SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Flixotide 50 micrograms Evohaler
Flixotide 125 micrograms Evohaler

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Flixotide 50 micrograms Evohaler and Flixotide 125 micrograms Evohaler are pressurised inhalation, suspensions, delivering either 50 or 125 micrograms of fluticasone propionate per actuation, respectively.

3. PHARMACEUTICAL FORM

Pressurised inhalation, suspension
Flixotide Evohaler does not contain any chlorofluorocarbons (CFCs).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluticasone propionate given by inhalation offers prophylactic treatment for asthma.

Adults:
Mild asthma (Peak Expiratory Flow values greater than 80% predicted at baseline with less than 20% variability): Patients requiring intermittent symptomatic bronchodilator asthma medication on more than occasional basis.
Moderate asthma (Peak Expiratory Flow values 60 - 80% predicted at baseline with 20 - 30% variability): Patients requiring regular asthma medication and patients with unstable asthma or worsening asthma on currently available prophylactic therapy or bronchodilator alone.
Severe asthma (Peak Expiratory Flow values less than 60% predicted at baseline with greater than 30% variability): Patients with severe chronic asthma. On introduction of inhaled fluticasone propionate, many patients who are dependent on systemic corticosteroids for adequate symptom control may be able to reduce significantly, or to eliminate, their requirement for oral corticosteroids.

Children:
Children who require preventive medication for asthma, including patients who are not under control by using currently available prophylactic medication.

4.2 Posology and method of administration

Flixotide Evohaler is for oral inhalation use only.

Patients should be made aware of the prophylactic nature of therapy with fluticasone propionate and that it should be taken regularly even when they are asymptomatic. The onset of therapeutic effect is within 4 to 7 days.
The fluticasone propionate dosage must be adjusted until the symptoms are controlled, or reduced to the minimum effective dose according to the individual response.

If patients find that relief with short-acting bronchodilator treatment becomes less effective or need more inhalations than usual, medical attention must be sought.
A spacer device may be used in patients who find it difficult to synchronise aerosol actuation with inspiration of breath.

Adults and children over 16 years:
100 to 1,000 micrograms twice daily.

The initial inhaled dose of fluticasone propionate should be appropriate to the severity of the disease.

Mild asthma:	100 to 250 micrograms twice daily.
Moderate asthma:	250 to 500 micrograms twice daily.
Severe asthma:	500 to 1000 micrograms twice daily.

The dose may then be adjusted until symptom control is achieved or reduced to the minimum effective dose, according to the individual response.

Alternatively, the starting dose of fluticasone propionate may be gauged at half the total daily dose of beclomethasone dipropionate or budesonide when administered via inhalation.

Typical starting doses for children over 4years of age:
50 to 100 micrograms twice daily.

Children should begin with a starting dose of inhaled fluticasone propionate which is appropriate for the severity of their disease. This dose regimen may be 50 or 100 micrograms twice daily.

The dose may then be adjusted until symptom control is achieved or reduced to the minimum effective dose, according to the individual response.

Children aged 1 to 4 years of age:
The administration of fluticasone propionate via inhalation is of benefit to younger children for the control of frequent and persistent asthma symptoms.

Clinical trials on 1 to 4 year old children have shown that optimal control of asthma symptoms is achieved with the administration of 100mcg twice daily, using a paediatric spacer device with a face mask.
The diagnosis and treatment of asthma should be reviewed on a regular basis.

Elderly patients and patients with hepatic or renal impairment
There is no need to adjust the dose in elderly patients or those with hepatic or renal impairment. In the event of severe hepatic impairment, cortical function should be monitored (see section 4.4).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

An increase in the use of short acting inhaled β2-agonists to control asthma symptoms indicates a deterioration in asthma control. If this situation arises, patient's therapy plan should be reassessed.
A sudden and progressive deterioration in asthma control can be potentially life-threatening to the patient and the possibility of increasing the dose of corticosteroids should be considered. In patients at risk, daily Peak Expiratory Flow monitoring may be considered.

Flixotide should not be used in acute attacks, but as a long-term, regular treatment. Patients will need to use a fast and short-acting inhaled bronchodilator to relieve acute asthma symptoms.
In the event of lack of response or mild to moderate exacerbations, the dose of inhaled fluticasone propionate may be increased, and if necessary, a systemic corticoid should be given and/or an antibiotic in the presence of an infection.

Patients' inhaler technique should be checked regularly to make sure that inhaler actuation is synchronised with inspiration to ensure optimum delivery to the lungs.

Patients with a severe hepatic disorder should have their adrenal cortex function monitored regularly. In the presence of cortical dysfunction, the dose of fluticasone propionate may be reduced gradually and under careful monitoring.

As with other inhalation therapies, paradoxical bronchospasm may occur with an immediate increase in wheezing immediately after administration. This must immediately be treated with a fast acting, short duration inhaled bronchodilator. The administration of Flixotide should be immediately discontinued, the patient should be assessed, and if necessary alternative therapy should be instituted (see section 4.8).

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged 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, 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 dose of inhaled corticosteroid is reviewed regularly and reduced to the lowest dose at which effective control of asthma is maintained (see section 4.8).

Prolonged treatment with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children and adolescents under the age of 16 who receive higher than approved doses of fluticasone (typically $\geq$1000mcg/day) may be at particular risk. 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 and hypotension, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored.

Patients switching from oral corticosteroids to inhaled fluticasone propionate therapy should be treated with special care and their adrenocortical function should be regularly monitored since adrenal function can be altered. Following the introduction of inhaled fluticasone propionate, withdrawal of systemic therapy should be gradual and patients and/or relatives should be warned that under stress situations such as hospital admissions or surgeries, they should inform their physician about the treatment, so that the physician may assess the need for additional therapy with systemic corticoids.

Similarly, replacement of systemic steroid treatment with inhaled therapy may unmask extra-pulmonary allergic processes, such as allergic rhinitis or eczema, previously being under control by the systemic drug. These allergies should be treated symptomatically with antihistamines and/or topical preparations, including topical steroids.

Treatment with Flixotide Evohaler should not be stopped abruptly.

There have been very rare reports of increases in blood glucose levels (see section 4.8). Therefore, this possibility should be taken into consideration when prescribing this medication to patients with a history of diabetes mellitus.
As with all inhaled corticosteroids, special care is necessary in patients with active or latent pulmonary tuberculosis.

During its post marketing use, there have been reports of clinically significant drug interactions in patients treated with propionate fluticasone and ritonavirIt is expected that concomitant treatment with CYP3A inhibitors, including medications that contain cobicistat, will increase the risk of systemic adverse reactions. This combination should be avoided; unless the potential benefit for the patient outweighs the risk of corticosteroid type systemic side-effects in which case the patients should undergo monitoring so as to check the systemic adverse reactions to corticosteroids (see section 4.5).

Visual disturbance

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.

Sportspeople should be informed that this medication can return a positive analytical result in doping controls.

4.5 Interaction with other medicinal products and other forms of interaction

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first-pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the intestine and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent inhibitor of cytochrome P450 3A4) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post marketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenocortical suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid like side-effects.

Co-treatment with other potent CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. This combination should be avoided, unless the benefit exceeds the increased risk of systemic adverse reactions associated with corticosteroids, in which case the patients should undergo monitoring so as to check the systemic adverse reactions to corticosteroids.

Several studies have shown that other inhibitors of cytochrome P450 3A4 produce negligible increases (erythromycin) and minor increases (ketoconazole) in systemic exposure to fluticasone propionate, without notable reductions in serum cortisol concentrations. All the same, care is advised when administering combinations with potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole) given the potential for increased systemic exposure to fluticasone propionate.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate and well controlled studies of fluticasone propionate in pregnant women.

The administration of fluticasone propionate during pregnancy should only be considered if the expected benefit to the mother outweighs any potential risk to the foetus.

The results of a retrospective cohort observational epidemiological study do not show a greater risk of major congenital malformations (MCM) after exposure to fluticasone propionate compared to exposure to other inhaled corticosteroids in the first trimester of pregnancy.

The reproductive studies conducted in animals have only shown effects characteristic of glucocorticosteroids in greater systemic exposures than those observed with the recommended inhaled therapeutic dose.

Breast-feeding

The excretion of fluticasone propionate in human breast milk has not been investigated. Subcutaneous administration of fluticasone propionate to lactating laboratory rats produced measurable plasma levels and evidence of fluticasone propionate in the milk. However, plasma levels in humans after inhalation at recommended doses are likely to be low.

The administration of fluticasone propionate to breast-feeding mothers should only be considered if the benefit expected for the mother is greater than the potential risk for the child.

Fertility

Fertility: There is no fertility data in humans.
Animal studies indicate that fluticasone propionate has no effect on fertility either in men or women.

4.7 Effects on ability to drive and use machines

Fluticasone propionate is unlikely to produce an effect.

4.8 Undesirable effects

The undesirable effects below are listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and < 1/10), uncommon (≥1/1,000 and < 1/100), rare (≥ 1/10,000 and 1 < 1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data) including isolated reports. Very common, common and uncommon effects have been identified based on clinical trial data. Rare and very rare effects have been identified based on healthcare professionals' reports.

System Organ Class	Adverse Event	Frequency
Infections & Infestations	Candidiasis of the mouth and throat Pneumonia (in COPD patients) Bronchitis (in patients with COPD). Oesophageal candidiasis	Very Common Common Common Rare

Immune System Disorders	Cutaneous hypersensitivity reactions Angioedema (mainly facial and oropharyngeal oedema), Respiratory symptoms (dyspnoea and/or bronchospasm), Anaphylactic reactions	Uncommon Very Rare Very Rare Very Rare
Eye disorders	Vision, blurred	Not known
Endocrine Disorders	Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density, cataract, glaucoma	Very Rare
Metabolism & Nutrition Disorders	Hyperglycaemia (see 4.4 'Special Warnings and Precautions for Use')	Very Rare
Psychiatric Disorders	Anxiety, sleep disorders, behavioural changes, including hyperactivity and irritability (predominantly in children)	Very Rare
Respiratory, Thoracic & Mediastinal Disorders	Hoarseness/dysphonia Paradoxical bronchospasm Epistaxis	Common Very Rare Unknown
Skin & Subcutaneous Tissue Disorders	Contusions	Common

Some patients may suffer hoarseness and candidiasis in the mouth and throat. Both conditions can be alleviated by gargling with water after using this product. Symptomatic candidiasis can be treated with topical antifungal therapy while continuing treatment with Flixotide.

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 to Pharmaceutical Services, Ministry of Health, CY-1475, www.moh.gov.cy/phs Fax: + 357 22608649.

4.9 Overdose

Symptoms and signs

Acute inhalation of doses of fluticasone propionate in excess of recommended approved doses may lead to temporary suppression of the hypothalamus-pituitary-adrenal axis. This does not necessitate emergency action being taken. In these patients treatment with fluticasone propionate by inhalation should be continued at a dose sufficient to control asthma adrenal function recovers in a few days and can be verified by measuring plasma cortisol.

If there is continued use with higher doses than authorised for prolonged periods of time, it is possible that significant adrenal suppression will occur. Very rare cases have been reported of acute adrenal crisis in children exposed to higher doses than authorised (in general 1000 micrograms daily or more) for prolonged periods (several months or years); hypoglycaemia and after effects of reduced consciousness and/or seizures are among the characteristics observed. Among the situations that could potentially trigger an acute adrenal crisis are exposure to trauma, surgery infection or any rapid reduction in dosage.

Treatment
Patients receiving higher than approved doses should be monitored closely. The dose should be reduced gradually.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC code: R03BA05.

Mechanism of action
Fluticasone propionate given by inhalation at recommended doses has a potent glucocorticoid anti-inflammatory action within the lungs, resulting in a reduction of both symptoms and exacerbations of asthma, with a lower incidence and severity of adverse effects than those observed when corticosteroids are administered systemically.

Adrenal function

The total daily production of adrenal hormones remains within the normal range during chronic treatment with inhaled fluticasone propionate, even at the highest recommended doses for children and adults. After switching to inhaled fluticasone propionate from other inhaled steroids, daily production gradually improves despite intermittent past and current use of oral steroids, which indicates normal adrenal function returns with the use of inhaled fluticasone propionate. The adrenal reserve also remains normal during chronic treatment with inhaled fluticasone propionate, which is verified by a normal increase in a stimulation test. Some residual adrenal reserve function impairment may remain for a considerable length of time as a result of previous treatments, however, which should be taken into account (see section 4.4).

5.2 Pharmacokinetic properties

Absorption
The absolute bioavailability of fluticasone propionate for each of the available inhalation devices has been estimated based on studies and comparisons between studies of inhaled and intravenous fluticasone propionate pharmacokinetic data. In healthy adult subjects the absolute bioavailability is estimated at 10.9 % for fluticasone propionate inhaler. In patients with asthma a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed. Systemic absorption occurs primarily through the lungs; initially, this absorption is fast, and afterwards it occurs during a prolonged period. The remainder of the inhaled dose may be swallowed; however, it contributes minimally to the systemic exposure due to its low aqueous solubility and its pre-systemic metabolism; this results in an oral availability of less than 1%. There is a linear increase of systemic exposure with the inhaled dose increases.

Distribution
Fluticasone propionate has a large volume of distribution at steady-state (approximately 300 L). The plasma protein binding is moderately high (91%).

Metabolism or Biotransformation
Fluticasone propionate is cleared very rapidly from the systemic circulation, mainly by metabolism to an inactive carboxylic acid, by means of the cytochrome P450 enzyme CYP3A4. Care should be taken when it is co-administrated with known inhibitors of CYP3A4, since the systemic exposure to fluticasone propionate may be potentially increased.

Elimination
Fluticasone propionate is characterized by high plasma clearance (1,150 ml/min) and a terminal half-life of approximately 8 hours. The renal clearance of fluticasone propionate is negligible (less than 0.2%) and less than 5% as metabolite.

5.3 Preclinical safety data

Toxicology has shown only those class effects typical of potent corticosteroids, and these only at doses greatly in excess of that proposed for therapeutic use.
Fluticasone propionate was not found to be mutagenic in the standard Ames, *E. coli* fluctuation, *S. cerevisiae* gene mutation, or Chinese hamster ovary cell tests. It was not-found to be clastogenic in micronuclei tests on mice and cultivated human lymphocytes.

In a general reproductive function and fertility study carried out on rats, the subcutaneous administration of 50 micrograms/kg/day of fluticasone propionate to females and 100 micrograms/kg/day to males (the dose was later reduced to 50 micrograms/kg/day) did not have any effect on mating or fertility.

Animal studies have been undertaken to evaluate the action of fluticasone propionate on embryonic development in mice, rats, and rabbits. Subcutaneous administration of fluticasone propionate to pregnant mice caused the typical drug class effects. The administration of a toxic dose of 150 micrograms/kg for the pregnant female led to a reduction in weight gain in the mothers and caused cleft palate in some foetuses as was to be expected.

The administration of a high dose of 100 micrograms/kg in rats was toxic for the mothers, given that weight gain was reduced and it caused a delay in embryonic development, which was evident due to the appearance of bone formation retardation, and a small incidence of omphalocele. Studies on rabbits showed a particular sensitivity among the species to this class of drug. Doses of 30 micrograms/kg and over were not compatible with conserving a pregnancy, and with doses of 0.57 and 4.0 micrograms/kg, the higher dose caused a reduction in foetal weight and cleft palate. However, oral administration of a dose up to 300 micrograms/kg did not cause toxicity to either the mother or embryo. In fertility studies on rats, doses of up to 50 micrograms/kg affected the body weight of the mothers and there were dose associated effects on the growth of the F_0 and F_1 generations. There was no effect on fertility or mating, however. A dose of up to 50 micrograms/kg of fluticasone propionate did not show perceivable effects on pre and postnatal development in rats.

There are neither sufficient nor well controlled tests on pregnant women. It is unknown if fluticasone propionate secretes in human milk after inhaled administration. Small quantities of systemically administered glucocorticosteroids are secreted in human milk. There is currently no evidence of teratogenic activity in humans.

There is no evidence of toxicity with the non-CFC propellant, HFA 134a, in a wide range of animal species exposed on a daily basis over two year periods to very high concentrations of the gas, which are much higher than those likely to be received by patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

HFA 134a.

6.2 Incompatibilities

None reported.

6.3 Shelf life

24 months

6.4 Special precautions for storage

As with most medicines in pressurised canisters, the therapeutic effect of this medication may decrease when the canister is cold.
Do not store above 30°C. Do not refrigerate or freeze. Protect from frost and direct sunlight.
The canister should not be punctured, broken or burnt even when apparently empty.

6.5 Nature and contents of container

An inhaler comprising an aluminium alloy can, sealed with a metering valve, actuator and dust cap. Each canister contains 120 metered actuations of either 50 or 125 micrograms of fluticasone propionate. 60 metered actuation packs are available in the 125 microgram product.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and handling

The elimination of unused medicinal product and all the materials that have come into contact with it, should be carried out in accordance with local regulations.

The aerosol spray is inhaled through the mouth into the lungs. After shaking the inhaler the patient should exhale, the mouthpiece should be placed in the mouth and the lips closed around it. The actuator is depressed to release a spray, which must coincide with inspiration of breath.

Instructions for use/handling

Checking the inhaler

Before using the inhaler for the first time or if it has not been used for a week or for a longer period, remove the cover from the mouthpiece by pressing gently on the sides, **shake the inhaler thoroughly**, and free two doses in the air to ensure proper operation of the inhaler.

Use of the inhaler

1.- Remove the mouthpiece cover by gently squeezing the sides of the cover.

2.- Check inside and outside of the inhaler including the mouthpiece for the presence of loose particles.

3.- Shake the inhaler well to ensure that any loose foreign particles are removed and that the contents of the inhaler are evenly mixed.

4. Hold the inhaler upright between the index finger and thumb, placing the thumb on the base, below the mouthpiece.

5. Breathe out as far as is comfortable and then place the mouthpiece in your mouth between your teeth and close your lips around it but do not bite it.

6. Just after starting to breathe in through your mouth, press down the inhaler to release fluticasone propionate while still breathing in steadily and deeply.

7. Hold your breath and take the inhaler from your mouth. Continue holding your breath for as long as is comfortable.

8. If you are to take further puffs, keep the inhaler upright and wait about half a minute before repeating steps 3 to 7.
9. Then, rinse your mouth with water and spit out.
10. Replace the mouthpiece cover by firmly pushing and snapping the cap until a click is heard.

Important

Do not rush steps 5, 6 and 7. It is important that you start to breathe in as slowly as possible, just before you press the inhaler. Practice in front of a mirror for the first few times. If you see a kind of "mist" coming from the top of the inhaler or from the sides of your mouth, you should start again from step 2 onward.

Patients with difficulty in coordinating the handling of the inhaler with the inspiration can, alternatively, use an inhalation chamber.

Persons with fragile hands must hold the inhaler with both hands; for this they will place both index fingers in the upper part of the inhaler and both thumbs at the bottom, below the mouthpiece.

Children

Young children may need help, and an adult would need to handle the inhaler for them.
Encourage your child to breathe out and operate the inhaler just before the child begins to breathe in. Practice the technique together.

There are pediatric spacer devices which are used with a mask, to ensure proper administration of the medication in children.

Cleaning

Clean the inhaler at least once a week.

a.- Remove the mouthpiece cover.

b.- Do not remove the metallic canister from the plastic casing.

c.- Clean both the inside and the outside of the mouth piece with a handkerchief or dry cloth.

d.- Replace and mouthpiece cover.

DO NOT PUT THE METALLIC CANISTER IN THE WATER.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Flixotide 50 micrograms Evohaler 16810
Flixotide 125 micrograms Evohaler 16809

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Flixotide Evohaler 50 micrograms: 19.11.96 / 21.03.12
Flixotide Evohaler 125 micrograms: 19.11.96 / 21.03.12

10. DATE OF REVISION OF THE TEXT

5 April 2019