

# Fluticasone/formoterol combination therapy versus budesonide/formoterol for the treatment of asthma: a randomised, controlled, non-inferiority trial of efficacy and safety

Bodzenta-Lukaszuk A, Buhl R, Balint B, Lomax M, Spooner K, Dissanayake S. *J Asthma* 2012;49:1060–70.

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

## Fast facts

- This 12-week study compared the efficacy and tolerability of fluticasone propionate/formoterol fumarate (fluticasone/formoterol) combination therapy with those of budesonide/formoterol in 279 adolescents ( $\geq 12$  years) and adults with moderate-to-severe persistent, reversible asthma.
- Fluticasone/formoterol (250/10  $\mu\text{g}$  twice daily [b.i.d.]; pressurized metered-dose inhaler) provided comparable efficacy to budesonide/formoterol (400/12  $\mu\text{g}$  b.i.d.; dry powder inhaler) for the primary efficacy endpoint, mean change in pre-dose forced expiratory volume in the first second from baseline to week 12.
- The two treatments also showed comparable efficacy for all secondary endpoints.
- Fluticasone/formoterol was well tolerated, with a similar safety and tolerability profile to budesonide/formoterol.

## Introduction

- Current Global Initiative for Asthma (GINA) guidelines recommend a step-wise approach to asthma control. If asthma is not controlled with a low-dose inhaled corticosteroid (ICS) and a rapid-acting  $\beta_2$ -agonist, combination therapy with an ICS and a long-acting  $\beta_2$ -agonist (LABA) is recommended.
  - Addition of a LABA to ICS therapy has been shown to achieve better asthma control than more than doubling the ICS dose.
  - Use of a single inhaler to administer both ICS and LABA is likely to improve patient adherence compared with the treatments administered using separate inhalers.
- Fluticasone propionate (fluticasone) is an ICS with potent, sustained anti-inflammatory effects and a well established efficacy and safety profile. Formoterol fumarate (formoterol) is the only LABA approved for use in asthma with both a fast onset of action (1–3 minutes) and a prolonged bronchodilatory effect.
- Fluticasone and formoterol have been combined in a single hydrofluoroalkane-based pressurized metered-dose inhaler (pMDI; fluticasone/formoterol, **flutiform**<sup>®</sup>). This combination provides clinicians with a new treatment option for the maintenance treatment of persistent asthma.

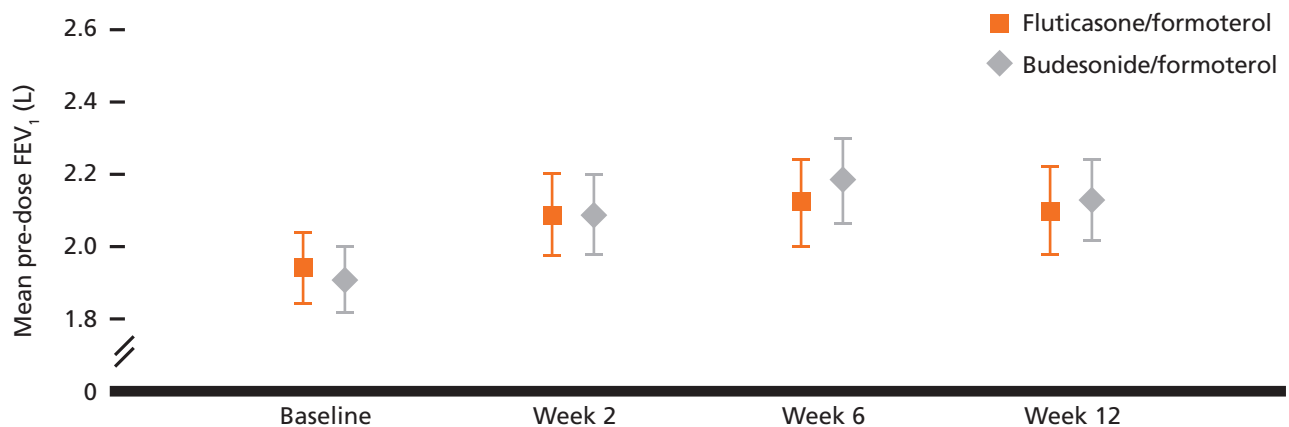
## Study design

- This 12-week, randomized, double-blind, double-dummy, parallel-group, multicentre study compared the efficacy and safety of fluticasone/formoterol 250/10  $\mu\text{g}$  twice daily (b.i.d.; administered via a pMDI) with those of budesonide/formoterol 400/12  $\mu\text{g}$  b.i.d. (administered via a dry powder inhaler [DPI]) in 279 adolescent ( $\geq 12$  years) and adult patients with moderate-to-severe, persistent, reversible asthma with a forced expiratory volume in the first second (FEV<sub>1</sub>) 50–80% of predicted normal values.

## Results

- Fluticasone/formoterol was non-inferior to budesonide/formoterol for the primary endpoint, with an adjusted mean increase in morning pre-dose FEV<sub>1</sub> of 0.164 L (n = 126) and 0.207 L (n = 120), respectively, from baseline to week 12 (per-protocol set [PPS]).
  - The least-squares mean treatment difference was –0.044 L and the lower limit of the 95% confidence interval (95% CI: –0.130, 0.043) was greater than the pre-defined non inferiority acceptance limit of –0.2 L.
  - The results of a supportive analysis on the full analysis set (FAS) confirmed the conclusion of non-inferiority at week 12.
  - Fluticasone/formoterol was also shown to be non-inferior to budesonide/formoterol for changes from baseline in pre-dose FEV<sub>1</sub> at weeks 2 and 6 (*post hoc* analysis in both the PPS and the FAS).
- Mean pre-dose FEV<sub>1</sub> values at each visit are presented in Figure 1 (PPS).

**Figure 1. Mean morning pre-dose FEV<sub>1</sub> from baseline to week 12.**



Data are shown as mean FEV<sub>1</sub> ± 95% CIs for the PPS.

CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in the first second; PPS, per-protocol set.

- Fluticasone/formoterol was also non-inferior to budesonide/formoterol for the secondary endpoints:
  - mean change in morning FEV<sub>1</sub> from pre-dose at baseline to 2 hours post-dose at week 12 (PPS)
  - number of patients who discontinued due to lack of efficacy (PPS).
- Fluticasone/formoterol was comparable to budesonide/formoterol for mean change in morning and evening peak expiratory flow rates (PEFR) from baseline to week 12 (based on diary data, FAS).
- Other secondary endpoints (including asthma symptom scores, percentage of symptom-free days, sleep disturbance scores, percentage of awakening-free nights, percentage of asthma control days, percentage of rescue medication-free days and Asthma Quality of Life Questionnaire [AQLQ] scores) were also similar, with no statistically significant differences between treatment groups (FAS).
- Fluticasone/formoterol and budesonide/formoterol had similar tolerability profiles. The overall adverse event (AE) rate was 20.7% in the fluticasone/formoterol group and 18.7% in the budesonide/formoterol group (safety set). The majority of AEs were mild or moderate in intensity.

## Discussion

- This study demonstrated that fluticasone/formoterol (250/10 µg b.i.d.) was comparable to budesonide/formoterol (400/12 µg b.i.d.) for the primary endpoint, mean increase in pre-dose FEV<sub>1</sub> from baseline to week 12.
- Both treatments were associated with substantial and clinically relevant improvements in lung function during the treatment period.
- Fluticasone/formoterol treatment was comparable to budesonide/formoterol treatment for all secondary efficacy endpoints, including:
  - mean increase in FEV<sub>1</sub> from pre-dose at baseline to 2 hours post-dose at week 12, as well as for mean change in morning and evening PEFR
  - discontinuations due to lack of efficacy
  - asthma symptom scores, symptom-free days, sleep disturbance scores, awakening-free nights, asthma control days, rescue medication use and AQLQ scores.
- In conclusion, this study demonstrated that fluticasone/formoterol (250/10 µg b.i.d; pMDI) has comparable efficacy to budesonide/formoterol (400/12 µg b.i.d.; DPI), as assessed by lung function parameters and several measures of asthma control, over 12 weeks of treatment in adults and adolescents with moderate-to-severe, persistent, reversible asthma.
- These data suggest that fluticasone/formoterol offers an efficacious treatment option for patients with asthma.

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

® SYMBICORT and TURBOHALER are registered trademarks of AstraZeneca AB.

# **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  $\beta_2$ -agonist) is appropriate.

For patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting  $\beta_2$ -agonist (SABA), or for patients already adequately controlled on both an inhaled corticosteroid and a long-acting  $\beta_2$ -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  $\beta_2$ -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.

ICSs 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; aneurysm or other severe cardiovascular disorders.

There is risk of potentially serious hypokalaemia with high doses of  $\beta_2$ -agonists or concomitant treatment with  $\beta_2$ -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, 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  $\beta$ -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 procarbazine, may precipitate hypertensive reactions.

$\beta$ -blockers and formoterol fumarate may inhibit the effect of each other.  $\beta$ -blockers may produce severe bronchospasm in asthma patients, and they should not normally be treated with  $\beta$ -blockers including those that are used as eye drops to treat glaucoma. Under certain circumstances, e.g. as prophylaxis after myocardial infarction, cardioselective  $\beta$ -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; Cushing's 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