Version: 1

Harmony AMS Artwork Information Panel

Manufacturing Site Number: 62000000084645	
Manufacturing Site(s): GSK_ARANDA_SPAIN	
Product Market Trade Name: Flixotide;Flixotide evohaler	
Approving Market(s): Singapore-SGP	
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PHARMA CODE N° 8575

FLIXOTIDE EVOHALER

Fluticasone propionate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluticasone propionate 50, 125 and 250 micrograms.

FLIXOTIDE 50 Evohaler, 125 Evohaler and 250 Evohaler are pressurised metered-dose inhalers which deliver 50 micrograms, 125 micrograms and 250 micrograms of fluticasone propionate per actuation into the mouthpiece of a specially designed actuator.

Each canister of *FLIXOTIDE* 50 Evohaler supplies 120 actuations.

Each canister of *FLIXOTIDE* 125 Evohaler and 250 Evohaler supplies 60 or 120 actuations.

CLINICAL INFORMATION

Indications

ASTHMA

FLIXOTIDE has a marked anti-inflammatory effect in the lungs.

It reduces symptoms and exacerbations of asthma in patients previously treated with bronchodilator alone or with other prophylactic therapy.

Severe asthma requires regular medical assessment as death may occur. Patients with severe asthma have constant symptoms and frequent exacerbations, with limited physical capacity, and PEF values below 60% predicted at baseline with greater than 30% variability, usually not returning entirely to normal after a bronchodilator. These patients will require high dose inhaled (*see Dosage and Administration*) or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

- **Adults**

Prophylactic management in:

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

- **Children**

Any child who requires preventative asthma medication, including patients not controlled on currently available prophylactic medication.

Dosage and Administration

Pharmaceutical form: Pressurised metered-dose aerosol

Patients should be made aware of the prophylactic nature of therapy with inhaled *FLIXOTIDE* and that it should be taken regularly even when they are asymptomatic.

FLIXOTIDE is for inhalation by oral inhalation only.

It is intended that each prescribed dose is given by a minimum of two inhalations.

In patients who find co-ordination of a pressurised metered dose inhaler difficult, a spacer may be used with *FLIXOTIDE* inhaler.

ASTHMA

The onset of therapeutic effect is four to seven days, although some benefit may be apparent as soon as 24 hours for patients who have not previously received inhaled steroids.

If patients find that relief with short-acting bronchodilator treatment becomes less effective or they need more inhalations than usual, medical attention must be sought.

- **Adults and children over 16 years of age**

100 to 1000 micrograms twice daily.

Patients should be given a starting dose of inhaled *FLIXOTIDE* which is appropriate for the severity of their 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 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 equivalent as administered by metered-dose inhaler.

- **Children 4 years of age and over**

50 to 100 micrograms twice daily.

Children should be given a starting dose of inhaled *FLIXOTIDE* that is appropriate for the severity of the disease.

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

It should be noted that only the 50 microgram device is suitable for the administration of this dose.

This presentation of *FLIXOTIDE* may not offer the required paediatric dose, in which case an alternative presentation of *FLIXOTIDE* should be considered (e.g. dry powder inhalers).

- **Children aged 1 to 4 years**

Inhaled *FLIXOTIDE* is of benefit to younger children in the control of frequent and persistent asthma symptoms.

Clinical trials in 1 to 4 year old children have shown that the optimal control of asthma symptoms is achieved with 100 micrograms twice daily, administered via a paediatric spacer device with a face mask (such as the *BABYHALER*™). The diagnosis and treatment of asthma should be kept under regular review.

- **Special patient groups**

There is no need to adjust the dose in elderly patients or in those with hepatic or renal impairment.

Contraindications

Hypersensitivity to any ingredient of the preparation.

Warnings and Precautions

Increasing use of short-acting inhaled beta$_2$-agonists to control asthma symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed.

Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to increasing corticosteroid dosage. In patients considered at risk, daily peak flow monitoring may be instituted.

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 (*see Overdose*). 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 central serous chorioretinopathy. It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained (*see Adverse Reactions*).

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

Because of the possibility of impaired adrenal response, patients transferring from oral steroid therapy to inhaled *FLIXOTIDE* therapy should be treated with special care, and adrenocortical function regularly monitored.

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SIDE 1

Following introduction of inhaled *FLIXOTIDE*, withdrawal of systemic therapy should be gradual and patients encouraged to carry a steroid warning card indicating the possible need for additional therapy in times of stress.

The possibility of impaired adrenal response should always be considered in emergency situations (including surgery), and also in elective situations likely to produce stress, especially in patients taking high doses for an extended duration of time. Additional corticosteroid treatment appropriate to a given clinical situation must be considered (*see Overdose*).

Similarly, replacement of systemic steroid treatment with inhaled therapy may unmask allergies such as allergic rhinitis or eczema previously controlled by the systemic drug.

Treatment with *FLIXOTIDE* should not be stopped abruptly.

There have been very rare reports of increases in blood glucose levels (*see Adverse Reactions*) and this should be considered when prescribing to patients with a history of diabetes mellitus.

As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis.

During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal 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 side-effects (*see Interactions*).

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. *FLIXOTIDE* Evohaler should be discontinued immediately, the patient assessed, and alternative therapy instituted if necessary (*see Adverse Reactions*).

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

Interactions

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 gut 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 cytochrome P450 3A4 inhibitor) 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 adrenal 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 side-effects.

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are co-administered with fluticasone propionate. In a drug interaction study, co-administration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol. In another multiple-dose drug interaction study, co-administration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Pregnancy and Lactation

Fertility

There are no data on human fertility. Animal studies indicate no effects of fluticasone propionate on male or female fertility (*see Pharmacodynamic Properties*).

Pregnancy

There are limited data in pregnant women. Administration of *FLIXOTIDE* during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Results from a retrospective epidemiological study did not find an increased risk of major congenital malformations (MCMs) following exposure to fluticasone propionate when compared to other inhaled corticosteroids, during the first trimester of pregnancy (*see Clinical Studies*).

Reproductive studies in animals have shown only those effects characteristic of glucocorticosteroids at systemic exposures in excess of those seen at the recommended inhaled therapeutic dose.

Lactation

The excretion of fluticasone propionate into human breast milk has not been investigated. When measurable plasma levels were obtained in lactating laboratory rats following subcutaneous administration there was evidence of fluticasone propionate in the breast milk. However, plasma levels in patients following inhaled application of fluticasone propionate at recommended doses are likely to be low.

Administration during lactation should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Effects on Ability to Drive and Use Machines

FLIXOTIDE is unlikely to produce an effect.

Adverse Reactions

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. Rare and very rare events were generally determined from spontaneous data.

Infections and infestations

Very common: Candidiasis of mouth and throat

Candidiasis of the mouth and throat (thrush) occurs in some patients. Such patients may find it helpful to rinse out their mouth with water after using their medication. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with *FLIXOTIDE*.

Rare: Oesophageal candidiasis

Immune system disorders

Hypersensitivity reactions with the following manifestations have been reported:

Uncommon: Cutaneous hypersensitivity reactions

Very rare: Angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (dyspnoea and/or bronchospasm) and anaphylactic reactions

Endocrine disorders

Possible systemic effects include (*see Warnings and Precautions*):

Very rare: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation, decreased bone mineral density, cataract, glaucoma

Metabolism and nutrition disorders

Very rare: Hyperglycaemia

Psychiatric disorders

Very rare: Anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children)

Respiratory, thoracic and mediastinal disorders

Common: Hoarseness

In some patients inhaled *FLIXOTIDE* may cause hoarseness. It may be helpful to rinse out the mouth with water immediately after inhalation.

Very rare: Paradoxical bronchospasm (*see Warnings and Precautions*)

Skin and subcutaneous tissue disorders

Common: Contusions

Overdose

Acute inhalation of *FLIXOTIDE* doses in excess of those approved may lead to temporary suppression of the hypothalamic-pituitary-adrenal axis. This does not usually require emergency action, as normal adrenal function typically recovers within a few days.

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SIDE 2

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If higher than approved doses are continued over prolonged periods, significant adrenocortical suppression is possible. There have been very rare reports of acute adrenal crisis occurring in children exposed to higher than approved doses (typically 1000 micrograms daily and above), over prolonged periods (several months or years); observed features included hypoglycaemia and sequelae of decreased consciousness and/or convulsions. Situations which could potentially trigger acute adrenal crisis include exposure to trauma, surgery, infection or any rapid reduction in dosage.

Patients receiving higher than approved doses should be managed closely and the dose reduced gradually.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmacodynamic Properties

FLIXOTIDE given by inhalation at recommended doses has a potent glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma.

Pharmacokinetics

Absorption

The absolute bioavailability of fluticasone propionate for each of the available inhaler devices has been estimated from within and between study comparisons of inhaled and intravenous pharmacokinetic data. In healthy adult subjects the absolute bioavailability has been estimated for fluticasone propionate Accuhaler/Diskus (7.8%), fluticasone propionate Diskhaler (9.0%) and fluticasone propionate Evohaler (10.9%) respectively. In patients with asthma or COPD, a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed. Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and pre-systemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose.

Distribution

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

Metabolism

Fluticasone propionate is cleared very rapidly from the systemic circulation, principally by metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Care should be taken when co-administering known CYP3A4 inhibitors, as there is potential for increased systemic exposure to fluticasone propionate.

Elimination

The disposition of fluticasone propionate is characterised by high plasma clearance (1150 ml/min) and a terminal half-life of approximately 8 h. The renal clearance of fluticasone propionate is negligible (less than 0.2%) and less than 5% as the metabolite.

Clinical Studies

Fluticasone propionate containing medications in asthma during pregnancy

An observational retrospective epidemiological cohort study utilising electronic health records from the United Kingdom was conducted to evaluate the risk of MCMs following first trimester exposure to inhaled fluticasone propionate (FP) alone and salmeterol-FP combination relative to non-FP containing ICS. No placebo comparator was included in this study. Within the asthma cohort of 5362 first trimester ICS-exposed pregnancies, 131 diagnosed MCMs were identified; 1612 (30%) were exposed to FP or salmeterol-FP of which 42 diagnosed MCMs were identified. The adjusted odds ratio for MCMs diagnosed by 1 year was 1.1 (95% CI: 0.5-2.3) for FP exposed vs non-FP ICS exposed women with moderate asthma and 1.2 (95% CI: 0.7-2.0) for women with considerable to severe asthma. The adjusted odds ratio for MCMs diagnosed by 1 year was 0.9 (95% CI: 0.3-2.9) for FP alone and 1.3 for salmeterol-FP (95% CI: 0.5-3.2) for women with moderate asthma. The adjusted odds ratio for MCMs diagnosed by 1 year was 1.3 (95% CI: 0.6-3.0) for FP alone and 1.1 for salmeterol-FP (95% CI: 0.6-2.0) for women with severe asthma. Absolute risks of MCM across the asthma severity strata ranged from 2.0 to 2.9 per 100 FP-exposed pregnancies which is comparable to results from a study of 15,840 pregnancies unexposed to asthma therapies in the General Practice Research Database (2.8 MCM events per 100 pregnancies).

Non-Clinical Information

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. No novel effects were identified in repeat dose toxicity tests, reproductive studies or teratology studies.

Fluticasone propionate is devoid of mutagenic activity *in vitro* and *in vivo* and showed no tumorigenic potential in rodents. It is both non-irritant and non-sensitising in animal models.

The non-CFC propellant, HFA 134a, has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of two years.

Reproductive Toxicology

Fluticasone propionate, administered subcutaneously at doses of up to 50 mcg/kg/day (up to 100 mcg/kg/day in males, prior to Day 36), did not affect the fertility or mating performance of the F0 and F1 generation rats, when given throughout the periods of gametogenesis, mating, gestation, parturition and lactation.

PHARMACEUTICAL INFORMATION

List of Excipients

Hydroxyfluoroalkane 134a, 1, 1, 1, 2-tetrafluoroethane (HFA 134a).

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

Replace the mouthpiece cover firmly and snap it into position.

Protect from frost and direct sunlight.

As with most inhaled medications in pressurised canisters, the therapeutic effect of this medication may decrease when the canister is cold.

Pressurised container. Do not expose to temperatures higher than 50°C. The canister should not be punctured, broken or burnt even when apparently empty.

Nature and Contents of Container

FLIXOTIDE Evohaler comprises a suspension of fluticasone propionate in the non-CFC propellant HFA 134a. The suspension is contained in an aluminium alloy can sealed with a metering valve. The canisters are fitted into plastic actuators incorporating an atomising orifice and fitted with dustcaps.

Incompatibilities

None reported.

Use and Handling

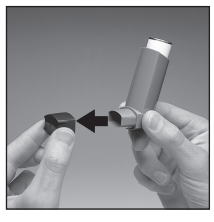
Instructions for use of your *FLIXOTIDE* Evohaler

Testing your inhaler:

Before using for the first time or if your inhaler has not been used for a week or more remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, and release two puffs into the air to make sure that it works.

Using your inhaler:

1. Remove the mouthpiece cover by gently squeezing the sides of the cover.
2. Check the inside and outside of the inhaler including the mouthpiece for the presence of loose objects.



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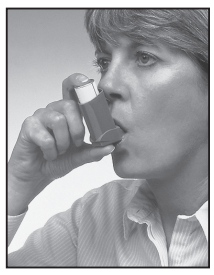
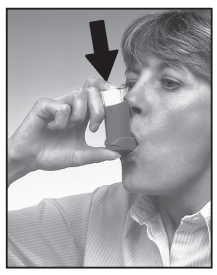
3. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.

4. Hold the inhaler upright between fingers and thumb with your 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 on the top of the inhaler to release *FLIXOTIDE* while still breathing in steadily and deeply.



7. While holding your breath, take the inhaler from your mouth and take your finger from the top of the inhaler. 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. Afterwards, rinse your mouth with water and spit it out.
10. Replace the mouthpiece cover by firmly pushing and snapping the cap into position.

IMPORTANT:

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

If your doctor has given you different instructions for using your inhaler, please follow them carefully. Tell your doctor if you have any difficulties.

Cleaning:

Your inhaler should be cleaned at least once a week.

1. Remove the mouthpiece cover.
2. Do not remove the canister from the plastic casing.
3. Wipe the inside and outside of the mouthpiece with a dry cloth or tissue.
4. Replace the mouthpiece cover.

DO NOT PUT THE METAL CANISTER INTO WATER.

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SIDE 4