

# DATA SHEET

## **FLIXOTIDE® Inhaler**

***Fluticasone propionate Inhaler (CFC-Free) (50, 125 or 250 micrograms per actuation).***

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### **Qualitative and quantitative composition**

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FLIXOTIDE 50 Inhaler is a pressurised metered-dose inhaler which delivers 50mcg of fluticasone propionate per actuation into the mouthpiece of a specially designed actuator. Each canister supplies 120 actuations.

FLIXOTIDE 125 Inhaler is a pressurised metered-dose inhaler which delivers 125mcg of fluticasone propionate per actuation into the mouthpiece of a specially designed actuator. Each canister supplies 120 actuations.

FLIXOTIDE 250 Inhaler is a pressurised metered-dose inhaler which delivers 250mcg of fluticasone propionate per actuation. Each canister supplies 120 actuations.

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### **Pharmaceutical form**

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Pressurised metered-dose aerosol.

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### **Clinical particulars**

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#### ***Therapeutic Indications***

##### **Asthma:-**

Fluticasone propionate 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 instructions) 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 fluticasone propionate 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 preventive asthma medication, including patients not controlled on currently available prophylactic medication.

### ***Posology and Method of Administration***

FLIXOTIDE Inhaler (CFC-Free) is for oral inhalation only.

The diagnosis and treatment of asthma should be kept under regular review.

Patients should be made aware of the prophylactic nature of therapy with inhaled fluticasone propionate and that it should be taken regularly even when they are asymptomatic. The onset of therapeutic effect is 4 to 7 days, although some benefit may be apparent as soon as 24 hours for patients who have not previously received inhaled steroids.

The dosage of fluticasone propionate should be adjusted according to the individual response.

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.

It is intended that each prescribed dose is given by a minimum of 2 inhalations.

In patients who find co-ordination of a pressurised metered dose inhaler difficult, a spacer may be used with FLIXOTIDE Inhaler (CFC-Free).

## **Asthma:**

*Adults and children over 16 years of age:* 100 to 1000mcg twice daily.

Patients should be given a starting dose of inhaled fluticasone propionate which is appropriate for the severity of their disease:-

Mild asthma: - 100 to 250mcg twice daily.

Moderate asthma: - 250 to 500mcg twice daily.

Severe asthma: - 500 to 1000mcg 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 over 4 years of age:* - 50 to 200mcg twice daily.

Many children's asthma will be well controlled using the 50 to 100mcg twice daily dosing regime. For those patients whose asthma is not sufficiently controlled, additional benefit may be obtained by increasing the dose up to 200mcg twice daily.

Children should be given a starting dose of inhaled fluticasone propionate which is appropriate for the severity of their disease.

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

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

*Children aged 1 to 4 years:* - 100mcg twice daily administered via a paediatric spacer device with a face mask.

Inhaled fluticasone propionate 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 100mcg twice daily. Higher doses of inhaled fluticasone propionate are required in younger children compared to older children because of reduced efficiency of drug delivery due to smaller airways, use of a spacer device and increased nasal breathing.

### **Special patient groups:-**

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

### ***Contra-indications***

Hypersensitivity to any ingredient of the preparation.

### ***Special Warnings and Special Precautions for Use***

The management of asthma should follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

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.

FLIXOTIDE Inhaler (CFC-Free) is not for use in acute asthma attacks, but for routine long-term management. Patients will require a fast- and short-acting inhaled bronchodilator to relieve acute asthmatic symptoms.

Lack of response or severe exacerbations of asthma should be treated by increasing the dose of inhaled fluticasone propionate and, if necessary, by giving a systemic steroid and/or an antibiotic if there is an infection.

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

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 and glaucoma. It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained (see Undesirable Effects).

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

Certain individuals can show greater susceptibility to the effects of inhaled corticosteroid than do most patients.

Adrenal function and adrenal reserve usually remain within the normal range on recommended doses of fluticasone propionate therapy. The benefits of inhaled fluticasone propionate therapy should minimise the need for oral

steroids. However, the possibility of adverse effects in patients, resulting from prior or intermittent administration of oral steroids, may persist for some time. The extent of the adrenal impairment may require specialist advice before elective procedures.

The possibility of impaired adrenal response should always be borne in mind in emergency and elective situations likely to produce stress and appropriate corticosteroid treatment must be considered (see Overdose).

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

Following introduction of inhaled fluticasone propionate, 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.

In rare cases inhaled therapy may unmask underlying eosinophilic conditions (e.g. Churg Strauss syndrome). These cases have usually been associated with reduction or withdrawal of oral corticosteroid therapy. A direct causal relationship has not been established.

Similarly replacement of systemic steroid treatment with inhaled therapy may unmask allergies such as allergic rhinitis or eczema previously controlled by the systemic drug. These allergies should be symptomatically treated with antihistamine and/or topical preparations, including topical steroids.

Treatment with FLIXOTIDE Inhaler (CFC-Free) should not be stopped abruptly.

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

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 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.

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

### ***Use During Pregnancy and Lactation***

## **Pregnancy**

There is inadequate evidence of safety of fluticasone propionate in human pregnancy. Reproductive studies in animals have shown only those effects characteristic of glucocorticosteroids at systemic exposure in excess of those seen at the recommended inhaled therapeutic dose. Tests for genotoxicity have shown no mutagenic potential.

However, as with other medicines the administration of fluticasone propionate during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

## **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.

## ***Effects on Ability to Drive and Use Machines***

Fluticasone propionate is unlikely to produce an effect.

## ***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 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 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.

Studies have shown that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Nevertheless, care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole) as there is potential for increased systemic exposure to fluticasone propionate.

## ***Undesirable Effects***

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  and  $< 1/1000$ ) 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 the inhaler. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the FLIXOTIDE Inhaler (CFC-Free).

### **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 Special Warning and Special Precautions for Use):

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 fluticasone propionate may cause hoarseness. It may be helpful to rinse out the mouth with water immediately after inhalation.

Very rare: Paradoxical bronchospasm.

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 Inhaler (CFC-Free) should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

### **Skin and subcutaneous tissue disorders**

Common: Contusions

### **Overdose**

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

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 1000mcg 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.

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## **Pharmacological properties**

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### ***Pharmacodynamic properties***

Fluticasone propionate given by inhalation at recommended doses has a potent glucocorticoid anti-inflammatory action within the lungs which results in reduced symptoms and exacerbations of asthma.

### ***Pharmacokinetic properties***

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 Flixotide Accuhaler (7.8%) and Flixotide Inhaler (10.9%) respectively. In patients with asthma 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. The disposition of fluticasone propionate is characterised by high plasma clearance (1150mL/min), a large volume of distribution at steady-state (approximately 300L) and a terminal half-life of approximately 8 hours. Plasma protein binding is moderately high (91%). 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. The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% as the metabolite. Care should be taken when co-administering known CYP3A4 inhibitors, as there is potential for increased systemic exposure to fluticasone propionate.

### ***Preclinical safety data***

Toxicology has shown only those class effects typical of potent corticosteroids, and these only at doses in excess of those 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.

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## **Pharmaceutical particulars**

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### ***List of excipients***

HFA 134a

### ***Incompatibilities***

None reported.

### ***Shelf life***

2 years.

### ***Special precautions for storage***

Replace the mouthpiece cover firmly and snap it into position.

FLIXOTIDE Inhaler (CFC-Free) should be stored below 30°C.

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.

The canister should not be punctured, broken or burnt even when apparently empty.

### ***Nature and contents of container***

FLIXOTIDE Inhaler (CFC-Free) 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. FLIXOTIDE Inhaler (CFC-Free) has been formulated in three strengths, 50mcg, 125mcg or 250mcg of fluticasone propionate per actuation, 120 actuations per inhaler.

### ***Instructions for use/handling***

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 inside and outside of the inhaler including the mouthpiece for the presence of loose objects.
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 fluticasone propionate 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.

**Children:-**

Young children may need help and an adult may need to operate the inhaler for them. Encourage the child to breathe out and operate the inhaler just after the child starts to breathe in. Practice the technique together. Older children or people with weak hands should hold the inhaler with both hands. Put the two forefingers on top of the inhaler and both thumbs on the base below the mouthpiece.

**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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**Medicines classification**

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Prescription Only Medicine

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**Name and address**

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