Research Review™
PRODUCT REVIEW

Beclometasone dipropionate/formoterol (Fostair®) for patients with asthma

Making Education Easy 2020

Independent expert commentary provided by Prof Frank Thien

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Abbreviations used in this issue:

ACT = Asthma Control Test™
BDP = beclometasone dipropionate
CI = confidence interval
FEV1 = forced expiratory volume in one second
GINA = Global Initiative for Asthma
ICS = inhaled corticosteroid
LABA = long-acting beta2-agonist
MART = maintenance and reliever therapy
PEF = peak expiratory flow
pMDI = pressurised metered-dose inhaler
PRISMA = PRospectIve Study on asthMA control
QoL = quality of life
SABA = short-acting beta2 agonist

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Introduction

Asthma is a heterogeneous disease, usually characterised by inflammation of the airways, and defined by the history of respiratory symptoms such as episodes of wheezing, chest tightness, shortness of breath and coughing.[1] Expiratory airflow can be variable and limited, and the airflow limitation may become persistent.[1]

Globally, asthma is estimated to impact 272 million individuals.[2] In Australia (2017-2018), one in nine Australians had a diagnosis of asthma, with 389 deaths attributed to asthma in 2018.[3] Symptoms and airflow limitation may resolve spontaneously or in response to management, and may be absent for weeks or months.[1] However, patients may experience episodic flare-ups (exacerbations) which can be life-threatening and associated with significant burden.[1]

Untreated asthma is usually characterised by airway hyper-responsiveness, and intermittent airway narrowing (due to bronchoconstriction, congestion or oedema of bronchial mucosa, mucus, or a combination of these), with the underlying pathophysiology attributed primarily to inflammatory processes.[4, 5]

The long-term goals of asthma management treatment are to achieve good symptom control, and to minimise the future risk of exacerbations, persistent airflow limitations, side-effects of treatment and asthma-related mortality.[1, 5] Importantly, the patient's goals regarding their asthma and its treatment should be included as part of the management of this disease.[1, 5] Patients who achieve good asthma control report an improvement in their quality of life (QoL).[6]

Pharmacological treatment in asthma is based on a continuous cycle of assessment, treatment, and review of the patient's response in terms of symptom control and risk factors (side-effects and exacerbations).[1, 4]

For adolescents and adults with asthma, international guidelines (including the Global Initiative for Asthma 2020 guidelines) recommend an inhaled corticosteroid (ICS)-containing controller treatment to reduce the risk of serious exacerbations and to control symptoms.[1, 7] Similarly, the Australian Asthma Handbook recommends that most newly diagnosed patients can start initial treatment with a regular daily maintenance ICS (low dose) plus a short-acting beta2 agonist (SABA) reliever as needed; or budesonide–formoterol (low dose) as needed.[8]

If the asthma remains uncontrolled despite good adherence and inhaler technique, international guidelines recommend the next step should be a combination of low-dose ICS and a long-acting beta2-agonist (LABA).[1, 7] The addition of LABA to a daily regimen of ICS improves symptoms and lung function.[1] Treatment with an ICS/LABA combination in a single inhaler may also encourage better adherence to treatment, and ensure that the LABA is always accompanied by an ICS.[9, 10]

Similarly, the Australian Asthma Handbook (version 2.1) recommends that the next step in adults with poorly controlled asthma are:[8]

- maintenance treatment with low-dose budesonide/formoterol or beclometasone/formoterol, plus extra doses of the same inhaler taken as needed for relief of symptoms (maintenance and reliever therapy; MART); or
- maintenance treatment with a combination of an ICS and a LABA, plus as needed SABA as a reliever.

A figure illustrating the recommended steps for selecting and adjusting medication for adults and adolescents with asthma patients is available here.

Expert comment

Single inhaler fixed-dose combinations of ICS/LABA have been the mainstay of asthma pharmacotherapy for nearly 20 years. This treats both the airway inflammation and the airway smooth muscle reactivity with good symptom control and reduced risk of exacerbations. A fast onset LABA such as formoterol also provides rapid bronchodilation for symptom relief. In the Australian context, fixed-dose beclometasone dipropionate/formoterol is an alternative to budesonide/formoterol in the next step of asthma therapy as a single inhaler maintenance and reliever therapy.

Beclometasone dipropionate/formoterol (Fostair®)

Please refer to the full Fostair® Product information before prescribing.

Fostair® is a hydrofluoroalkane-propelled pressurised metered-dose inhaler (pMDI) containing a fine particle fixed-dose combination of beclometasone dipropionate (BDP) and formoterol (eformoterol) fumarate dihydrate (hereafter Fostair® will be referred to as BDP/formoterol).[11]

Each metered dose (ex-valve) contains 100 µg of BDP and 6 µg of formoterol which is equivalent to a delivered dose (ex-actuator) of 86.4 µg of BDP and 5 µg of formoterol.[11] The extra fine particle size (<1.37 µm) of this solution formulation allows the drug particles to be delivered homogeneously throughout the lungs.[12] Consequently, the effective agents are able to target inflammation and bronchoconstriction in the entire bronchial tree, including the smaller peripheral airways which are involved in the progression of asthma and COPD.[13]

The average lung deposition of extra-fine BDP/formoterol was similar in patients with asthma (31% of the nominal dose) to that in healthy volunteers (34%).[13] The improved airway delivery with this formulation allows a 2.5-fold lower dose of BDP to be used compared with chlorofluorocarbon BDP, and reduces the overall systemic exposure to the ICS.[14, 15]

Mechanism of action

BDP is an ICS that has an anti-inflammatory action within the lungs.[11]

Formoterol is a beta-2 agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction.[11] The bronchodilating effect is rapid, within 1–3 minutes after inhalation, and has a duration of 12 hours after a single dose.[11, 16, 17]

Indications

BDP/formoterol is indicated in adults (aged ≥18 years) for the regular treatment of asthma where use of a combination product (ICS and LABA) is appropriate:[11]

- patients not adequately controlled with an ICS and as needed inhaled rapid-acting beta2-agonist, or
- patients already adequately controlled on both ICS and a LABA.

BDP/formoterol is also indicated for the symptomatic treatment of adults with severe COPD (FEV_1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.[11] However, this indication is not the focus of this review and will not be discussed further.

Dosage

When used for maintenance therapy, the recommended dosage of BDP/formoterol for adults aged ≥18 years is one to two inhalations twice daily and the maximum daily dose is four inhalations daily.[11] Patients should have their separate rapid-acting bronchodilator available for rescue use at all times.

When used as maintenance and reliever therapy, patients should take their daily maintenance dose of BDP/formoterol and additionally take BDP/formoterol as needed in response to asthma symptoms.[11] Patients should be advised to always have BDP/formoterol available for rescue use. For these patients, the recommended maintenance dose is one inhalation twice daily (one inhalation in the morning and one inhalation in the evening). Patients should take one additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Patients should not take more than six inhalations on any single occasion. The maximum daily dose is eight inhalations.[11]

Contraindications

The fix-dose combination is contraindicated in individuals with hypersensitivity to beclometasone dipropionate, formoterol fumarate dihydrate, or any of the excipients.[11]

Interaction profile

BDP is very rapidly metabolised by esterase enzymes and is less dependent on cytochrome P450 3A (CYP3A) metabolism than some other corticosteroids. Therefore, interactions are generally unlikely; however, systemic effects with concomitant use of strong CYP3A inhibitors (e.g. ritonavir, cobicistat) cannot be excluded, and so caution and appropriate monitoring is advised with the use of these agents.[11]

If beta-blockers (including in eye drops) are administered for compelling reasons in patients with asthma, the effect of formoterol will be reduced or negated.[11]

Concomitant use of other beta-adrenergic drugs can have potentially additive effects, and so caution is required when beta-adrenergic drugs such as theophylline are prescribed concomitantly with formoterol.[11]

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines, monoamine oxidase inhibitors, and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias.[11]

L-dopa, L-thyroxine, oxytocin, and alcohol can impair cardiac tolerance towards beta2-sympathomimetics.[11]

Concomitant treatment with monoamine oxidase inhibitors including agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.[11]

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.[11]

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Concomitant treatment with xanthine derivatives, steroids or diuretics may potentiate a possible hypokalaemic effect of beta2-agonists.[11] Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Fostair® contains a small amount of ethanol and there is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.[11]

Adverse events

The type and severity of adverse events associated with the fix-dose combination of BDP/formoterol are those associated with each of the individual compounds.[11] There is no incidence of additional adverse events following concurrent administration of the two compounds.[11]

Adverse reactions typically associated with formoterol use are: hypokalaemia, headache, tremor, palpitations, cough, muscle spasms, and prolongation of QTc interval.[11]

Adverse reactions typically associated with the administration of beclometasone dipropionate are: oral fungal infections, oral candidiasis, dysphonia, and throat irritation.[11]

Systemic effects of ICS may occur particularly when administered at high doses and for prolonged periods, and may include adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract, and glaucoma.[11]

Hypersensitivity reactions including rash, urticaria pruritus, erythema, and oedema of the eyes, face, lips, and throat may also occur.[11]

Clinical trials involving BDP/formoterol

Maintenance therapy

The fixed-dose BDP/formoterol combination has demonstrated efficacy, and was well tolerated, when used as maintenance treatment for asthma in randomised double-blind, multicentre trials in patients with different degrees of asthma severity.[11, 18-21]

In an 8-week study, patients with mild-to-moderate asthma who were still symptomatic despite receiving low-dose ICS alone were randomly assigned to receive BDP/formoterol twice daily or a double equipotent dose of non-extra fine BDP.[11, 18] At study end, there was a significant increase in mean morning peak expiratory flow (PEF) in patients receiving BDP/formoterol compared with BDP alone.

In a 24-week randomised trial, 645 patients with moderate-to-severe asthma with symptoms despite previous treatment with ICS, BDP/formoterol administered as two inhalations twice daily was as effective as non-extrafine BDP and formoterol administered via separate inhalers, and superior to non-extrafine BDP alone in improving lung function.[11, 19]

Phase 3 non-inferiority, head-to-head studies

Two 12-week, phase 3, non-inferiority, randomised, double-blind, multicentre studies compared BDP/formoterol with other fixed combinations (budesonide/formoterol[20] or fluticasone/salmeterol[21]) in patients with moderate-to-severe asthma. Both studies included a 2-week run-in period during which patients received an ICS at a daily dose ≤1000 µg of BDP-equivalent. Patients whose asthma was not adequately controlled after the 2-week run-in period (n=219[20] or n=228[21]) were administered two inhalations twice daily of BDP/formoterol 100/6 µg or the comparator (budesonide/formoterol 200/6 µg[20] or fluticasone/salmeterol 125/25 µg[21]).

BDP/formoterol was non-inferior to the comparator fixed-dose combination (budesonide/formoterol; study 1[20] or fluticasone/salmeterol; study 2[21]) with regard to the morning PEF in the last 2 weeks of treatment (primary endpoint) in the two studies. BDP/formoterol,[20, 21] budesonide/formoterol,[20] and fluticasone/salmeterol[21] demonstrated significant improvements from baseline in lung function, and symptoms, and reduced rescue medication use.[20] BDP/formoterol had a significantly faster onset of bronchodilation than fluticasone/salmeterol, with the difference maintained for up to 1 h after dosing (**Figure 1**).

No differences were observed between treatments in the rate of asthma exacerbations or frequency of adverse events in either study.

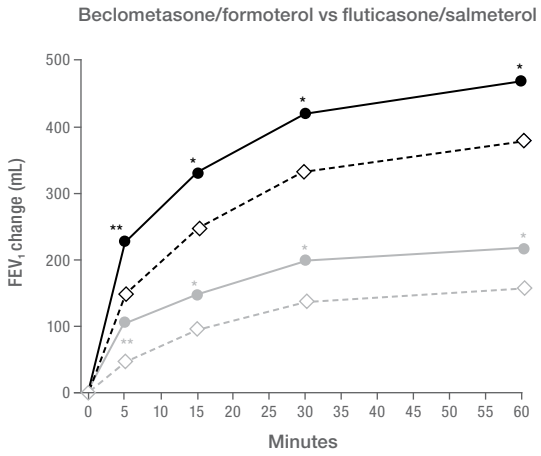

Figure 1. Change forced expiratory volume in 1 s (FEV1) from pre-dose to 1 h post-dose in patients with moderate to severe asthma treated with BDP/formoterol or fluticasone/salmeterol[21]

Black lines refer to values registered at baseline visit (BDP/formoterol:●–––●; fluticasone/salmeterol: ◊—◊); grey lines refer to values registered at the end of treatment, last visit (beclomethasone/formoterol: ●—●; fluticasone/salmeterol: ◊—◊); **p< 0.01 between treatments; *p<0.05 between treatments.

Maintenance and reliever therapy (MART)

Given the fast onset of action of formoterol, combined with its extra-fine particle size, the combined use of BDP/formoterol has potential for the provision of quick symptom relief on an as needed basis.[22] This regimen of treating asthma, namely using a single inhaler of BDP/formoterol for both maintenance and the provision of symptom relief has been investigated in patients with asthma in a 48-week randomised, controlled study involving 1701 patients with uncontrolled moderate-to-severe asthma (a FEV_1 of at least 60% predicted). This study compared the efficacy and tolerability of:[22]

- BDP/formoterol 100/6 µg administered as maintenance (one inhalation twice daily) and reliever therapy (up to a total of eight puffs per day) (MART), with
- BDP/formoterol 100/6 µg administered as maintenance therapy (1 inhalation twice daily) plus as needed salbutamol.

BDP/formoterol used as MART, compared with BDP/formoterol used as maintenance plus as needed salbutamol, significantly prolonged the time to the first severe exacerbation by 75 days (209 days vs 134 days), with a 36% reduction in risk (**Table 1**).[22] The rate of mild exacerbations was also decreased with BDP/formoterol used as MART (**Table 1**).

Patients in both treatment groups achieved a clinically meaningful improvement in asthma control.[22] The mean number of inhalations/day of reliever medication and the proportion of patients using reliever medication decreased similarly in both groups.[22]

Both treatments were well tolerated.[22]

Table 1. **Severe and mild exacerbations in patients treated with BDP/formoterol used as MART, or maintenance BDP/formoterol plus as needed salbutamol[22]**

	MART (n=852)	Maintenance BDP/formoterol + as needed salbutamol (n=849)	Hazard ratio (95% CI)	p-value
Severe exacerbations				
Patients with event, %	12	18	0.64 (0.49, 0.82)	0.0005
Rate, events per 100 patients per year	14.76	22.39	0.66 (0.55,0.80)	<0.0001
Mild exacerbations				
Rate, events per 100 patients per year	6.14	9.11	0.67 (0.54, 0.84)	0.0003

BDP = beclometasone dipropionate; **CI** = confidence interval.

Severe exacerbations were defined as deterioration in asthma resulting in hospitalisation or emergency room treatment or resulting in the need for systemic steroids for >3 days.

Expert comment

These studies provide reassurance that the fixed-dose combination BDP/formoterol is comparable in efficacy and real-world effectiveness with older ICS/LABA combinations of fluticasone/salmeterol and budesonide/formoterol. They also replicate studies with budesonide/formoterol that demonstrate that maintenance and reliever therapy (MART) is superior to maintenance ICS/LABA with as needed SABA in reducing exacerbations. The advantage of MART is to provide an increased dose of ICS at the early symptomatic phase, thereby treating the increased airway inflammation associated with asthma exacerbations.

Real-life studies involving BDP/formoterol

PRISMA

PRISMA (PRospectIve Study on asthMA control) was an observational study involving patients with asthma conducted in Italy.[23] Patients (n=1017) who reported uncontrolled (55.7%) or partly controlled (44.3%) asthma during a cross-sectional visit were included in a 12-month prospective phase of the study.

After 12 months, 739 patients were evaluable, with 22.2% achieving full asthma control (Asthma Control Test™ [ACT] score: 25) and 58.7% reached good control (ACT score: 20–24).[23] At the 12-month visit, 81.5% of patients reported using fixed-combination therapy with an inhaled corticosteroid and a LABA.[23] Of those treated with the fixed-dose combination, a greater proportion of patients achieved asthma control with BDP/formoterol than with either budesonide/formoterol or fluticasone/salmeterol (**Figure 2**), with significantly more patients treated with BDP/formoterol, compared with budesonide/formoterol, achieving full control of their asthma.

Patients treated with BDP/formoterol had higher QoL at the end of the 12-month observation period than with either budesonide/formoterol when assessed on the EuroQoL-5D score (0.88 vs 0.82; p=0.001).[23] Patients also reported having better health when assessed on a visual analogue scale (0 to 100; 100 corresponding to best health) with BDP/formoterol (82.7) than with budesonide/formoterol (74.9; p<0.0001) or fluticasone/salmeterol group (77.0; p<0.001).[23]

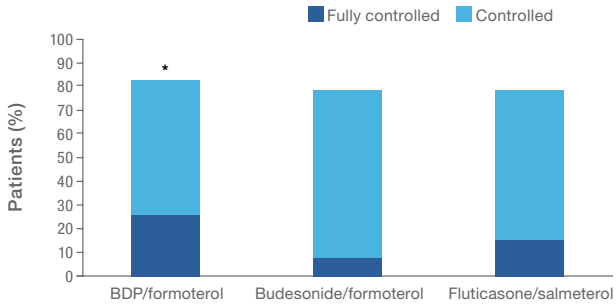

Figure 2. Percentage of patients treated with different ICS/LABA fixed combinations with fully controlled (ACT score: 25) or controlled (ACT score: 24–20) asthma

* p<0.001 vs budesonide/formoterol for fully controlled patients. **BDP** = beclometasone dipropionate.

REACH study

The retrospective REACH (Real-world Effectiveness in Asthma therapy of Combination inHalers) observational study investigated the clinical and cost effectiveness of switching 1528 patients with asthma from fluticasone/salmeterol to BDP/formoterol.[24] Using information from a database, patients remaining on fluticasone/salmeterol (n=1146) were compared with patients who switched to BDP/formoterol at an equivalent or lower ICS dosage (n=382).[24]

BDP/formoterol was non-inferior to fluticasone/salmeterol in regards to the rate of severe exacerbations (according to the American Thoracic Society and European Respiratory Society definition) during the 12 months after the switch (outcome year).[24] Patients who switched to BDP/formoterol were more likely to achieve better overall asthma control, have lower daily short-acting beta2-agonist usage, and be adherent to ICS therapy (**Table 2**). The average daily ICS dosage over the course of the outcome year was significantly lower with BDP/formoterol, by a mean of 130 µg/day in fluticasone-equivalent doses.

Switching to BDP/formoterol was associated with reduced mean asthma-related healthcare costs (by £93.63/patient/year; p<0.001).

Table 2. **Results during the outcome year in the REACH (Real-world Effectiveness in Asthma therapy of Combination inHalers) study**

Adjusted odds ratio (95% CI)	Switching to BDP/formoterol (n=382)	Patients remaining on fluticasone/salmeterol (n=1146)
Overall asthma control*	1.56 (1.14, 2.14)	1.0
Average daily short-acting beta2-receptor agonist usage	0.74 (0.60, 0.91)	1.0
Adherence to ICS therapy	1.40 (1.13, 1.73)	1.0

BDP= beclometasone dipropionate; **CI**=confidence interval; **ICS**=inhaled corticosteroid.
*Asthma control defined as no asthma-related hospitalisations, bronchial infections, acute oral steroids, and average salbutamol ≤200 µg/day.

Expert comment

The PRISMA head-to-head study comparing BDP/formoterol with fluticasone/salmeterol and budesonide/formoterol support an advantage of inhaled therapy with extrafine particle BDP providing improved asthma control with better lung and airway deposition. The REACH switch study from fluticasone/salmeterol to BDP/formoterol confirms this. In addition, better control is achieved with a reduced ICS dose.

Take home messages

- Fostair® 100/6 µg (BDP/formoterol) pMDI is an extra-fine hydrofluoroalkane-propelled solution formulation that allows the drug particles to be delivered homogeneously throughout the lungs
- The improved airway delivery with this formulation allows lower dose of BDP to be used, thus reducing the overall systemic exposure to the ICS
- BDP given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma
- Formoterol is a selective beta$_2$-adrenergic agonist that has a bronchodilating effect that is rapid (within 1–3 minutes after inhalation), and has a duration of effect of 12 hours after a single dose
- BDP/formoterol is an effective maintenance therapy in patients with asthma, and improves asthma symptoms and lung function, and reduces exacerbations
- When used as maintenance and reliever therapy, BDP/formoterol significantly prolonged the time to the first severe exacerbation compared with BDP/formoterol used as maintenance plus as needed salbutamol

Expert's concluding remarks

Fostair® is a welcome addition to the asthma pharmaco-therapeutic armamentarium. It builds on the established advantages of combination ICS/LABA therapy, as well as single inhaler MART therapy, with extrafine particle BDP improving airway delivery and lung deposition of ICS. It can be considered as first-line ICS/LABA in a MART regimen, as well as switching from established ICS/LABA therapies to improve effectiveness, or to maintain effectiveness at a lower dose of ICS.

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