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Fluticasone/formoterol: a new single-aerosol combination therapy for patients with asthma

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Summary
International asthma management guidelines recommend a long-acting β_2-agonist (LABA) as add-on therapy in patients whose asthma is not controlled by low-dose inhaled corticosteroid (ICS) monotherapy. Treatment with a single inhaler containing an ICS/LABA combination is advocated because it may facilitate adherence to a regimen. When prescribing ICS/LABA combination therapy, the potency of the ICS and the speed of onset of the LABA are considered important factors; therefore, an inhaled therapy containing components with these properties may be valued by physicians. The ICS fluticasone propionate (fluticasone) has potent and sustained anti-inflammatory effects, and the LABA formoterol fumarate (formoterol) provides rapid bronchodilation; the efficacy and safety profiles of these agents have been well established in clinical practice. Fluticasone and formoterol have been combined, for the first time, in a single hydrofluoroalkane-based aerosol (*flutiform*®; fluticasone propionate/formoterol fumarate). Here, we review data from the published randomized, controlled, clinical trials that demonstrate the efficacy and tolerability of this product. It has been shown that fluticasone/formoterol is more efficacious than fluticasone or formoterol given alone, and provides similar improvements in lung function to fluticasone and formoterol administered concurrently via separate inhalers. Fluticasone/formoterol has similar efficacy and tolerability profiles to budesonide/formoterol and fluticasone/salmeterol, but with the additional benefit of more rapid bronchodilation than fluticasone/salmeterol.

Introduction

International asthma management guidelines recommend that a long-acting β_2-agonist (LABA) is prescribed as an add-on therapy for patients whose asthma is not controlled by low-dose inhaled corticosteroid (ICS) monotherapy.[1] A substantial evidence base shows that co-administration of a LABA and an ICS results in better clinical effectiveness than that achieved with an ICS alone.[2–4] It has also been shown that the addition of a LABA to existing low-dose ICS therapy is more effective at reducing the risk of a severe exacerbation or a poorly controlled asthma day than doubling the dose of ICS administered.[5] Combining an ICS and a LABA in a single inhaler may encourage improved adherence to the treatment regimen and may be preferred by patients to the use of separate inhalers.[6,7] Until recently, only three ICS/LABA fixed-dose combinations were available in Europe, and data from randomized, controlled, clinical trials have demonstrated that each of these products is highly efficacious.[8–13] However, many patients do not achieve control of their asthma even when they are prescribed ICS/LABA therapy.[14,15] There are several possible reasons for this: the effectiveness of any inhaled asthma therapy in everyday clinical practice is influenced by drug efficacy and delivery, and requires the correct inhalation technique, handling of the device and patient adherence to their treatment regimen.[16,17]

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Incomplete control of asthma disrupts the lives of patients and has a large impact on their health and health-related quality of life.[15,18,19] As a consequence, morbidity associated with uncontrolled asthma remains a significant worldwide health and economic problem.[1] The development of alternative therapies is therefore required, especially for the treatment of patients whose asthma responds poorly to current therapies.[20] A recent Delphi initiative (sponsored by Mundipharma International Limited) has shown that a panel of expert respiratory specialists considered the potency of the ICS and speed of onset of the LABA among the factors to be most important when prescribing an ICS/LABA combination therapy for asthma.[21] A rapid onset of action is also important to patients; data show that patients want to feel their combination therapy working quickly, while providing lasting therapeutic benefits.[22–24] Importantly, patients who were non-adherent to a regimen identified rapid bronchodilation ('If I could feel it helping my asthma soon after taking it') among the leading factors that would encourage adherence; indeed, a key reason given for poor adherence to asthma maintenance therapy is the lack of a rapid effect.[25,26] Taken together, these data might suggest that the combination of the ICS fluticasone propionate (fluticasone), which has potent anti-inflammatory effects, and the LABA formoterol fumarate (formoterol), which provides rapid bronchodilation,[27] provides an additional treatment option for asthma that may be valued by both physicians (see Price and Bousquet[28] in this supplement) and patients.[22–26]

The efficacy and safety profile of fluticasone is well established; it is a widely prescribed,[29] highly effective maintenance treatment for asthma, both as a single-inhaler therapy[30] and as the ICS component of the fixed-dose combination fluticasone/salmeterol.[12,13] Fluticasone exhibits potent anti-inflammatory activity *in vitro* and *in vivo*.[31–33] Furthermore, it undergoes a high level of first-pass metabolism and has a significantly lower oral bioavailability than budesonide or beclometasone dipropionate (<1% versus ~11% and 13–26%, respectively [26–40% for the active metabolite beclometasone-17-monopropionate]).[34–36] The efficacy and safety profile of formoterol is also well established.[37] Formoterol provides significantly more rapid bronchodilation than salmeterol – comparable to that of the short-acting β_2-agonist salbutamol.[38–41] Formoterol is the LABA component of the fixed-dose combinations of budesonide/formoterol and beclometasone/formoterol. Fluticasone and formoterol have been combined for the first time in a single hydrofluoroalkane (HFA)-based pressurized metered-dose inhaler (pMDI; *flutiform*®). Fluticasone/formoterol is formulated as a suspension aerosol; other available ICS/LABA aerosol combinations are prepared in suspension (fluticasone/salmeterol; also available as a dry-powder inhaler) or solution (beclometasone/formoterol) formulations. Across most of Europe, budesonide/formoterol is only available in a dry-powder inhaler.

Fluticasone/formoterol has been approved in Europe for the regular treatment of asthma in adults and adolescents (12 years and above) with symptoms that are uncontrolled on an ICS alone, or controlled using an ICS in combination with a LABA.[27] This review provides an overview of the published data from a comprehensive clinical trial programme that demonstrates the efficacy and tolerability profiles of fluticasone/formoterol.

Efficacy of fluticasone/formoterol versus its components administered alone

Data from four clinical trials have demonstrated that fluticasone/formoterol is superior to its components administered as monotherapies for improvement in measures of lung function and asthma control.[42–45] Two of these studies have been published and are summarized here.[42,43] Both studies compared fluticasone/formoterol with fluticasone or formoterol administered as monotherapies, and with a placebo over a 12-week period, and both were of double-blind, placebo- and active-controlled, parallel-group design. These studies assessed the contribution of the individual components to the efficacy of the ICS/LABA combination as co-primary endpoints. The contribution of the ICS component was assessed by comparing fluticasone/formoterol with formoterol alone for mean change in forced expiratory volume in 1 second (FEV_1) from morning pre-dose at baseline to pre-dose at week 12. The contribution of the LABA component was assessed by comparing fluticasone/formoterol with fluticasone alone for mean change in FEV_1 from morning pre-dose at baseline to 2 hours post-dose at week 12. The third co-primary endpoint, time to discontinuation due to lack of efficacy, was used to evaluate the efficacy of fluticasone/formoterol compared with placebo. Primary efficacy analyses were carried out using the full analysis set (all patients who received at least one dose of treatment and had measurements for pre-dose baseline FEV_1, at least one post-baseline pre-dose FEV_1 and at least one post-baseline post-dose FEV_1).

The first study assessed the efficacy of low-dose fluticasone/formoterol in 475 adolescent and adult patients with asthma (60–85% predicted FEV_1 at baseline), who were randomly assigned to receive fluticasone/formoterol (100/10 μg twice daily [b.i.d.]), fluticasone alone (100 μg b.i.d.), formoterol alone (10 μg b.i.d.) or placebo, all administered via an HFA-based pMDI (EudraCT number: 2007-002866-36; US NCT number: NCT00393991).[43]

Fluticasone/formoterol was superior to formoterol administered alone for increase from baseline to week 12 in mean morning pre-dose FEV_1 (least-squares [LS] mean between-treatment difference: 0.101 L; 95% confidence interval [CI]: 0.002, 0.199; $p = 0.045$), demonstrating the contribution of the fluticasone component of the combination treatment. In addition, fluticasone/formoterol provided significantly greater improvement in mean morning FEV_1 than fluticasone monotherapy from pre-dose at baseline to 2 hours post-dose at week 12 (LS mean between-treatment difference: 0.200 L (95% CI: 0.109, 0.292; $p < 0.001$), which highlighted the contribution of formoterol to the combination. Fluticasone/formoterol was associated with a significantly longer time to discontinuation due to lack of efficacy (assessed as either an asthma exacerbation or a loss of asthma control; $p = 0.015$), compared with placebo. Furthermore, fewer patients in