Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flutiform K-haler 125 microgram/5 microgram per actuation pressurised inhalation, suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose (ex-valve) contains:

· 125 micrograms of fluticasone propionate and 5 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 115 micrograms of fluticasone propionate and 4.5 micrograms of formoterol fumarate dihydrate.

Excipient with known effect
Each actuation contains 1 mg ethanol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation, suspension

The canister contains white to off-white liquid suspension. The canister is sealed inside a pale grey breath-triggered actuator with an integrated dose indicator and an orange mouthpiece cover.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This fixed-dose combination of fluticasone propionate and formoterol fumarate (Flutiform K-haler) is indicated in the regular treatment of asthma where the use of a combination product (an inhaled corticosteroid and a long -acting β_2 agonist) is appropriate:

· For patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting β_2 agonist.
Or
· For patients already adequately controlled on both an inhaled corticosteroid and a long-acting β_2 agonist.

Flutiform K-haler is indicated in adults and adolescents aged 12 years and above.

4.2 Posology and method of administration

Posology
Patients will need to be trained on the use of the inhaler and their asthma should be regularly reassessed by a doctor, so that the strength of Flutiform K-haler they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Once control of asthma is achieved with the lowest strength of Flutiform K-haler administered twice daily, treatment should be reviewed and consideration given as to whether patients should be stepped down to an inhaled corticosteroid alone. As a general principle the dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Regular review of patients as treatment is stepped down is extremely important.

There are no data available for use of Flutiform K-haler in patients with COPD. Flutiform K-halershould not be used in patients with COPD.

Patients should be given the strength of Flutiform K-halercontaining the appropriate fluticasone propionate dosage for the severity of their disease. Note: Flutiform K-haler50 microgram/5 microgram per actuation, is not appropriate in adults and adolescents with severe asthma. Prescribers should be aware that, in patients with asthma, fluticasone propionate is as effective as some other inhaled steroids when administered at approximately half the total daily dose (in micrograms). If an individual patient should require doses outside the recommended dose regimens, appropriate doses of the β_2 agonist and the inhaled corticosteroid in separate inhalers, or appropriate doses of the inhaled corticosteroid alone, should be prescribed.

Flutiform K-haleris delivered by a breath-actuated (breathtriggered) pressurised metered dose inhaler (pMDI) which also contains an integrated dose indicator. Each inhaler will provide at least 120 actuations (60 doses).

Recommended dose for adults and adolescents aged 12 years and above:
Flutiform K-haler50 microgram/5 microgram per actuation pressurised inhalation, suspension - two inhalations twice daily, normally taken in the morning and in the evening.

If the patient's asthma remains poorly controlled the total daily dose of the inhaled corticosteroid can be increased by administering a higher strength of this combination product – i.e. Flutiform K-haler125 microgram/5 microgram per actuation pressurised inhalation, suspension - two inhalations twice daily.

For adults only
The total daily dose of this fixed-dose combination can be further increased if asthma remains poorly controlled by switching from the breath-triggered Flutiform K-haler125 microgram/5 microgram per actuation to the higher strength of Flutiform 250 microgram/10 microgram per actuation administered by a press-and breathe inhaler in a dose of two inhalations twice daily.

Children under 12 years:
Experience in children under the age of 12 years is limited to the press-and-breathe inhaler rather than this breath-triggered inhaler (see sections 4.4, 4.8, 5.1 & 5.3). **Flutiform K-halerpressurised inhalation, suspension in any strength is not recommended for use in children less than 12 years of age;Flutiform K-haler should not be used in this young age group.**

Special patient groups:
There is no need to adjust the dose in elderly patients.

There are no data available for use of Flutiform K-halerin patients with hepatic or renal impairment (see section 5.2). These patients should be regularly monitored by a physician to ensure titration to the lowest dose at which effective control of symptoms is maintained. As the fractions of fluticasone and formoterol which reach systemic circulation are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe hepatic impairment.

General information:
Inhaled corticosteroids alone are the first line of treatment for most patients. Flutiform K-haleris not intended for the initial treatment of mild asthma. For patients with severe asthma the inhaled corticosteroid therapy should be established before prescribing a fixed-dose combination product.

Patients should be made aware that Flutiform K-halermust be used daily for optimum benefit, even when asymptomatic.

Patients using Flutiform K-halershould not use additional long-acting β_2 agonists for any reason. If asthma symptoms arise in the period between doses, an inhaled, short-acting β_2 agonist should be taken for immediate relief.

For patients who are currently receiving medium to high doses of inhaled corticosteroid therapy, and whose disease severity clearly warrants treatment with two maintenance therapies, the recommended starting dose is two inhalations twice daily of Flutiform K-haler125 microgram/5 microgram per actuation.

Patients should be instructed in the proper use and care of their inhaler and their technique checked to ensure optimum delivery of the inhaled drug to the lungs.

Method of administration

For inhalation use.

To ensure proper administration of the drug, the patient should be shown how to use the inhaler correctly by a physician or other health professionals. The correct use of the inhaler is essential for successful treatment. The patient should be advised to read the Patient Information Leaflet carefully and follow the instructions for use and pictograms in the leaflet.

The actuator has an integrated counter which counts down to show the number of actuations remaining. This counter is also colour coded. When there are less than 28 actuations left it starts changing to red and the patient should be advised to contact their prescriber for a replacement inhaler. The inhaler should not be used after the dose indicator reads "0" or has turned completely red.

Priming the inhaler (Setting up)
Before using the inhaler for the first time, or if the inhaler has not been used for 3 days or more, the inhaler must be primed -:
· Shake the inhaler well before each actuation.
· Actuate the inhaler whilst pointing it away from the face by opening the mouthpiece cover as far as possible then close it again. As the mouthpiece is closed it releases one actuation (puff). This step must be performed 4 times.

If the inhaler is dropped, exposed to freezing conditions (see section 6.4) or the mouthpiece cover has been left open for more than 10 minutes, then the inhaler must be actuated once by opening the mouthpiece cover as far as possible and closing it again.

Whenever possible patients should stand or sit in an upright position when using their inhaler.

Steps for the patient to follow when using the inhaler:
1. The inhaler should be shaken immediately before each actuation (puff) to ensure that the contents of the inhaler are evenly mixed.
2. Breathe out as slowly and deeply as possible.
3. Hold the inhaler upright, open the orange mouthpiece cover fully and put the lips around the mouthpiece. Do not bite the mouthpiece.
4. Breathe in slowly and deeply through the mouthpiece to release an actuation (puff).
5. While holding the breath, remove the inhaler from the mouth and close the mouthpiece cover. Patients should continue to hold their breath for as long as is comfortable. The patient must not breathe out into the inhaler. If the inhaler releases an actuation on closing the mouthpiece cover then the patient will not have received their medication and should be advised to repeat steps 1 to 5.
6. For the second actuation, hold the inhaler upright and repeat steps 1 to 5.

Patients should rinse their mouth, gargle with water or brush their teeth after inhaling and spit out the residue to minimise the risk of oral candidiasis or dysphonia.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The management of asthma should normally follow a stepwise programme and patients' responses should be monitored clinically and by lung function tests.

Flutiform K-halershould not be used to treat acute asthma symptoms for which a fast and short-acting bronchodilator is required. Patients should be advised to have their medicine to be used for relief in an acute asthma attack available at all times.

The prophylactic use of Flutiform K-haler in exercise-induced asthma has not been studied. For such use, a separate rapid-acting bronchodilator should be considered.

Patients should be reminded to take their Flutiform K-halermaintenance dose as prescribed, even when asymptomatic.

Patients should not be initiated on Flutiform K-halerduring an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Serious asthma-related adverse events and exacerbations may occur during treatment with Flutiform K-haler. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Flutiform K-haler.

Flutiform K-halershould not be used as the first treatment for asthma.

If increasing use of short-acting bronchodilators to relieve asthma is required, if short-acting bronchodilators become less effective, or ineffective or if asthma symptoms persist, the patient should be reviewed by their doctor as soon as possible as any of these may indicate a deterioration in asthma control and their treatment may need to be changed.

Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should undergo urgent medical assessment. Consideration should be given to increasing corticosteroid therapy. The patient should also be medically reviewed when the current dosage of Flutiform K-halerhas failed to give adequate control of asthma. Consideration should be given to additional corticosteroid therapies.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Flutiform K-haler. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Flutiform K-halershould be used (see section 4.2).

Treatment with Flutiform K-halershould not be stopped abruptly in patients with asthma due to risk of exacerbation. Therapy should be down-titrated under the supervision of a prescriber.

An exacerbation of the clinical symptoms of asthma may be due to an acute respiratory tract bacterial infection and treatment may require appropriate antibiotics, increased inhaled corticosteroids and a short course of oral corticosteroids. A rapid-acting inhaled bronchodilator should be used as rescue medication. As with all inhaled medication containing corticosteroids, Flutiform K-halershould be administered with caution in patients with pulmonary tuberculosis, quiescent tuberculosis or patients with fungal, viral or other infections of the airway. Any such infections must always be adequately treated if Flutiform K-haleris being used.

Flutiform K-halershould be used with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, cardiac arrhythmias or severe heart failure.

Potentially serious hypokalaemia may result from high doses of β_2 agonists. Concomitant treatment of β_2 agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the β_2 agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalaemia adverse effects is increased. It is recommended that serum potassium levels are monitored during these circumstances.

Caution must be observed when treating patients with existing prolongation of the QTc interval. Formoterol itself may induce prolongation of the QTc interval.

As for all β_2 agonists, additional blood sugar controls should be considered in diabetic patients.

Care should be taken when transferring patients to Flutiform K-haler therapy, particularly if there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straight away. Flutiform K-haler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children and adolescents <16 years taking high doses of fluticasone propionate (typically ≥ 1000 micrograms/day) may be at particular risk. Very rare cases of adrenal suppression and acute adrenal crisis have also been described with doses of fluticasone propionate between 500 and less than 1000 micrograms. Situations, which could potentially trigger acute adrenal crisis include trauma, surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid treatment should be considered during periods of stress or elective surgery.

The benefits of inhaled fluticasone propionate therapy should minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Patients who have required high dose emergency corticosteroid therapy in the past may also be at risk. This possibility of residual impairment should always be borne in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered. The extent of the adrenal impairment may require specialist advice before elective procedures. In situations of possible impaired adrenal function hypothalamic pituitary adrenocortical (HPA) axis function should be monitored regularly.

There is an increased risk of systemic side effects when combining fluticasone propionate with potent CYP3A4 inhibitors (see section 4.5).

The patient should be made aware that this fixed-dose combination inhaler is a prophylactic therapy and as such, for optimum benefit, has to be used regularly even when asymptomatic.

As the fractions of fluticasone and formoterol which reach systemic circulation are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe hepatic impairment.

Patients should be advised that ***Flutiform K-haler*** contains contains 2 mg of alcohol (ethanol) in each dose (2 inhalations). The amount in each dose is equivalent to less than 1 ml of beer or 1 ml of wine. The small amount of alcohol in this medicinal product will not have any noticeable effects.

Paediatric population

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

Possible systemic effects as reported for the individual components of Flutiform K-halerinclude Cushing's syndrome, Cushingoid features, adrenal suppression and growth retardation in children and adolescents. Children may also experience anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (see section 4.8).

Clinical data are only available on the use of this fixed dose combination in children under 12 years of agedelivered by the press-and-breath inhaler. Flutiform K-haler breath-actuated inhaler is therefore NOT recommended for use in children under 12 years of age until further data become available.

4.5 Interaction with other medicinal products and other forms of interactions

No formal drug interaction studies have been performed with Flutiform K-haler.

Flutiform K-halercontains sodium cromoglicate at non-pharmacological levels. Patients should not discontinue any cromoglicate containing medication.

Fluticasone propionate, an individual component of Flutiform K-haler, is a substrate of CYP 3A4. Co-treatment with CYP3A inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nelfinavir, saquinavir, ketoconazole, telithromycin, cobicistat) is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

The ECG changes and/or hypokalaemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by β agonists, especially when the recommended dose of the β agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of a β agonist with non-potassium sparing diuretics. Xanthine derivates and glucocorticosteroids may add to a possible hypokalaemic effect of the β agonists.

In addition L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards β_2 sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors, including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions.

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

Concomitant use of other β adrenergic drugs can have a potentially additive effect.

Hypokalaemia may increase the risk of arrhythmias in patients who are treated with digitalis glycosides.

Formoterol fumarate, as with other β_2 agonists, should be administered with caution to patients being treated with tricyclic antidepressants or monoamine oxidase inhibitors, and during the immediate two week period following their discontinuation, or other drugs known to prolong the QT_c interval such as antipsychotics (including phenothiazines), quinidine, disopyramide, procainamide, and antihistamines. Drugs that are known to prolong the QT_c interval can increase the risk of ventricular arrhythmias (see section 4.4).

If additional adrenergic drugs are to be administered by any route, they should be used with caution, because the pharmacologically predictable sympathetic effects of formoterol may be potentiated.

Beta adrenergic receptor antagonists (β blockers) and formoterol fumarate may inhibit the effect of each other when administered concurrently. Beta blockers may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with β blockers and this includes β blockers used as eye drops for treatment of glaucoma. However, under certain circumstances, e.g. as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of β blockers in patients with asthma. In this setting, cardioselective β blockers could be considered, although they should be administered with caution.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data on the use of fluticasone propionate and formoterol fumarate, either administered alone or together but administered from separate inhalers, or on the use of this fixed-dose combination, Flutiform K-haler in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Administration of Flutiform K-haleris not recommended during pregnancy, and should only be considered if expected benefit to the mother is greater than any possible risk to the fetus. If this is the case, then the lowest effective dose needed to maintain adequate asthma control should be used.

Because of the potential for β agonist interference with uterine contractility, use of Flutiform K-halerfor management of asthma during labour should be restricted to those patients in whom the benefit outweighs the risks.

Breastfeeding
It is not known whether fluticasone propionate or formoterol fumarate are excreted in human breast milk. A risk to the suckling child cannot be excluded. Therefore, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Flutiform K-halertherapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
There are no data available on effects on fertility following administration of Flutiform K-haler. In animal studies, no effects on fertility have been seen following administration of the individual active substances at clinically relevant doses (see section 5.3).

4.7 Effects on ability to drive and use machines

Flutiform K-halerhas no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects which have been associated with Flutiform K-halerduring clinical development are given in the table below, listed by system organ class. The following frequency categories form the basis for classification of the undesirable effects as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 < 1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class

Infections and Infestations
Metabolism and Nutrition Disorders
Psychiatric Disorders
Abnormal dreams
Agitation
Psychomotor hyperactivity, anxiety, depression, aggression, behavioural changes (predominantly in children)
Nervous System Disorders
Dysgeusia
Eye disorders
Ear and labyrinth disorders
Cardiac Disorders
Angina pectoris
Tachycardia
Vascular disorders
Respiratory, Thoracic and Mediastinal Disorders
Dyspnoea
Cough

Gastrointestinal disorders
Diarrhoea
Dyspepsia
Skin and subcutaneous tissue disorders
Pruritus
Musculoskeletal and Connective Tissue Disorders
General disorders and administration site conditions

Adverse Event	**Frequency**
Oral candidiasis Oral fungal infections Sinusitis	Rare
Hyperglycaemia	Rare
Sleep disorders including insomnia	Uncommon
Rare	
Not known	
Headache Tremor Dizziness	Uncommon
Rare	
Vision blurred	Not known
Vertigo	Rare
Palpitations Ventricular extrasystoles	Uncommon
Rare	
Hypertension	Rare
Exacerbation of asthma Dysphonia Throat irritation	Uncommon
Rare	
Dry mouth	Uncommon
Rare	
Rash	Uncommon
Rare	
Muscle spasms	Rare
Peripheral oedema Asthenia	Rare

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straight away. Flutiform K-haler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Since Flutiform K-halercontains both fluticasone propionate and formoterol fumarate, the same pattern of undesirable effects as reported for these substances may occur. The following undesirable effects are associated with fluticasone propionate and formoterol fumarate, but have not been seen during the clinical development of Flutiform K-haler:

Fluticasone propionate: Hypersensitivity reactions including, urticaria, pruritus, angiooedema (mainly facial and oropharyngeal), anaphylactic reactions. Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These may include Cushing's Syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma, contusion, skin atrophy and susceptibility to infections. The ability to adapt to stress may be impaired. The systemic effects described, however, are much less likely to occur with inhaled corticosteroids than with oral corticosteroids. Prolonged treatment with high doses of inhaled corticosteroids may result in clinically significant adrenal suppression and acute adrenal crisis. Additional systemic corticosteroid cover may be required during periods of stress (trauma, surgery, infection).

Formoterol fumarate: Hypersensitivity reactions (including hypotension, urticaria, angioneurotic oedema, pruritus, exanthema), QTc interval prolongation, hypokalaemia, nausea, myalgia, increased blood lactate levels. Treatment with β_2 agonists such as formoterol may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Hypersensitivity reactions have been reported in patients using inhaled sodium cromoglicate as an active ingredient. Whilst Flutiform K-haler contains only a low concentration of sodium cromoglicate as an excipient, it is unknown if hypersensitivity reactions are dose dependent.

In the unlikely event of a hypersensitivity reaction to Flutiform K-haler, treatment should be initiated in accordance with standard treatment for any other hypersensitivity reaction, which may include the use of antihistamines and other treatment as required. Flutiform K-halermay need to be discontinued immediately and an alternative asthma therapy may need to be initiated if necessary.

Dysphonia and candidiasis may be relieved by gargling or rinsing the mouth with water or brushing the teeth after using the product. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst continuing the treatment with Flutiform K-haler.

Paediatric population

Possible systemic effects as reported for the individual components of Flutiform K-halerinclude Cushing's syndrome, Cushingoid features, adrenal suppression and growth retardation in children and adolescents. Children may also experience anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability. Studies conducted with the press-and-breathe fixed dose combination inhalerof fluticasone propionate and formoterol fumarate demonstrated similar safety and tolerability profile as compared to fluticasone monotherapy in children aged 5-12 years and fluticasone/salmeterol in children aged 4-12. Long term treatment with the press-and-breathe inhaler for 6 months in children did not show any indication of growth retardation or adrenal suppression. Another pharmacodynamic study conducted in children showed similar effect on lower leg growth rate as measured by knemometry after treatment with the press-and-breathe inhaler as compared to fluticasone monotherapy for 2 weeks.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

There are no data available from clinical trials on overdose with Flutiform K-haler, however, data on overdose with both individual components are given below:

Formoterol fumarate:

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for β_2 agonists; in which case the following adverse experiences may occur: angina, hypertension or hypotension, palpitations, tachycardia, arrhythmia,

prolonged QT_c-interval, headache, tremor, nervousness, muscle cramps, dry mouth, insomnia, fatigue, malaise, seizures, metabolic acidosis, hypokalaemia, hyperglycaemia, nausea and vomiting.

Treatment of formoterol overdose consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of cardio selective β receptor blockers may be considered, bearing in mind that such medication can induce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial in cases of formoterol overdose. Cardiac monitoring is recommended.

If Flutiform K-haler therapy has to be withdrawn due to overdose of the β agonist component of the drug, provision of appropriate replacement steroid therapy should be considered. Serum potassium levels should be monitored as hypokalaemia can occur. Potassium replacement should be considered.

Fluticasone propionate:
Acute overdose with fluticasone propionate usually does not constitute a clinical problem. The only harmful effect after inhalation of a large amount of the drug over a short period is suppression of hypothalamic pituitary adrenocortical (HPA) axis function. HPA axis function usually recovers in a few days, as verified by plasma cortisol measurements. Treatment with the inhaled corticosteroid should be continued at the recommended dose to control asthma.

There are reports of rare cases of acute adrenal crisis. Children and adolescents <16 years taking high doses of fluticasone propionate: (typically ≥1000 microgram/day) may be at particular risk. Presenting symptoms can be vague (anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting and hypotension). Typical symptoms of an adrenal crisis are decreased level of consciousness, hypoglycaemia and/or seizures.

Following chronic use of very high doses a degree of atrophy of the adrenal cortex and HPA axis suppression may occur. Monitoring of adrenal reserve may be necessary. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma (see section 4.4).

In the management of chronic overdose, oral or systemic corticosteroids may be required in situations of stress. All patients deemed to be chronically overdosed should be treated as if steroid dependent with a suitable maintenance dose of a systemic corticosteroid. When stabilised, treatment should be continued with an inhaled corticosteroid at the recommended dose for symptom control.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Drugs for obstructive airways, adrenergics in combination with corticosteroids or other drugs excl. anticholinergics

ATC code: R03AK11

Mechanism of Action and Pharmacodynamic Effects
Flutiform K-halercontains both fluticasone propionate and formoterol fumarate. The mechanisms of action are described below for the individual components. These drugs represent two classes of medications (a synthetic corticosteroid and a selective, long-acting β_2 adrenergic receptor agonist) and as with other inhaled corticosteroid and long-acting β_2 adrenergic agonist combinations additive effects are seen in terms of a reduction in asthma exacerbations.

Fluticasone propionate
Fluticasone propionate is a synthetic, trifluorinated glucocorticoid with potent anti-inflammatory activity in the lungs when given by inhalation. Fluticasone propionate reduces symptoms and exacerbations of asthma with less adverse effects than when corticosteroids are administered systemically.

Formoterol fumarate
Formoterol fumarate is a long-acting selective β_2 adrenergic receptor agonist. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. The onset of bronchodilating effect is rapid, within 1 - 3 minutes, and the duration of effect is at least 12 hours after a single dose.

Flutiform K-haler
In 12-week clinical trials in adults and adolescents, using the press-and-breathe inhaler, the addition of formoterol to fluticasone propionate improved asthma symptoms and lung function and reduced exacerbations. Therapeutic effect of the combination of fluticasone propionate and formoterol fumarate exceeded that of fluticasone propionate alone. There are no long-term data comparing the combination of fluticasone propionate and formoterol fumarate with fluticasone propionate.

In an 8-week clinical trial the effect on lung function with using the press-and-breathe inhaler was at least equal to that of the combination of fluticasone propionate and formoterol fumarate when administered as separate inhalers. Long-term comparative data of the press-and-breathe inhaler versus fluticasone propionate and formoterol fumarate are not available. There were no signs of attenuation of therapeutic effects of the press-and-breathe inhaler in trials lasting up to 12 months including adult and adolescent patients.

Dose-response trends for the press-and-breathe inhaler were evident for symptom-based endpoints, with incremental benefits from high versus low dose the press-and-breathe inhaler being most likely in patients with more severe asthma.

A single dose pharmacokinetic /pharmacodynamic study was performed to compare the pharmacokinetics and pharmacodynamics of fluticasone propionate and formoterol fumarate delivered by Flutiform K-halerand by the press-and-breathe combined inhaler (with and without spacer). The pharmacokinetic data from this study is discussed in Section 5.2. The pharmacodynamic part of the study evaluated the effect of formoterol fumarate delivered by the breath-triggered inhaler on serum potassium, serum glucose, heart rate, systolic blood pressure and diastolic blood pressure. For each of these parameters, formoterol fumarate delivered by the breath-triggered inhaler was found to have effects of a magnitude which were not clinically relevant and intermediate between those of the press-and-breathe inhaler with and without a spacer.

Paediatric population
In a 12-week double-blind study 512 children aged 5 – 12 years were randomised to the press-and-breathe inhaler (2 inhalations of 50/5 micrograms twice daily), fluticasone/salmeterol or fluticasone monotherapy. The press-and-breathe inhaler (2 inhalations of 50/5 micrograms twice daily) was superior to fluticasone monotherapy and non-inferior to fluticasone/salmeterol. Lung function improvements with the press-and-breathe inhaler (2 inhalations of 50/5 micrograms twice daily) consistently exceeded those with fluticasone monotherapy.

In a second 12-week paediatric study including a 6-month extension phase 210 children aged 4 - 12 years were treated with a maintenance dose of the press-and-breathe inhaler (2 inhalations of 50/5 micrograms twice daily) or with fluticasone/salmeterol. Following the 12 week study, 208 patients entered into a 6-month single-arm extension phase. Two hundred and five patients subsequently completed the 6 month extension phase during which the press-and-breathe inhaler was safe and well tolerated.

5.2 Pharmacokinetic properties

Fluticasone propionate:

Absorption
Following inhalation, systemic absorption of fluticasone propionate occurs mainly through the lungs and has been shown to be linearly related to dose over the dose range 500 to 2000 micrograms. Absorption is initially rapid then prolonged.

Published studies using oral dosing of labelled and unlabelled drug have demonstrated that the absolute oral systemic bioavailability of fluticasone propionate is negligible (<1%) due to a combination of incomplete absorption from the GI tract and extensive first-pass metabolism.

Distribution
Following intravenous administration, fluticasone propionate is extensively distributed in the body. The initial disposition phase for fluticasone propionate is rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averages 4.2 L/kg. The percentage of fluticasone propionate bound to human plasma proteins averages 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Biotransformation
The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The very high clearance rate indicates extensive hepatic clearance. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 isoform subfamily (CYP 3A4) pathway. This metabolite has less affinity (approximately 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro*. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Elimination
87 - 100% of an oral dose is excreted in the faeces, up to 75% as parent compound. There is also a non-active major metabolite.

Following intravenous dosing, fluticasone propionate shows polyexponential kinetics and has a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabelled dose is excreted in the urine as metabolites, and the remainder is excreted in the faeces as parent drug and metabolites.

Formoterol fumarate:

Data on the plasma pharmacokinetics of formoterol were collected in healthy volunteers after inhalation of doses higher than the recommended range and in COPD patients after inhalation of therapeutic doses.

Absorption
Following inhalation of a single 120 microgram dose of formoterol fumarate by healthy volunteers, formoterol was rapidly absorbed into plasma, reaching a maximum concentration of 91.6 pg/mL within 5 minutes of inhalation. In COPD patients treated for 12 weeks with formoterol fumarate 12 or 24 micrograms b.i.d. the plasma concentrations of formoterol ranged between 4.0 and 8.9 pg/mL and 8.0 and 17.3 pg/mL respectively at 10 minutes, 2 hours and 6 hours post inhalation.

Studies investigating the cumulative urinary excretion of formoterol and/or its (RR) and (SS)-enantiomers, after inhalation of dry powder (12 - 96 micrograms) or aerosol formulations (12-96 micrograms), showed that absorption increased linearly with the dose.

After 12 weeks administration of 12 micrograms or 24 micrograms formoterol powder b.i.d., the urinary excretion of unchanged formoterol increased by 63 - 73% in adult patients with asthma, by 19 - 38% in adult patients with COPD and by 18 - 84% in children, suggesting a modest and self-limiting accumulation of formoterol in plasma after repeated dosing.

Distribution
The plasma protein binding of formoterol is 61 - 64% (34% primarily to albumin).

There is no saturation of binding sites in the concentration range reached with therapeutic doses.
The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120 microgram dose.

Biotransformation
Formoterol is eliminated primarily by metabolism, direct glucuronidation being the major pathway of biotransformation, with O-demethylation followed by further glucuronidation being another pathway. Minor pathways involve sulphate conjugation of formoterol and deformylation followed by sulphate conjugation. Multiple isozymes catalyze the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP 2D6, 2C19, 2C9 and 2A6) of formoterol, and so consequently the potential for metabolic drug-drug interaction is low. Formoterol did not inhibit cytochrome P450 isozymes at therapeutically relevant concentrations. The kinetics of formoterol is similar after single and repeated administration, indicating no auto-induction or inhibition of metabolism.

Elimination
In asthmatic and COPD patients treated for 12 weeks with 12 or 24 micrograms formoterol fumarate b.i.d., approximately 10% and 7% of the dose, respectively, were recovered in the urine as unchanged formoterol. In asthmatic children, approximately 6% of the dose was recovered in the urine as unchanged formoterol after multiple dosing of 12 and 24 micrograms. The (R,R) and (S,S)-enantiomers accounted for 40% and 60% respectively of urinary recovery of unchanged formoterol, after single doses (12 to 120 micrograms) in healthy volunteers and after single and repeated doses in asthma patients.

After a single oral dose of ^{3}H-formoterol, 59 - 62% of the dose was recovered in the urine and 32 - 34% in the faeces. Renal clearance of formoterol is 150 mL/min.

After inhalation, plasma formoterol kinetics and urinary excretion rate data in healthy volunteers indicate a biphasic elimination, with the terminal elimination half-lives of the (R, R) - and (S, S)-enantiomers being 13.9 and 12.3 hours, respectively. Peak excretion occurs rapidly, within 1.5 hours.
Approximately 6.4 - 8% of the dose was recovered in the urine as unchanged formoterol, with the (R, R) - and (S, S)-enantiomers contributing 40% and 60%, respectively.

Flutiform K-haler - (fluticasone propionate/formoterol fumarate combination)

Two single-dose pharmacokinetic studies have been performed to investigate the pharmacokinetics of fluticasone propionate and formoterol fumarate delivered by Flutiform K-haler. The first study compared the pulmonary bioavailability of fluticasone propionate and formoterol fumarate delivered by either Flutiform K-haleror the press-and-breathe inhaler (with and without spacer) whilst using a charcoal block method to prevent formoterol absorption from the gastrointestinal tract. The second study compared the total systemic bioavailability of fluticasone propionate and formoterol fumarate delivered by Flutiform K-halerwith that delivered by the press-and-breathe inhaler (with and without spacer), and included a pharmacodynamic comparison stage if pharmacokinetic equivalence failed to be demonstrated for either of the components.

These studies demonstrated that the pulmonary bioavailability of and total systemic exposure to fluticasone propionate with usage of Flutiform K-haler is intermediate between that attained with the press-and-breathe inhaler with and without spacer. The pulmonary bioavailability of formoterol with usage of Flutiform K-haleris greater than that attained with the press-and-breathe inhaler, and equivalent to that attained with the press-and-breathe inhaler plus spacer. Total systemic exposure to formoterol with the Flutiform K-haleris similar to that with the press-and-breathe inhaler (although bioequivalence was not confirmed), and greater than attained with the press-and-breathe inhaler plus spacer (which precludes appreciable oral absorption of formoterol). Overall these data, supplemented by pharmacodynamic safety data (see section 5.1), indicate that Flutiform K-halerwill have an efficacy and safety profile consistent with that demonstrated for the fluticasone propionate and formoterol fumarate press-and-breathe inhaler, with and without a spacer.

Pharmacokinetic equivalence between Flutiform K-halerand the constituent monoproducts has not been demonstrated. Long-term comparative data of Flutiform K-halerversus fluticasone propionate and formoterol fumarate are not available (see section 5.1).

Absorption
Flutiform K-haler– fluticasone propionate
Following inhalation of a 250 microgram dose of fluticasone propionate from 2 actuations of Flutiform K-haler125 microgram/5 microgram by healthy volunteers who had previously been administered a charcoal block, fluticasone propionate was rapidly absorbed into the plasma, mean maximum plasma fluticasone concentration of 25.0 pg/mL occurred approximately 1.3 hours after inhalation.

Following inhalation of a 250 microgram dose of fluticasone propionate from 2 actuations of Flutiform K-haler125 microgram/5 microgram by healthy volunteers, fluticasone propionate was rapidly absorbed into the plasma, mean maximum plasma fluticasone concentration of 17.6 pg/mL occurred at 1.25 hours after inhalation.

Flutiform K-haler– formoterol fumarate
Following inhalation of a 10 microgram dose of formoterol fumarate from 2 actuations of Flutiform K-haler125 microgram/5 microgram by healthy volunteers who had previously been administered a charcoal block, mean maximum plasma formoterol concentration of 7.8 pg/mL occurred approximately 6 minutes after inhalation, representing formoterol fumarate bioavailability from pulmonary absorption.

Following inhalation of a 10 microgram dose of formoterol fumarate from 2 actuations of Flutiform K-haler125 microgram/5 microgram by healthy volunteers, mean maximum plasma formoterol concentration of 6.0 pg/mL occurred approximately 10 minutes after inhalation, representing formoterol fumarate bioavailability from both pulmonary and gastrointestinal absorption.

Distribution
There is currently no plasma protein binding information specific to fluticasone propionate or formoterol fumarate from Flutiform K-haler.

Biotransformation
There are currently no data relating to the metabolism of fluticasone propionate or formoterol fumarate specifically from the inhalation of Flutiform K-haler.

Elimination
Fluticasone propionate
Following inhalation of 2 actuations of Flutiform K-haler125 microgram/5 microgram, fluticasone propionate has a terminal elimination half-life of approximately 13 h.

Formoterol fumarate
Following inhalation of 2 actuations of Flutiform K-haler125 microgram/5 microgram, formoterol fumarate has a terminal elimination half-life of approximately 9.2 h.

5.3 Preclinical safety data

The toxicity observed in animal studies with formoterol fumarate and fluticasone propionate, given in combination or separately consisted mainly of effects associated with exaggerated pharmacological activity. Effects on the cardiovascular system are related to formoterol administration and included hyperaemia, tachycardia, arrhythmias and myocardial lesions. Neither increase in toxicity nor occurrence of unexpected findings was observed upon administration of the combination.

Reproduction studies in rats and rabbits with fluticasone propionate and formoterol fumarate confirmed the known embryo-fetal effects of the two individual components including fetal growth retardation, incomplete ossification, embryo lethality, cleft palate, oedema and skeletal variations. These effects were seen at lower exposures than those expected by using the clinical maximum recommended dose. A somewhat reduced fertility in male rats was observed at very high systemic exposure to formoterol.

Neither formoterol fumarate nor fluticasone propionate were found to be genotoxic in standard *in vitro* and *in vivo* tests, when tested individually. No carcinogenicity studies have been performed with the combination. No carcinogenic potential has been identified for fluticasone propionate. A slight increase in the incidence of benign tumours was observed in the reproductive tract of female mice and rats following administration of formoterol. This effect is looked upon as a class effect in rodents after long exposure to high doses of β_2 agonists and does not suggest any potential risk of carcinogenicity in man.

Pre-clinical studies with HFA 227 reveal no special hazard for man based on studies of repeated-dose toxicity, genotoxicity, carcinogenicity and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Cromoglicate
Ethanol Anhydrous
Apaflurane HFA 227

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 Years
In use shelf – life: 3 months after opening the foil pouch.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze. If the inhaler is exposed to freezing conditions then the patient must be advised to allow the inhaler to warm at room temperature for 30 minutes then actuate the inhaler once before use (see section 4.2).

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn, even when apparently empty.

6.5 Nature and contents of container

120 actuations per inhaler

The breath-triggered actuator is pale grey with an integrated dose indicator and an orange mouthpiece cover. The suspension is contained in an aluminium pressurised container crimped with a standard metering valve. This canister is sealed inside the breath-triggered actuator fitted with a mouthpiece cover (both made of polypropylene) and an integrated dose indicator which indicates the number of actuations remaining. Each container delivers 120 actuations. The assembled inhaler is pouched in an aluminium foil laminate and is packed in a cardboard carton.

Pack sizes:
1 inhaler (120 actuations)
multipack of 3 x 1 inhaler (120 actuations)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For detailed instructions on the use of the medicinal product see section 4.2.

7 MARKETING AUTHORISATION HOLDER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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