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BUDESONIDE AND FORMOTEROL (SYMBICORT®): A REVIEW

Donna L. Smith, Pharm. D. Candidate

More than 22 million people in the United States have asthma according to the Centers for Disease Control and Prevention (CDC).[1] Asthma is a chronic inflammatory disorder of the airways which can be life threatening if not properly managed. Without appropriate treatment, asthma can significantly limit individuals' activities and result in asthma exacerbations, resulting in hospitalization and death. The CDC estimates that 4,000 Americans die from asthma exacerbations each year.[1]

The goal of pharmacologic therapy is to prevent and control asthma symptoms, improve quality of life, reduce frequency and severity of asthma exacerbations and reverse airflow obstruction with the minimum effective drug dose to reduce risk of adverse effects.[2] The evidence in the recently revised NIH Asthma 2007 guidelines continue to support the use of low-dose inhaled corticosteroids (ICS) as standard maintenance therapy with the use of short-acting beta agonists (SABA) for relief of acute exacerbations. For asthma inadequately controlled with the low-dose ICS, the 2007 guidelines give the option of increasing the dose of ICS equal weight to adding a long-acting beta agonist (LABA). This change acknowledges the potential risks associated with LABA, and at the same time validating the evidence showing greater improvements in lung function, symptoms, and less use of short-acting beta agonists (SABA) with adding LABA compared to doubling the ICS dose.

Symbicort®, AstraZeneca's combination product of the ICS budesonide and the LABA formoterol in a pressurized meter dose inhaler (pMDI) was released to US markets in June 2007. It was approved for long-term maintenance for asthma in adults, including elderly, adolescents and children ≥ 12 years old. Though not recommended or approved for acute exacerbations, the quick onset of action of formoterol is similar to albuterol.[3] This has generated interest in the potential of the combination product of budesonide/formoterol to be used as both maintenance and rescue treatment for asthma. This article will review budesonide/formoterol's safety and efficacy in asthma maintenance therapy and the potential use in treatment of acute exacerbations.

Pharmacology and Pharmacokinetics

Budesonide

Budesonide is an inhaled corticosteroid with

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mainly glucocorticoid activity. Corticosteroids are the most potent and effective anti-inflammatory medication available.[2] Glucocorticoids have a direct inhibitory effect on many cells involved in airway inflammation in asthma, including macrophages, T-lymphocytes, eosinophils and airway epithelial cells. After inhalation, the lipophilic property of budesonide allows for rapid absorption into the cell cytoplasm where it binds to glucocorticoid receptors resulting in changes in gene transcription within the nucleus. The result can include inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, and suppression of humoral immune responses.[3]

Budesonide is rapidly absorbed from the lungs after oral inhalation with peak plasma concentrations within 20 minutes. Most of the dose delivered to lungs is systemically absorbed. Budesonide is metabolized in the liver into weakly active metabolites via the CYP 3A4 enzyme and excreted in urine and feces. The mean terminal half life is 4.7 hours.[4]

Formoterol

Formoterol is a highly selective beta-2 adrenergic agonist with duration of action over 12 hours compared to three hours for the short acting beta-2 agonist albuterol. The lipophilic side chain of formoterol enters the cell membrane and forms a depot that is gradually released into the aqueous phase to stimulate the beta-2 receptor. The length of the side chain prolongs the duration of action, but maintains a quick onset of action after inhalation that is similar to albuterol.[3, 5] Once the airway receptors are stimulated, the mechanism of action is similar to other beta-2 agonists resulting in relaxation of bronchial smooth muscle.

Formoterol is rapidly absorbed in the lungs after inhalation, with peak plasma levels occurring in 5-10 minutes. Most of the drug systemically absorbed is due to swallowing and absorbed through GI tract. Formoterol is metabolized CYP 2D6, 2C19, 2C9 and 2A6, then excreted in urine and feces over 104 hours. The mean terminal half-life is around 8 hours.[4]

Clinical Trials

Maintenance Therapy

Two recent US multi-center randomized, placebo-controlled trials compared the use of budesonide/formoterol combination in one pMDI to the individual components and placebo for safety and efficacy in asthma patients ≥12 years old. The designs of the studies are similar with the major difference being one targeted mild-to-moderate asthma and the second targeted moderate-to-severe.

Clinical Trial Targeting Mild-to-Moderate Asthma

A total of 480 mild to moderate asthma patients were randomized to compare safety and efficacy of twice daily budesonide/formoterol pMDI 80/4.5 mcg (Symbicort® pMDI) x 2 inhalations, budesonide pMDI 80 mcg (Pulmicort® DPI) x 2 inhalations, formoterol DPI 4.5 mcg (Oxis® Turbuhaler®) x 2 inhalations or placebo for 12 weeks.[7] Study participants included patients with a documented diagnosis of asthma for at least 6 months treated with ICS consistently 4 weeks prior to screening and with a FEV_1 of ≥ 60% to 90% of predicted normal on ICS treatment. Excluded were patients that were hospitalized once or > 1 emergency department (ED) visit in the previous 6 months, requiring systemic corticosteroids in the 4 weeks prior to the study, and >10 pack-per-year smokers. After a two week run-in in which patients were given a singe-blinded placebo pMDI and rescue albuterol, patients who demonstrating reversibility in FEV_1 from a baseline of ≥ 12% and ≥ 0.20 L within 15-30 minutes after a standard dose of albuterol were randomized.[7]

The primary end points of the study were pre-dose FEV_1 and 12-hour mean FEV_1. The end points were selected to measure the contributions of the individual components with pre-dose FEV_1, to assess the efficacy of budesonide with regards to pulmonary function and the 12 hour mean FEV_1, and to assess the bronchodilator effect of formoterol. Modified intention-to-treat approach was used to calculate primary end points, including data for all subjects who received at least one dose of study drug and recorded sufficient data points for the calculation of at least one primary end point[7]

Secondary end points included morning and evening peak expiratory flow (PEF), daytime and nighttime symptom scores, nighttime awakenings due to asthma, and daily rescue medication use. Safety was assessed based on adverse events, routine

Table 1. Primary endpoints for patients with mild-to-moderate asthma[7]

Parameter	BUD/FM minus BUD (95% CI)	BUD/FM minus FM (95% CI)	BUD/FM minus placebo (95% CI)
Pre-dose FEV_1 (L)	0.15 (0.05 to 0.26)*	0.20 (0.09 to 0.31)*	0.34 (0.23 to 0.45)*
12-hour mean FEV_1 (L)			
Day 1	0.24 (0.17 to9 0.31)*	-0.04 (-0.11 to 0.02)	0.25 (0.19 to 0.32)*
Week 2	0.18 (0.09 to 0.27)*	0.07 (-0.02 to 0.16)	0.35 (0.26 to 0.44)*
End of trial	0.20 (0.11 to 0.29)*	0.09 (0.00 to 0.19)*	0.39 (0.30 to 0.47)*

BUD = budesonide; FM = formoterol; FEV_1 = forced expiratory volume in 1 sec; CI = confidence interval
* $p < 0.05$

laboratory analysis, ECG, 24-hour Holter monitor assessment, and physical exam including vital signs.[7]

The mean change from baseline in pre-dose FEV_1 at end of study was significantly greater in the budesonide/formoterol pMDI group compared to the formoterol, budesonide, and placebo group (0.37 vs. 0.23, 0.17, and 0.3 L, respectively; all, $p \leq 0.05$). At the end of the 12 week study, the mean change from baseline in 12 hour FEV_1 was significantly greater with budesonide/formoterol pMDI (0.50 L) compared with budesonide pMDI (0.32 L) or placebo (0.12 L) (all, $p > 0.001$). The bronchodilatory effect of budesonide/formoterol pMDI remained relatively constant between week 2 and week 12.[7] (**Table 1**)

Mean increases from baseline in morning and evening PEF were significantly greater with budesonide/formoterol pMDI compared with budesonide pMDI and formoterol DPI (all, $p \leq 0.001$). Changes in baseline daytime and nighttime symptom scores and increases in symptom free days were similar between the budesonide/formoterol pMDI and the budesonide pMDI. No severe adverse events considered study drug related were recorded for patients receiving treatment with budesonide/formoterol. Overall incidence of asthma related adverse events in the study for all groups was 2.5% but none occurred in the budesonide/formoterol groups. No changes in baseline heart rate, mean post-dose serum glucose, potassium or physical examination were identified between treatment groups.[7]

Clinical Trial Targeting Moderate-to-Severe Asthma

A total of 596 patients with moderate-to-severe asthma were randomized in this 12-week study evaluating the efficacy and safety of the 160 mcg/4.5 mcg budesonide and formoterol pressurized metered dose inhaler with 160 mcg budesonide pMDI , 4.5 mcg formoterol DPI , 160 mcg budesonide and 4.5 mcg formoterol in separate inhalers and placebo.[8] Each treatment group received 2 inhalations twice daily. Inclusion criteria were a diagnosis of asthma for > 6 months with a $FEV_1 \geq 45\%$ to < 85% of predicted normal and treated with a moderate-to-high dose of ICS for at least 4 weeks prior to the study. Excluded were patients hospitalized once or > 1 ED visit in the previous 6 months, patients who required systemic corticosteroids in the 4 weeks prior to study, and > 10 pack-per-year smokers.[8]

During a 2-week run-in period, patients discontinued use of their current therapy and received two inhalations of 80 mcg budesonide pMDI twice daily and rescue SABA as needed. Patients with documented daytime and night-time symptoms of ≥ 3 of 7 days during the run-in period were randomized. Randomization was stratified into 2 groups according to patient's current ICS dosage (high, moderate) allowing investigators to analyze the response to treatment based on severity of asthma.[8]

The primary efficacy measure was the change from baseline in morning pre-dose FEV_1 and the 12-

Table 2. Primary efficacy variables for patients with moderate-to-severe asthma[8]

Parameter	BUD/FM minus BUD (95% CI)	BUD/FM minus FM (95% CI)	BUD/FM minus-BUD+FM (95% CI	BUD/FM minus placebo (95% CI)
Pre-dose FEV_1 (L)	0.10 (0.0 to 0.21)*	0.31 (0.20 to 0.41)*	0.05 (-0.05 to 0.15)	0.37 (0.27 to 0.47)*
12-h mean FEV_1 (L)				
Day 1	0.26 (0.20 to 0.33)*	0.02 (-0.04 to 0.08)	-0.01 (-0.07 to 0.06)	0.29 (0.22 to 0.35)*
Week 2	0.20 (0.11 to 0.28)*	0.15 (0.07 to 0.23)*	0.01 (-0.07 to 0.09)	0.37 (0.29 to 0.45)*
End of Trial	0.23 (0.14 to 0.31)*	0.19 (0.11 to 0.28)*	0.01 (-0.08 to 0.09)	0.40 (0.32 to 0.48)*

BUD = budesonide; FM = formoterol; FEV_1 = forced expiratory volume in 1 sec; CI = confidence interval
* $p < 0.05$

hour mean change in FEV_1 over a 12-hour period. Secondary efficacy measures included morning PEF, daytime and night-time symptom scores, night-time awakenings due to asthma and daily rescue medications required. The primary treatment comparison was budesonide/formoterol pMDI verses formoterol DPI for pre-dose FEV_1 and budesonide/formoterol pMDI verses budesonide pMDI for 12-hour mean FEV_1. Safety was evaluated based on adverse events, laboratory evaluations, vital signs, ECGs, 24-hour Holter monitoring and physical examination.[8]

Patient treated with budesonide/formoterol pMDI achieved a significant improvement ($p<0.001$) in pre-dose FEV_1 from baseline compared with formoterol DPI throughout the study. Mean changes from baseline in 12-hour FEV_1 were significantly ($p<0.001$) greater for patients treated with budesonide/formoterol pMDI compared with budesonide pMDI. The difference in formulation and device did not alter the efficacy or safety.[8] (**Table 2**)

The safety profile of budesonide/formoterol combination was similar to placebo, with no clinically relevant differences in mean post-serum glucose, potassium levels, vital signs or physical examination.[8]

Maintenance and Rescue Therapy

The safety and efficacy of budesonide/formoterol in a single inhaler (DPI) for both maintenance therapy and symptom relief was compared to a higher dose of budesonide plus as needed SABA terbutaline in a double-blind, randomized, parallel group, active-controlled study.[9] This 6-month study was conducted in 77 centers outside the US and included 697 subjects between the ages of 12-80 with mild-to-moderate asthma symptoms currently on any brand of ICS (doses 200-500 mcg/day) for at least 3 months. Patients were randomized into one of two groups; budesonide/formoterol (80 mcg/4.5 mcg) 2 inhalations daily for maintenance plus budesonide/formoterol as needed for relief or double the dose of budesonide (160 mcg) two inhalations daily plus terbutaline (0.4 mg) as needed for relief.[9]

After an open run-in period of 14 to 18 days, patients were randomized only if they required 7 or more doses of terbutaline on the last 10 days of the run-in period. At the end of the 6-month study, the primary outcome variable, morning PEF, showed greater improvement from baseline for the budesonide/formoterol group vs. the budesonide treatment. (34.5 L/min vs. 9.5 L/min, $p< 0.001$) Fewer total and severe asthma exacerbations were seen in the

Table 3. Mean efficacy variables for budesonide/formoterol compared to budesonide and terbutaline for both maintenance and symptom relief

Efficacy variables	Adjusted between group difference (BUD/FM minus-BUD) (95% CI)	P value
Morning PEF (L/min)	25.0 (19.4 to 30.6)	< 0.001
Evening PEF (L/min)	18.8 (13.3 to 24.3)	< 0.001
As needed inhalations/day	-0.34 (-0.51 to -0.17)	< 0.001
As needed medication free days (%)	8.1 (3.5 to 12.7)	< 0.001
Total asthma symptoms score (0-6)	-0.17 (-0.26 to -0.07)	< 0.001
Nighttime awakening (%)	-2.2 (-4.5 to 0.1)	< 0.065
Symptom free days	6.5 (2.0 to 11.0)	< 0.00043
Asthma control days	7.6 (3.0 to 12.3)	< 0.0012

BUD = budesonide; FM = formoterol; PEF = peak expiratory flow

budesonide/formoterol group compared to budesonide treatment (43 total/14 severe and 94 total/57 severe, respectively).[9] (**Table 3**)

Even though budesonide/formoterol was used in both treatment and relief, the overall mean daily dosage of ICS was 160-320mcg for 85% of patients. This was lower than the fixed dosage of 320 mcg of ICS in the budesonide treatment group. The frequency of adverse events was similar between treatment groups with no differences in lab values or ECG.[9]

Dosing and Administration

Budesonide/formoterol is indicated for long-term maintenance therapy for treatment of mild-to-moderate asthma when a low-dose inhaled corticosteroid is not adequately controlling asthma.[2] The recommended dosing is 2 inhalations of budesonide/formoterol 80 mcg/4.5 mcg twice daily or 2 inhalations of budesonide/formoterol 160 mcg/4.5 mcg twice daily. Maximum dosage in adults is 640 mcg of budesonide and 18 mcg of formoterol via oral inhalation.[5]

Toxicity & Safety

The FDA placed a black box warning on all LABA containing products, which includes budesonide/formoterol for the potential increased risk of death from asthma. A large clinical trial comparing daily treatment with salmeterol or placebo added to usual asthma therapy resulted in an increased risk of asthma-related deaths in patients treated with salmeterol.[10] In addition, an increased number of severe asthma exacerbations was noted in the formoterol trials submitted to the FDA for formoterol approval, particularly in the higher dose arms of the trials.[11]

Cost and Availability

Budesonide/formoterol pMDI is available in the US in two dosages, 80 mcg/4.5 mcg and 160 mcg/4.5 mcg of budesonide and formoterol, respectively. They are dispensed in a 10.2 gram canister

that provides 120 actuations. The average retail cost for one canister of 80 mcg/4.5 mcg is $164.55 and 160 mcg/4.5 mcg is $188.81 as determined by three community pharmacies in Gainesville, Florida. As of October 1, 2007, budesonide/formoterol (Symbicort®) is on the preferred Florida Medicaid drug list.

Summary

For asthma patients who are not controlled on low-dose ICS, the addition of a LABA is one of the two options currently recommended in recently updated asthma guidelines.[2] The combination product of budesonide/formoterol pMDI was associated with significantly greater efficacy than either component alone. Budesonide and formoterol are well tolerated at the recommended dosages.

Initial evidence on the use of budesonide/formoterol pMDI for maintenance and relief are promising, and could potentially simplify the administration of asthma medications for patients. However, the current guidelines and the FDA strongly warn against the use of LABA for relief until further studies are done to prove safety and efficacy.[2]

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