those receiving monotherapy with budesonide[14-16] or formoterol,[14,15] or placebo[14,15] in 12-[14,15] and 52-week[16] double-blind studies.

● The clinical significance of the small, but statistically significant, transient change in tolerance to salbutamol that developed with the long-term use of formoterol is unclear, as the response to salbutamol was retained over time.[16] In a subpopulation of ≈50 evaluable patients in each treatment group in one 52-week double-blind study, post-salbutamol maximum FEV_1 values decreased from baseline to a statistically significant greater extent ($p < 0.05$) with twice-daily budesonide/formoterol pMDI 320 μg/9 μg or 640 μg/18 μg than with twice-daily budesonide pMDI 640 μg at the end of week 6 and month 6, but not at the end of treatment or 12 months.[16]

2. Pharmacokinetic Profile

The pharmacokinetic properties of budesonide[6] and formoterol[7] as monotherapy and combination therapy[4,5] are well established. This section, therefore, only briefly reviews these properties, focusing on values relevant to the combination pMDI formulation. Data are derived from the manufacturer's prescribing information[3] and abstract reports of a 1-week multiple-dose study of twice-daily budesonide/formoterol pMDI 320 μg/9 μg in 26 patients with moderate asthma and 26 healthy volunteers,[17] and a randomized, crossover, single-dose study of 12 inhalations of budesonide/formoterol pMDI 160 μg/4.5 μg or its individual components (budesonide pMDI or DPI 160 μg, or formoterol DPI 4.5 μg) in patients with asthma.[18]

- Budesonide and formoterol are rapidly absorbed after oral inhalation.[3] In patients with asthma in the multiple-dose study, geometric mean values for maximum plasma concentration (C_{max}) and time to C_{max} for budesonide and formoterol were 1.2 nmol/L and 28 pmol/L,[3,17] and 21 and 10 minutes.[3]
- Although geometric mean C_{max} values for budesonide and formoterol were 27% and 42% lower in patients with asthma than in healthy volunteers (possibly due to differences in deposition or absorption characteristics of the drug in diseased vs healthy lungs), total systemic exposure was similar in the two groups.[17] The geometric mean values for the area under the plasma concentration-time curve from 0 to 12 hours for budesonide in patients with asthma and in healthy volunteers were 4.9 and 4.6 nmol • h/L; the corresponding values for formoterol were 158 and 167 pmol • h/L.[17]
- In the single-dose study, administration of budesonide plus formoterol via the combination pMDI resulted in systemic exposures to budesonide and formoterol that were somewhat lower (by ≈30% and 13%) than when the individual components were administered separately.[18]
- Budesonide has a volume of distribution of ≈3 L/kg and is 85–90% bound to plasma proteins.[3] Plasma protein binding of formoterol is ≈50%.[3]
- Budesonide is rapidly and extensively metabolized by the cytochrome P450 (CYP) isoenzyme 3A4 to two essentially inactive metabolites, and formoterol is metabolized primarily by direct glucuronidation, and by *O*-demethylation by CYP2D6 and CYP2C, followed by conjugation to inactive metabolites.[3]
- Sixty percent of a radiolabelled dose of budesonide was excreted via the urine and the rest in the faeces;[3] at steady-state, the geometric mean of the elimination half-life ($t_{1/2}$) was 3.7 hours in patients with asthma and 3.9 hours in healthy volunteers.[17] Sixty-two percent of radiolabelled formoterol (administered orally and intravenously, simultaneously) was excreted in the urine and 24% in the faeces;[3] the geometric mean of the $t_{1/2}$ at steady-state was 6.8 hours in patients with asthma and 6.5 hours in healthy volunteers.[17]
- There is no evidence of pharmacokinetic interactions between budesonide and formoterol when administered concurrently.[3]
- Although there are no data reported regarding pharmacokinetic interactions between inhaled budesonide/formoterol and other drugs, potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin) may increase budesonide plasma concentrations and their concomitant use requires caution.[3]

3. Therapeutic Efficacy

The efficacy of twice-daily budesonide/formoterol pMDI in adults and adolescents aged ≥12 years with persistent asthma has been investigated in three 12-week, randomized, double-blind, double-dummy, multicentre trials (two pivotal studies conducted in the US [one in 480 patients with mild to moderate asthma[14] and the other in 596 patients with moderate to severe asthma[15]] and one international study in 668 patients conducted in a number of other countries[19]). Some patient-reported outcome data from the US trials[14,15] are available as a subgroup analysis[20] of 405 patients aged ≥18 years in the trial in mild to moderate asthma[14] and as abstracts.[21,22] Secondary efficacy data for twice-daily budesonide/formoterol pMDI are also available from two 52-week, randomized safety studies (a US double-

blind study [n = 132][16] and an international open-label study [n = 446][23]).

In the 12-week trials, the efficacy of twice-daily budesonide/formoterol pMDI 160 μg/9 μg[14] or 320 μg/9 μg[15,19] was compared with that of the same nominal metered doses of twice-daily budesonide pMDI monotherapy[14,15,19] (available for clinical trial purposes only and not available commercially), formoterol DPI monotherapy,[14,15] budesonide pMDI plus formoterol DPI,[15] budesonide/formoterol DPI[19] (not available in the US; results not reported) and placebo.[14,15] The 52-week safety studies evaluated treatment with the maximum recommended dosage of twice-daily budesonide/formoterol pMDI 320 μg/9 μg.[16,23] Although the 52-week trials also included treatment arms in which patients received higher than approved dosages of combination therapy,[16] budesonide monotherapy[16] or budesonide/formoterol administered via a DPI,[23] only the results in the treatment arms receiving the dosage and formulation approved in the US (i.e. twice-daily budesonide/formoterol pMDI 320 μg/9 μg) are presented. For all trials, the reported dose is the total metered dose of the two inhalations administered at the same time (e.g. two inhalations of budesonide/formoterol pMDI 80 μg/4.5 μg is reported as budesonide/formoterol pMDI 160 μg/9 μg).

Patients had confirmed asthma of ≥6 months' duration that was inadequately controlled with low to medium[14] or medium to high[15,16,19,23] doses of ICSs alone[14,15,19] and/or in combination with other asthma medications.[14-16,19,23] Inclusion criteria included pre-bronchodilator FEV_1 values relative to predicted normal values of ≥60% to ≤90% (defined as mild to moderate asthma),[14] ≥50%,[23] ≥50% to ≤90%[19] or ≥45% to ≤85% (defined as moderate to severe asthma).[15,16]

Where stated, patients were randomized to one of the treatment arms after a run-in period of ≈2 weeks, during which their current asthma therapy was discontinued and patients received single-blind twice-daily placebo,[14] budesonide 160[15] or 320[16] μg, or their prestudy stable dose of an ICS,[19] plus rescue short-acting β_2-adrenoceptor agonist therapy as required.[14-16,19]

Permitted routine concomitant treatment was restricted to salbutamol[14-16] or terbutaline[19,23] for asthma symptom relief as necessary. In the 12-week US trials,[14,15] patients using a disallowed medication were discontinued from the study and were considered to have potentially met predefined criteria for asthma worsening. Results for the main efficacy endpoints are reported for the intent-to-treat-populations.

In the 12-week US trials, co-primary endpoints included the change from baseline in morning pre-dose FEV_1 (primary comparison for budesonide/formoterol pMDI vs formoterol DPI) and the change in 12-hour mean FEV_1 (primary comparison for budesonide/formoterol pMDI vs budesonide pMDI).[14,15] As these studies used predefined withdrawal criteria for worsening asthma, which caused a differential withdrawal rate in the treatment groups, some results provided are for the last available study visit (end of treatment).[14,15] In the other 12-week trial,[19] the primary endpoint was the change in morning peak expiratory flow (PEF) from baseline (mean value of the last 10 days of run-in period) to the mean value over the 12-week study period. A number of secondary clinical efficacy endpoints, including asthma control outcomes (morning[14,15] and evening[14,15,19] PEF; total,[19] daytime[14,15] and night-time[14,15] asthma symptom scores; percentage of reliever-free,[19] asthma-control,[19] and symptom-free[14,15,19] days and awakening-free nights;[14,15,19] and number of daily inhalations of rescue medication[14,15,19]) reported in patient diaries and asthma-related quality-of-life endpoints (assessed using standardized Asthma Quality of Life Questionnaire [AQLQ(S)] total and individual domain [symptoms, activity limitation, emotional function and exposure to environmental stimuli] scores)[14,15,19] were also evaluated.

Randomized, Double-Blind, 12-Week Trials

- Lung function improved to a significantly greater extent with twice-daily budesonide/formoterol pMDI than with the same nominal twice-daily dos-

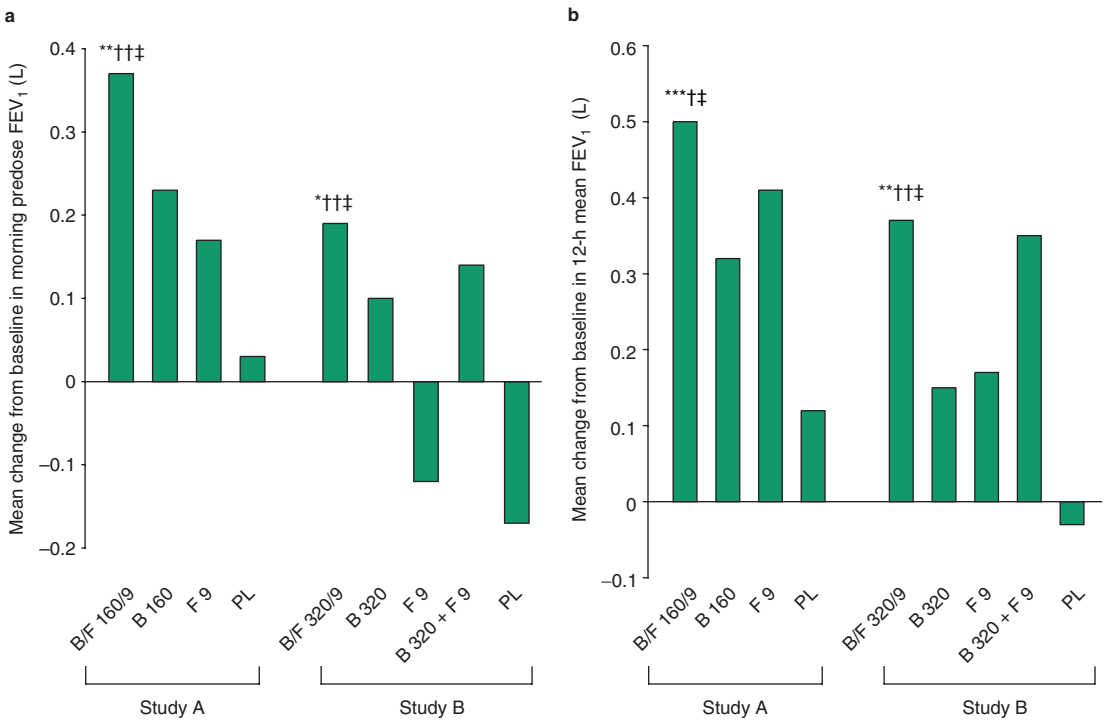

Fig. 2. Effect of twice-daily (bid) budesonide/formoterol (B/F) pressurized metered-dose inhaler (pMDI) on lung function in patients (pts) with asthma. Mean changes from baseline in (**a**) morning predose mean forced expiratory volume in 1 second (FEV_1) and (**b**) 12-hour mean FEV_1 in 12-week, randomized, double-blind, multicentre trials. In Study A, pts with mild to moderate asthma received bid B/F pMDI 160 μg/9 μg (n = 123), budesonide (B) pMDI 160 μg (n = 121), formoterol (F) dry powder inhaler (DPI) 9 μg (n = 114) or placebo (PL; n = 122).[14] In Study B, pts with moderate to severe asthma received bid B/F pMDI 320 μg/9 μg (n = 124), B pMDI 320 μg (n = 109), F DPI 9 μg (n = 123), B pMDI 160 μg plus F DPI 9 μg (n = 115) or PL (n = 125).[15] * $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs B; † $p \leq 0.05$, †† $p < 0.001$ vs F; ‡ $p \leq 0.001$ vs PL.

age of either of the components administered alone in patients with asthma.[14,15,19]

- In patients with mild to moderate[14] or moderate to severe[15] asthma, morning predose FEV_1 improved to a significantly greater extent with twice-daily budesonide/formoterol pMDI 160 μg/9 μg[14] or 320 μg/9 μg[15] than with twice-daily budesonide pMDI 160[14] or 320[15] μg, formoterol DPI 9 μg[14,15] (primary comparison) or placebo[14,15] at the end of treatment (figure 2a). Baseline values for morning predose FEV_1 were 2.32–2.43[14] and 2.19–2.90[15] L.
- Twice-daily budesonide/formoterol pMDI 160 μg/9 μg[14] or 320 μg/9 μg[15] was also associated with significantly greater mean increases in 12-hour mean FEV_1 at the end of treatment than twice-daily budesonide pMDI 160[14] or 320[15] μg (primary comparison), formoterol DPI 9 μg or placebo (figure 2b). Baseline values for 12-hour mean FEV_1 were 2.33–2.40[14] and 2.18–2.30[15] L.
- In addition, significantly ($p \leq 0.001$) greater mean improvements in 12-hour mean FEV_1 were shown with twice-daily budesonide/formoterol pMDI 160 μg/9 μg[14] or 320 μg/9 μg[15] than with twice-daily budesonide pMDI 160[14] or 320[15] μg or placebo after administration of the first dose and at week 2 in both trials,[14,15] and with twice-daily budesonide/formoterol pMDI 320 μg/9 μg than with twice-daily formoterol DPI 9 μg at the end of 2 weeks in the trial in moderate to severe asthma.[15]
- In the international study, lung function improved to a significantly greater extent with twice-daily budesonide/formoterol pMDI 320 μg/9 μg (n = 233) than with the same nominal metered dose

of twice-daily budesonide pMDI (n = 217).[19] The between-group difference in the increase from baseline in morning PEF was 28.6 L/min (95% CI 20.9, 36.4; $p \leq 0.001$).

- Secondary asthma symptom and control outcomes improved to a greater extent with twice-daily budesonide/formoterol pMDI 160 μg/9 μg[14] or 320 μg/9 μg[15] than with placebo and, for some outcomes, the individual components.[14,15,19,20]

- In the US trials in patients with mild to moderate[14] or moderate to severe asthma,[15] significantly ($p \leq 0.01$) fewer patients receiving twice-daily budesonide/formoterol pMDI versus twice-daily formoterol DPI or placebo met worsening asthma criteria (19% vs 42% and 57%,[14] and 30% vs 55% and 67%[15]) or withdrew because of worsening asthma (7% vs 18% and 33%,[14] and 11% vs 36% and 36%[15]).

- Moreover, in the trial in patients with moderate to severe asthma,[15] a significantly ($p \leq 0.05$) lower proportion of twice-daily budesonide/formoterol pMDI 320 μg/9 μg than twice-daily budesonide pMDI 320 μg recipients met worsening asthma criteria (30% vs 44%) or withdrew because of worsening asthma (11% vs 20%). However, in the trial in patients with mild to moderate asthma,[14] there was no significant difference between twice-daily budesonide/formoterol pMDI 160 ug/9 μg and twice-daily budesonide pMDI 160 ug in the proportion of patients who met worsening asthma criteria (19% vs 22%) or withdrew because of worsening asthma (7% in both groups).

- Patients receiving twice-daily budesonide/formoterol pMDI reported significantly ($p \leq 0.001$) better improvements from baseline than placebo recipients with regard to all patient diary-reported outcomes in both US trials.[14,15] In the subgroup analysis of patients aged ≥18 years in the trial with mild to moderate asthma, twice-daily budesonide/formoterol 160 μg/9 μg was also significantly ($p \leq 0.01$) better than placebo with regard to Medical Outcomes Study sleep scale scores, and the percentage of rescue medication-free and asthma control days.[20]

- Mean improvements from baseline in most patient diary variables were significantly ($p \leq 0.05$) greater with twice-daily budesonide/formoterol pMDI 160 μg/9 μg[14] or 320 μg/9 μg[15] than with twice-daily formoterol DPI 9 μg[14,15] in the US trials. The mean change from baseline in the percentage of awakening-free nights was the sole patient diary variable without a significant difference between twice-daily budesonide/formoterol and twice-daily formoterol DPI (22% vs 18% in patients with mild to moderate asthma[14] and 13% vs 9% in patients with moderate to severe asthma[15]).

- In the trials in patients with more severe asthma,[15,19] twice-daily budesonide/formoterol pMDI 320 μg/9 μg was also significantly ($p \leq 0.05$) more effective than twice-daily budesonide pMDI 320 μg monotherapy with regard to all patient diary variables, with the exceptions of the percentage of awakening-free nights and the number of inhalations per day of rescue medication in the US trial.[15] However, in patients with mild to moderate asthma,[14] the differences in improvements between twice-daily budesonide/formoterol pMDI 160 μg/9 μg and twice-daily budesonide pMDI 160 μg were significant ($p \leq 0.001$) only for morning and evening PEF.[14]

- Budesonide/formoterol pMDI was associated with clinically meaningful improvements from baseline (i.e. ≥0.5-point difference) in mean overall AQLQ(S) and most individual domain scores.[19-21] Relative to placebo, twice-daily budesonide/formoterol pMDI 160 μg/9 μg was associated with clinically meaningful improvements from baseline in mean overall AQLQ(S) score and three of four of the individual domain scores (with the exception of environmental exposure) in patients aged ≥18 years with mild to moderate asthma.[20] In patients with moderate to severe asthma,[21] twice-daily budesonide/formoterol pMDI 320 μg/9 μg was associated with clinically meaningful improvements from baseline in AQLQ(S) scores relative to both twice-daily formoterol DPI 9 μg and placebo.

- Moreover, the proportion of patients with mild to moderate asthma who experienced clinically meaningful improvements in overall AQLQ(S) score was

significantly greater with budesonide pMDI 160 μg/9 μg than with placebo (63% vs 35%; $p < 0.006$).[20]

- In patient- and physician-reported global assessments of overall health, the proportions of patients receiving budesonide/formoterol pMDI 160 μg/9 μg[20] or 320 μg/9 μg[21] who experienced health improvements or better management of asthma symptoms were significantly greater than the corresponding proportions in patients receiving placebo ($p \leq 0.001$),[20,21] or budesonide pMDI 160[20] or 320[21] μg (both $p \leq 0.05$).
- Patient Mean Satisfaction with Asthma Medication questionnaire scores for all three indices (control relief, perception of medication and comparison with other medications) were significantly ($p \leq 0.001$) higher in budesonide/formoterol pMDI recipients than in budesonide pMDI, formoterol DPI or placebo recipients in both US trials.[20,22]
- The combination of budesonide plus formoterol in a pMDI did not affect its therapeutic efficacy relative to administration via two separate inhalers.[15] There were no significant differences between twice-daily budesonide/formoterol pMDI 320 μg/18 μg and twice-daily budesonide pMDI 320 μg plus twice-daily formoterol DPI 9 μg with regard to any of the primary or secondary endpoints in the US trial in patients with moderate to severe asthma.[15]

52-Week Randomized Safety Studies

- Long-term inhalation treatment with twice-daily budesonide/formoterol pMDI 320 μg/9 μg (maximum recommended dosage) was associated with rapid and durable improvements in lung function[16,23] and asthma control,[16] which were apparent from the day after randomization and maintained throughout the 52-week US double-blind[16] and international open-label[23] studies. The statistical significance of the differences between endpoint and baseline values were not reported.
- Twice-daily budesonide/formoterol pMDI 320 μg/9 μg was associated with long-term improvements from baseline in lung function.[16,23] In the US trial, mean predose FEV_1 improved by 0.16 L, 2-hour postdose FEV_1 by 0.34 L and morning PEF by 33.6 L/min in patients receiving twice-daily budesonide/formoterol pMDI 320 μg/9 μg.[16] In the international study, twice-daily budesonide/formoterol pMDI 320 μg/9 μg improved mean predose FEV_1 from baseline by 0.27 L.[23]
- Long-term asthma control was also provided by twice-daily budesonide/formoterol pMDI 320 μg/9 μg.[16,23] Patients receiving twice-daily budesonide/formoterol pMDI 320 μg/9 μg had 0.185 asthma exacerbations per patient-treatment year in the US trial[16] and 0.13 severe asthma exacerbations per patient in the international trial.[23] The proportions of symptom-free days, rescue medication-free days and asthma-control days improved from baseline by 23.5%, 22.2% and 25.2%, respectively, and the use of rescue medication decreased from baseline by a mean of 0.7 puffs per day in patients receiving twice-daily budesonide/formoterol pMDI 320 μg/9 μg in the US trial.[16]

4. Tolerability

Descriptive tolerability data for budesonide/formoterol pMDI in patients aged ≥12 years with asthma are derived primarily from pooled data from three randomized, double-blind, placebo-controlled trials in 401 adult and adolescent patients reported in the manufacturer's prescribing information,[3] and the 12-[14,15,19] and 52-week[16,23] studies discussed in section 3.

- Inhalation therapy with budesonide/formoterol pMDI was generally well tolerated, with a low overall incidence of adverse events that was similar across treatment groups; the events were mostly of mild or moderate severity and were consistent with the known tolerability profiles of β_2-adrenoceptor agonist and ICS therapy.[3,14-16,19]
- Adverse effects associated with budesonide/formoterol pMDI were numerically similar to those associated with both of its individual components (as monotherapy or together via separate inhalers) or placebo, with no clinically important differences observed between treatment groups.[14-16,19,23]
- In pooled data from three 12-week trials,[3] some adverse events (regardless of causality) occurred numerically more frequently with twice-daily

budesonide/formoterol pMDI than with placebo. Of note, incidences were not adjusted for the longer mean duration of therapy with twice-daily budesonide/formoterol pMDI 60 μg/9 μg or 320 μg/9 μg than with placebo (77 and 74 vs 56 days).[3]

- Adverse events that occurred at an incidence of ≥3% in either of the twice-daily budesonide/formoterol pMDI 160 μg/9 μg or 320 μg /9 μg treatment arms and at a numerically greater incidence than in the placebo arm were nasopharyngitis (10.5%, 9.7% and 9%), headache (6.5%, 11.3% and 6.5%), upper respiratory tract infection (7.6%, 10.5% and 7.8%), pharyngolaryngeal pain (6.1%, 8.9% and 4.8%), sinusitis (5.8%, 4.8% and 4.8%), influenza (3.2%, 2.4% and 1.3%), back pain (3.2%, 1.6% and 0.8%), nasal congestion (2.5%, 3.2% and 1.0%), stomach discomfort (1.1%, 6.5% and 1.8%), vomiting (1.4%, 3.2% and 1.0%) and oral candidiasis (1.4%, 3.2% and 0.8%).[3]
- No clinically important changes in the incidence or type of adverse events were revealed in the long-term safety studies.[16,23] In the double-blind study, the only treatment-related adverse events reported in ≥1% of patients receiving twice-daily budesonide/formoterol pMDI 320 μg/9 μg were oral candidiasis (8.3%) and pharyngolaryngeal pain (1.5%).[16]
- Serious adverse events occurred infrequently in clinical trials of twice-daily budesonide/formoterol pMDI. Those considered to be drug related included one report each of ECG T-wave inversion,[15] supraventricular tachycardia[23] and ventricular tachycardia[23] in patients receiving twice-daily budesonide/formoterol pMDI 320 μg/9 μg. No serious drug-related adverse events were associated with twice-daily budesonide/formoterol pMDI 160 μg/9 μg[14] or 320 μg/9 μg[14,16,19] in the other trials.
- Drug-related adverse events that led to withdrawal from the study were experienced by 0.8%[14] and 2.4%[15] of patients receiving twice-daily budesonide/formoterol pMDI 160 μg/9 μg[14] or 320 μg/9 μg[15] in the 12-week US trials. Drug-related discontinuation rates in the other treatment arms ranged from 0.8% to 4.3%.[14,15] In the double-blind 52-week safety study, four patients (3%) in the twice-daily budesonide/formoterol pMDI 320 μg/9 μg group and three patients (2.3%) in the placebo group discontinued treatment because of drug-related adverse events.[16]
- As with all β_2-adrenoceptor agonists, there is a US FDA boxed warning that this class of drug may increase the risk of asthma-related death.[3]

5. Dosage and Administration

In patients aged ≥12 years with asthma in whom dual asthma maintenance therapy is clearly warranted, the recommended starting dosage is two inhalations twice daily of budesonide/formoterol pMDI 80 μg/4.5 μg in patients who are currently receiving low to medium doses of ICSs, two inhalations twice daily of budesonide/formoterol pMDI 160 μg/4.5 μg in patients who are currently receiving medium to high doses of ICSs, and two inhalations twice daily of either strength (depending on asthma severity) in patients not currently receiving ICSs. The maximum daily recommended dosage is two inhalations of budesonide/formoterol pMDI 160 μg/4.5 μg twice daily for a total daily dose of 640 μg/18 μg.[3]

Local prescribing information should be consulted for more detailed information on warnings, contraindications, precautions, drug interactions and use in special populations.[3]

6. Budesonide/Formoterol Pressurized Metered-Dose Inhaler: Current Status

The budesonide/formoterol pMDI delivering 80 μg/4.5 μg or 160 μg/4.5 μg per inhalation is approved for use in the US in the treatment of patients aged ≥12 years who have asthma that is inadequately controlled with other asthma controller treatment (i.e. low- to medium-dose ICSs) or that warrants treatment with two maintenance therapies.

In well designed clinical trials in patients with asthma, 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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