Introduction

The efficacy of an inhaled drug depends on the propensity for drug particles to deposit throughout the lungs. Airway deposition is affected by several, often interrelated factors, including the intrinsic inhaler properties, drug formulation and patient characteristics.

In vitro particle size profiles of emitted particles correlate with in vivo lung deposition. Particles > 5 µm in diameter are prone to being deposited in the mouth or throat, where they do not exert therapeutic effects and may increase the risk of local side effects. Fine particles (< 5 µm) are associated with deposition throughout the airways. The proportion of an emitted aerosolized drug dose that contains fine particles is referred to as the fine particle fraction (FPF).

The inhaled corticosteroid (ICS) fluticasone propionate (FP) and long-acting β₂-agonist (LABA) formoterol fumarate (FORM) have been combined in a single, hydrofluoroalkane (HFA)-based, aerosol inhaler (FP/FORM; flutiform®). FP/FORM is approved for maintenance treatment of asthma at twice-daily doses of 100/10 µg, 250/10 µg (patients aged ≥ 12 years) and 500/20 µg (patients aged ≥ 18 years only) when an ICS/LABA therapy is appropriate.

In this study, the in vitro FPF profile of FP/FORM was compared with fluticasone propionate/salmeterol (FP/SAL) and budesonide/formoterol (BUD/FORM) dry powder inhalers (DPIs). The beclometasone dipropionate/formoterol (BDP/FORM) pressurized metered-dose inhaler (pMDI) aerosol was included as a benchmark comparator.
### Results

FP/FORM produced a high and consistent FPF of ~ 40% for both the ICS and the LABA components at each flow rate (Figure 1).

- The FPF of FP/FORM was higher than that of the FP/SAL DPI at 28.3 L/min (ratio vs FP/FORM: ICS, 0.30 [90% CI: 0.28, 0.32]; LABA, 0.29 [90% CI: 0.28, 0.31]) and at 60.0 L/min (ICS, 0.41 [90% CI: 0.40, 0.41]; LABA, 0.35 [90% CI: 0.34, 0.37]).
- The FPF of FP/FORM was higher than that of the BUD/FORM DPI at 28.3 L/min (ratio vs FP/FORM: ICS, 0.20 [90% CI: 0.18, 0.22]; LABA, 0.17 [90% CI: 0.15, 0.19]) and at 60.0 L/min (ICS, 0.80 [90% CI: 0.73, 0.86]; LABA, 0.71 [90% CI: 0.65, 0.78]).
- The FPF of FP/FORM was higher than that of the BDP/FORM pMDI for the ICS at 28.3 L/min (ratio vs FP/FORM: 0.69 [90% CI: 0.66, 0.73]) and the LABA at 28.3 L/min (0.66 [90% CI: 0.63, 0.70]) and 60.0 L/min (0.94 [90% CI: 0.92, 0.96]).

- The FPF of FP/FORM was consistent across flow rates (FPF 60.0/28.3: 1.06 [90% CI: 1.02, 1.10] for FP; 1.08 [90% CI: 1.04, 1.11] for FORM).
- By contrast, the FPFs emitted from the FP/SAL and BUD/FORM DPIs demonstrated marked flow rate dependency. The FPF 60.0/28.3 ratio for the FP/SAL DPI was 1.43 (90% CI: 1.36, 1.51) for FP and 1.33 (90% CI: 1.20, 1.45) for SAL.
- Similarly, the FPF of BUD/FORM increased more than fourfold for the ICS and LABA components between flow rates, with FPF 60.0/28.3 ratios of 4.38 (90% CI: 3.71, 5.04) for BUD and 4.63 (90% CI: 3.92, 5.33) for FORM.

### Study design

This in vitro study compared the aerodynamic particle size distribution (APSD) profiles of FP/FORM, FP/SAL, BUD/FORM and BDP/FORM, at drug strengths which can be used to deliver similar treatment doses (via 1 or 2 actuations at a single dose strength for each inhaler).

- APSD profiles were assessed using an 8-stage Andersen Cascade Impactor at inhalation flow rates of 28.3 and 60.0 L/min.
- The FPF was calculated as a percentage of the labelled dose for the ICS and for the LABA component. Ratios were calculated between FPFs at both flow rates (FPF 60.0/28.3 L/min); equivalence was concluded if the 90% confidence interval (CI) was contained in the 0.85–1.18 (± 15%) acceptance interval.

**Figure 1. FPFs of the (a) ICS and (b) LABA components of the combination therapies.**

Error bars show standard error.

BDP/FORM, beclometasone dipropionate/formoterol; BUD/FORM, budesonide/formoterol; FP/FORM, fluticasone propionate/formoterol; FP/SAL, fluticasone propionate/salmeterol; FPF, fine particle fraction; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist.
Discussion

- *In vitro,* FP/FORM emits a high and consistent FPF (approximately 40%) at 28.3 and 60.0 L/min that was greater than those of FP/SAL and BUD/FORM. The FPF of FP/FORM was less affected by changes in flow rate than the other products tested.

- A patient’s inhalation flow rate is not constant during an inhalation manoeuvre and may vary from breath to breath (and thus from dose to dose), and from patient to patient; therefore, an ICS/LABA with a consistent FPF that is relatively flow rate independent might facilitate more uniform dosing in the lungs.

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**European Prescribing Information**

**Please read the Summary of Product Characteristics before prescribing.**

**Presentation**
Pressurised inhalation suspension, in a pressurised metered dose inhaler (pMDI), containing fluticasone propionate and formoterol fumarate dihydrate at strengths of 50 μg/5 μg, 125 μg/5 μg or 250 μg/10 μg per actuation.

**Indications**
Regular treatment of asthma where the use of a combination product (inhaled corticosteroid and long-acting β₂-agonist) is appropriate.

For patients not adequately controlled with inhaled corticosteroids and ‘as required’ inhaled short-acting β₂-agonist (SABA), or for patients already adequately controlled on both an inhaled corticosteroid and a long-acting β₂-agonist (LABA).

**flutiform®** 50 μg/5 μg and 125 μg/5 μg per actuation are indicated for use in adults and adolescents 12 years and above. **flutiform®** 250 μg/10 μg per actuation is only indicated for use in adults.

**Dosage and administration**
For inhalation use. The patient should be shown how to use the inhaler correctly by a physician or other healthcare professional.

Patients should be given the strength of **flutiform** containing the appropriate fluticasone propionate dose for their disease severity (note that **flutiform** 50 μg/5 μg per actuation is not appropriate in patients with severe asthma). The appropriate strength should be taken as two inhalations, twice daily (normally in the morning and evening) and used every day, even when asymptomatic. **flutiform®** should not be used in children under 12 years. Prescribers should be aware that in asthmatics, fluticasone propionate is as effective as some other inhaled steroids when administered at approximately half the total daily microgram dose.

Total daily dose can be increased if asthma remains poorly controlled by administering a higher strength inhaler. Appropriate doses of the β₂-agonist and inhaled corticosteroid (ICS) in separate inhalers, or the ICS alone, should be prescribed if a patient requires doses outside the recommended dose regimen.

Patients should be assessed regularly and once asthma is controlled, treatment should be reviewed and stepped down to the lowest effective dose, or an ICS alone. It is extremely important to regularly review patients as their treatment is stepped down.

ICS alone are first line treatment for most patients. **flutiform®** is not intended for initial treatment of mild asthma. For patients with severe asthma the ICS therapy should be established before prescribing a fixed-dose combination product.

**Patients on flutiform®** must not use an additional LABA. An inhaled SABA should be prescribed if a patient requires doses outside the recommended dose regimen.

Patients should be advised to contact their prescriber when the **flutiform®** dose counter is getting near zero.

**Contraindications**
Hypersensitivity to the active substances or to any of the excipients.

**Precautions and warnings**
**flutiform®** should not be used for the first treatment of asthma, to treat acute asthma symptoms or for prophylaxis of exercise-induced asthma. It should not be initiated during an exacerbation, during significantly worsening or acutely deteriorating asthma, and should not be stopped abruptly. Patients should use their **flutiform®** maintenance treatment as prescribed, even when asymptomatic.

If a patient experiences serious asthma-related adverse events or exacerbations, they should continue treatment but also seek medical advice. Patients should be reviewed as soon as possible if there is any indication of deteriorating asthma control. In the case of sudden and progressive deterioration, which is potentially life-threatening, an urgent medical assessment should be carried out.

Use with caution in patients with: pulmonary tuberculosis; quiescent tuberculosis; an urgent medical assessment should be carried out.

**Concomitant use with β₂-agonists or drugs that can induce or potentiate a β₂-adrenergic effect.**

**Concomitant use of LABA and ICS in severe asthma.**

**Effects of concurrent use.**

**Prolonged treatment with high doses of corticosteroids may result in adrenal suppression and acute adrenal crisis, particularly in adolescents and children or potentially as a result of trauma, surgery, infection or rapid dose reduction.**

**Patients should be advised that flutiform® contains a small amount of ethanol; however, this negligible amount does not pose a risk to patients.**

**flutiform®** is not recommended in children under 12 years of age.

**Interactions**
Caution is advised in long-term co-administration with strong CYP3A4 inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nelfinavir, saquinavir, ketoconazole and telithromycin), co-administration should be avoided if possible. Ritonavir in particular should be avoided, unless the benefits outweigh the risks of systemic side-effects.

Caution is advised with use of non-potassium sparing diuretics (e.g. loop or thiazide), xanthine derivatives, glucocorticosteroids, L-Dopa, L-thyroxine, oxytocin, alcohol or other adrenergic drugs.

There is an increased risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons. Hypokalaemia may increase the risk of arrhythmias in patients being treated with digitalis glycosides.

Concomitant use of β₂-adrenergic drugs can have a potentially additive effect.

Caution should be taken when using formoterol fumarate with drugs known to prolong the QTc interval, such as tricyclic antidepressants or MAOIs (and for two weeks following their discontinuation), as well as antipsychotics (including phenothiazines), quinidine, disopyramide, procainamide and antihistamines.

Concomitant use of an MAOI or a similar agent, such as furazolidone or procainamide, may precipitate hypertensive reactions. β-blockers and formoterol fumarate may inhibit the effect of each other. β-blockers may produce severe bronchospasm in asthma patients, and they should not normally be treated with β-blockers including those that are used as eye drops to treat glaucoma. Under certain circumstances, e.g. as prophylaxis after myocardial infarction, cardioselective β-blockers could be considered with caution.

**Pregnancy and lactation**
**flutiform®** is not recommended during pregnancy. It should only be considered if benefits to the mother outweigh risks to the foetus.

It is not known whether fluticasone propionate or formoterol are excreted in breast milk; a risk to the breast feeding infant cannot be excluded. A decision should be made on whether to discontinue breastfeeding or discontinue/abstain from **flutiform®**.

**Side-effects**
Potentially serious side-effects: hyperglycaemia; depression; aggression; behavioural changes (predominantly in children); paradoxical bronchospasm; agitation; vertigo; palpitations; ventricular extrasystoles; angina pectoris; tachycardia; hypertension; dyspnoea; peripheral oedema; Cushings syndrome; adrenal suppression; growth retardation; cataract and glaucoma; hypersensitivity reactions and QTc interval prolongation.

Please consult the SPC for details of non-serious side-effects and those reported for the individual molecules.

**Legal category**
POM

**Package quantities**
One inhaler containing 120 actuations

Multipack of 3 x 1 inhaler (120 actuations)

Not all pack sizes may be marketed

**Shelf life**
2 years

In-use shelf life: 3 months after opening the foil pouch

**Date of preparation**
July 2015

**Date effective**
August 2015

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**Adverse events should be reported. Reporting to the applicable regulatory authorities should be in accordance with National requirements and to the applicable holder of the marketing authorization for flutiform®, details of which can be found on the product packaging and/or inserts.**