Plume characteristics of two HFA-driven inhaled corticosteroid/long-acting beta2-agonist combination pressurized metered-dose inhalers


Publication summary

Introduction

- Chlorofluorocarbon (CFC)-based inhalers produced high-velocity, forceful and cold plumes that could result in drug impaction in the oropharynx, leading to cough and throat irritation.
  - CFC-based inhalers were also associated with paradoxical bronchoconstriction and the cold-Freon effect (a reflex interruption of inhalation caused by the cold, high-velocity spray impacting the back of the throat).
  - High-velocity plumes with a short duration made the coordination of actuation and inhalation more difficult.

- Modern hydrofluoroalkane (HFA)-based inhalers, which have largely replaced the CFC-based devices, have improved plume characteristics, with higher fine particle fractions, and warmer plumes with reduced force and velocity.
  - Several of these new HFA-based inhalers show improved lung deposition, which may be due at least in part to the more favourable plume characteristics. However, there are notable differences in device properties.

- The inhaled corticosteroid fluticasone propionate (FP) and the long-acting β₂-agonist formoterol fumarate (FORM) have been combined in a single, HFA-based inhaler (FP/FORM; flutiform®), which provides an alternative to the fluticasone propionate/salmeterol xinafoate pressurized metered-dose inhaler (pMDI) (FP/SAL; Seretide® Evohaler®). These combination devices use different HFA propellants and also differ in formulation composition and delivery device geometry.

- In this in vitro study, the plume characteristics of the FP/FORM 125/5 µg pMDI were compared with those of the FP/SAL pMDI 125/25 µg. Plume temperature, velocity, force and duration were analysed.

Modern hydrofluoroalkane (HFA)-based inhalers have improved plume characteristics compared with earlier chlorofluorocarbon (CFC)-based devices, with higher fine particle fractions, and warmer plumes with reduced force and velocity. However, there are notable differences in device properties.

This in vitro study compared the plume characteristics of two inhaled corticosteroid/long-acting β₂-agonist combinations, administered via HFA-based pressurized metered-dose inhalers: fluticasone propionate/formoterol (FP/FORM; flutiform®) 125/5 µg and fluticasone propionate/salmeterol (FP/SAL; Seretide® Evohaler®) 125/25 µg.

 Compared with FP/SAL, the plume emitted by FP/FORM:
  - had longer average duration (168.3 ms vs 114.0 ms with FP/SAL)
  - had a consistently slower mean maximum velocity (10.1 m/s vs 15.6 m/s with FP/SAL), which remained relatively constant before declining steadily
  - was warmer (minimum impaction temperature: +5.9°C vs −37.8°C for FP/SAL at 25 mm distance); this difference became less pronounced over distance (25–95 mm)
  - was less forceful at all distances tested (25–95 mm; maximum force: 138.2 mN vs 278.9 mN with FP/SAL).

FP/FORM emits a slower, warmer and less forceful plume with a longer duration, than FP/SAL. Forceful plumes are associated with greater drug deposition in the throat than less forceful plumes.¹ ²
The European prescribing information can be found at the end of this document.

**Results**

- The average plume duration of FP/FORM was almost 50% longer than that of FP/SAL (168.3 vs 114.0 ms).
  - In terms of intensity, the FP/FORM plume peaked later than that of FP/SAL (40 vs 20 ms) and declined more slowly (FP/FORM: 25% of the dose appeared within 38 ms, 50% within 59 ms, and 75% within 87 ms; FP/SAL: 25% of the dose appeared within 23 ms, 50% within 40 ms, and 75% within 61 ms).
- Mean maximum plume velocities were at least 30% slower with FP/FORM than with FP/SAL at each distance measured (Figure 1a).
  - The velocity of the FP/SAL plume declined rapidly after the initial peak, whereas that of FP/FORM had a slower velocity at the outset and declined steadily.
- The FP/FORM plume was approximately 50% less forceful than that of FP/SAL (Figure 1b).
  - Mean force was 104.0 mN for FP/FORM and 218.0 mN for FP/SAL, with a maximum force of 138.2 mN and 278.9 mN, respectively.
- FP/FORM emitted a warmer plume than FP/SAL.
  - The minimum impaction temperature was +5.9°C for FP/FORM compared with −37.8°C for FP/SAL at a distance of 25 mm. This difference became less pronounced with increasing distance of the device from the sensor; there was no difference between the two devices at 95 mm.

**Figure 1. Plume characteristics of FP/FORM pMDI and FP/SAL Evohaler. (a) Mean maximum velocities at different distances from the device to the sensor and (b) mean force of plume on copper target disc.**

Error bars represent standard error.
FP/FORM, fluticasone propionate/formoterol; FP/SAL, fluticasone propionate/salmetrol; pMDI, pressurized metered-dose inhaler.

The inhalers were held in a fixed position during actuation and fired into ambient air.

- Plume velocity and duration were measured using a high-speed camera (operating at 1000 frames per second) and a short-pulse laser light source. Impaction temperature was recorded using a thermal imaging video camera operating at 30 frames per second. Plume force was measured using a copper disc attached to a sensitive load cell.

- Measurements were made at varying distances up to 95 mm from the device (95 mm is representative of the average distance from mouth to throat of an adult with asthma).

**Study design**

- The inhalers were held in a fixed position during actuation and fired into ambient air.
- Plume velocity and duration were measured using a high-speed camera (operating at 1000 frames per second) and a short-pulse laser light source. Impaction temperature was recorded using a thermal imaging video camera operating at 30 frames per second. Plume force was measured using a copper disc attached to a sensitive load cell.
- Measurements were made at varying distances up to 95 mm from the device (95 mm is representative of the average distance from mouth to throat of an adult with asthma).
Discussion

- This *in vitro* study identified notable differences between the plumes emitted by the FP/FORM pMDI and the FP/SAL Evohaler.
- Forceful plumes are associated with greater drug deposition in the throat than less forceful plumes.\(^1,2\)
- The FP/FORM plume was slower, less forceful and had a longer duration than that produced by FP/SAL. FP/FORM also emitted a warmer plume than FP/SAL over short distances.
  - Although there was no difference in plume temperature between the two devices at 95 mm (the distance that corresponds to the back of the throat in adults), the large temperature difference at shorter distances (corresponding to the position of the tongue) may be perceived by patients and thus affect their experience of using the device and their preference.
  - A slower and longer spray duration, such as that seen with FP/FORM, may help coordination of actuation and inhalation because the drug plume is resident in the mouth for longer.

References


® FLUTIFORM is a registered trademark of Jagotec AG and is used under licence.

® SERETIDE and EVOHALER are registered trademarks of Glaxo Group Limited.
**flutiform® (fluticasone propionate and formoterol fumarate)**

**Pressurised Inhalation Suspension**

**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' β₂-agonists, 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 regimens.

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 taken for immediate relief of asthma symptoms arising between doses.

The AeroChamber Plus® spacer device is recommended in patients who find it difficult to use inhalers; re-titration should always follow the introduction of a spacer device.

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; fungal, viral or other infections of the airway; thytoxicosis; pheochromocytoma; diabetes mellitus (consider additional blood sugar controls); hypertension; predisposition to low levels of serum potassium; impaired adrenal function (monitor HPA axis function regularly); hypothyroidism; idiopathic subvalvular aortic stenosis; severe hypertension; aneurysm or other severe cardiovascular disorders.

There is risk of potentially serious hypokalaemia with high doses of β₂-agonists or concomitant treatments with β₂-agonists and drugs that can induce or potentiate a hypokalaemic effect. Particular caution is recommended in unstable or acute severe asthma and other conditions when the likelihood for hypokalaemia adverse effects is increased. Monitoring of serum potassium levels is recommended during these circumstances. Formoterol may induce prolongation of the QTc interval. Caution must be observed when treating patients with existing prolongation of QTc interval.

**flutiform** should be discontinued immediately if there is evidence of paradoxical bronchospasm.

Systemic effects with an ICS may occur, particularly at high doses for prolonged periods or when combined with potent CYP3A4 inhibitors, but are less likely than with oral corticosteroids. Use of a spacer device may also cause an increased systemic exposure. Increased exposure can be expected in patients with severe hepatic impairment.

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, iraconazole, neflinavir, 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, oxtocin, 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 ß-adrenergic drugs can have a potentially additive effect.

Caution should be taken when using inhaled corticosteroids 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 procarbazine, 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

® FLUTIFORM is a registered trademark of Jagotec AG, and is used under licence.

® The “lung” device (logo) is a registered trademark of Mundipharma AG.

® AEROCHAMBER and AEROCHAMBER PLUS are registered trademarks of Trudell Medical International.

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.

MINT/FLU-16046