Efficacy of fluticasone propionate/formoterol fumarate in the treatment of asthma: a pooled analysis


Publication summary

This paper summary has been written and produced by Mundipharma International Limited

Fast facts

- This pooled analysis of data from five randomized 8-week or 12-week studies compared the efficacy of fluticasone propionate/formoterol (flutiform®) (100/10, 250/10 or 500/20 μg twice daily [b.i.d.]) combination therapy with that of fluticasone propionate (100, 250 or 500 μg b.i.d.) alone in patients with asthma (aged ≥ 12 years) who had previously received inhaled corticosteroids (ICSs).

- Fluticasone propionate/formoterol (n = 528) provided significantly greater increases than fluticasone propionate monotherapy (n = 527) in the following lung function parameters:
  - change in mean morning forced expiratory volume in 1 second (FEV₁) from pre-dose at baseline to 2 hours post-dose at study end (least-squares mean [LSM] treatment difference: 0.146 L; 95% confidence interval [CI]: 0.101, 0.190; p < 0.001)
  - change in pre-dose FEV₁ from baseline to study end (LSM treatment difference: 0.048 L; 95% CI: 0.002, 0.095; p = 0.043).

- Fluticasone propionate/formoterol provided significant improvements compared with fluticasone propionate alone in the percentage of asthma control days (LSM treatment difference: 8.6%; 95% CI: 4.2, 12.9; p < 0.001).

- The annualized rate of asthma exacerbations was significantly lower with fluticasone propionate/formoterol than with fluticasone propionate monotherapy (rate ratio: 0.71; 95% CI: 0.54, 0.94; p = 0.014); the rate of severe exacerbations was low with either treatment.

- The overall tolerability profile of fluticasone propionate/formoterol was as expected for an ICS/long-acting β₂-agonist combination therapy, and was similar to that of fluticasone propionate alone.

Introduction

- The potent inhaled corticosteroid (ICS) fluticasone propionate and the fast-acting long-acting β₂-agonist (LABA) formoterol are available in a single aerosol inhaler (fluticasone propionate/formoterol; flutiform®), approved for asthma maintenance therapy in adults and adolescents (aged ≥ 12 years) where use of an ICS/LABA combination product is appropriate.

- The efficacy and safety profile of fluticasone propionate/formoterol has been demonstrated in a comprehensive programme of randomized, controlled clinical trials. The authors report on a pooled analysis of data from five of these studies.

- The efficacy analysis was conducted in patients who had received prior ICS treatment, consistent with the approved indication of fluticasone propionate/formoterol.

Study design

- This was a pooled analysis of data from five randomized, double-blind, 8-week or 12-week studies of fluticasone propionate/formoterol therapy (100/10, 250/10 or 500/20 μg twice daily [b.i.d.]), administered via a pressurized metered-dose inhaler (pMDI), compared with fluticasone propionate (pMDI) monotherapy (100, 250 or 500 μg b.i.d.) in adults and adolescents with asthma (the study assessing fluticasone propionate/formoterol 500/20 μg b.i.d. was conducted in adults aged ≥ 18 years, in line with the licensed indication).

- Efficacy was assessed in patients who had received ICS therapy before study enrolment; the safety evaluation included all patients.
Results

- Fluticasone propionate/formoterol provided significantly greater increases than fluticasone propionate alone in the following lung function parameters:
  - change in mean morning forced expiratory volume in 1 second (FEV₁) from pre-dose at baseline to 2 hours post-dose at study end (least-squares mean [LSM] treatment difference: 0.146 L; 95% confidence interval [CI]: 0.101, 0.190; \( p < 0.001 \))
  - change in pre-dose FEV₁ from baseline to study end (LSM treatment difference: 0.048 L; 95% CI: 0.002, 0.095; \( p = 0.043 \)).

- Fluticasone propionate/formoterol therapy significantly increased the percentage of asthma control days (defined as days with no symptoms, no awakenings at night due to asthma and no use of rescue medication) from baseline to study end compared with fluticasone propionate monotherapy (secondary endpoints; LSM treatment difference: 8.6%; 95% CI: 4.2, 12.9; \( p < 0.001 \); Figure 1a).
  - Fluticasone propionate/formoterol was also superior to fluticasone propionate for individual measures of asthma control (proportion of symptom-free days, awakening-free nights and rescue medication-free days; all \( p < 0.001 \)).

- The annualized rate of asthma exacerbations was significantly lower with fluticasone propionate/formoterol than with fluticasone propionate monotherapy (secondary endpoint; rate ratio: 0.71; 95% CI: 0.54, 0.94; \( p = 0.014 \); Figure 1b). The incidence of severe exacerbations was low, with a similar incidence in both groups (secondary endpoint; Figure 1b).

- The types and incidence of adverse events were similar in both treatment groups (incidence: 30.2% for fluticasone propionate/formoterol and 34.4% for fluticasone propionate monotherapy).

Figure 1. Fluticasone propionate significantly improved asthma control and exacerbations. (a) Asthma control days and (b) annualized exacerbation rate.

Asthma control days were defined as days with no symptoms, no awakenings at night due to asthma and no use of rescue medication. Any exacerbation included mild–moderate and severe exacerbations. Exacerbations were categorized as ‘mild–moderate’ if the patient had a morning pre-dose peak expiratory flow rate that was > 30% below baseline on ≥ 2 consecutive days, or awoke at night due to asthma on ≥ 2 consecutive days, or used rescue medication at least four times per day above baseline usage (studies 1–4) or at least five times per day (study 5) for ≥ 2 consecutive days. Exacerbations were categorized as ‘severe’ if the patient had a deterioration in asthma that required additional therapy (e.g. systemic glucocorticosteroid), or an emergency visit or hospitalization due to asthma.

Full analysis set.

Ratios of the expected number of exacerbations with fluticasone propionate/formoterol relative to fluticasone propionate were analysed using a negative binomial regression model with treatment as a factor and log time on treatment as an offset variable and FEV₁ % predicted category as a covariate.

Between-treatment difference analysed using ANCOVA with treatment as a factor, and FEV₁ % predicted category at baseline and baseline value as covariates.

Values shown in square brackets are the total number of exacerbations.

ANCOVA, analysis of covariance; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; LSM, least-squares mean.
Discussion

- This pooled analysis showed that fluticasone propionate/formoterol provides significant improvements in lung function compared with fluticasone propionate monotherapy over a treatment period of up to 12 weeks in patients previously receiving ICS therapy.

- Fluticasone propionate/formoterol combination therapy also significantly reduced the incidence of asthma exacerbations and increased the percentage of asthma control days, compared with fluticasone propionate alone.

- Fluticasone propionate/formoterol was generally well tolerated, and the incidence and type of adverse events were as expected for an ICS/LABA combination treatment.

- Overall, this pooled analysis shows that fluticasone propionate/formoterol offers an additional option for adolescent and adult patients who require an ICS/LABA combination for maintenance treatment of asthma.

® FLUTIFORM is a registered trademark of Jagotec AG and is used under licence.
**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' 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 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; thyrotoxicosis; pheochromocytoma; diabetes mellitus (consider additional blood sugar controls); uncorrected hypokalaemia; predisposition to low levels of serum potassium; impaired adrenal function (monitor HPA axis function regularly); hypertrophic obstructive cardiomyopathy; idiopathic subvalvular aortic stenosis; severe hypertension; aneurysms or other severe cardiovascular disorders.

There is risk of potentially serious hypokalaemia with high doses of β₂-agonists or concomitant treatment with β₂-agonists and drugs that can induce or potentiate a hypokalemic 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 QT interval. Caution must be observed when prescribing formoterol to 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, nelfinavir, saquinavir, ketoconazole and teithromycin); 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 β-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 at least 2 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 procabazine, 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 × 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 Date of preparation: July 2016