

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

FLIXOTIDE Inhaler (CFC-Free) 50 micrograms/dose, aerosol inhaler, metered dose.

FLIXOTIDE Inhaler (CFC-Free) 125 micrograms/dose, aerosol inhaler, metered dose.

FLIXOTIDE Inhaler (CFC-Free) 250 micrograms/dose, aerosol inhaler, metered dose.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

FLIXOTIDE 250 Inhaler is a pressurised metered-dose inhaler which delivers 250 mcg of fluticasone propionate per actuation.

For full list of excipients, see Section 6.1 List of excipients.

## 3. PHARMACEUTICAL FORM

Aerosol inhaler, metered dose.

The canisters are fitted into plastic actuators incorporating an atomising orifice and fitted with dustcaps.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

FLIXOTIDE is indicated in adults and children aged from 1 year and above for prophylactic treatment of 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.

## **4.2 Dose and method of administration**

### Dose

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).

**Adults and children over 16 years of age:** 100 to 1000 mcg 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 250 mcg twice daily.

Moderate asthma: 250 to 500 mcg twice daily.

Severe asthma: 500 to 1000 mcg 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.

### **Paediatric population**

**Children over 4 years of age:** 50 to 200 mcg twice daily.

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

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

### **Method of administration**

For instructions on the use and handling of this medicine, see Section 6.6 Special precautions for disposal and other handling.

### **4.3 Contraindications**

Hypersensitivity to fluticasone propionate or to any of the excipients listed in Section 6.1 List of excipients..

### **4.4 Special warnings and special precautions for use**

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.

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 Section 4.9 Overdose). Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation and (very rarely) behavioural disturbances in children and adolescents, decrease in bone mineral density, cataract, glaucoma and central serous chorioretinopathy (CSCR). It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained (see Section 4.8 Undesirable effects).

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

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 Section 4.9 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.

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 Section 4.8 Undesirable effects) and this should be considered when prescribing to patients with a history of diabetes mellitus.

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 and short-acting inhaled bronchodilator. Fluticasone propionate should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary (see Section 4.8 Undesirable effects).

#### **4.5 Interaction with other medicines 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.

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

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

An observational retrospective epidemiological cohort study utilising electronic health records from the United Kingdom was conducted to evaluate the risk of major congenital malformations (MCMs) following first trimester exposure to inhaled fluticasone propionate alone and salmeterol-fluticasone propionate relative to non-fluticasone propionate containing inhaled corticosteroids. No placebo comparator was included in this study.

Within the asthma cohort of 5362 first trimester inhaled corticosteroids-exposed pregnancies, 131 diagnosed MCMs were identified; 1612 (30%) were exposed to fluticasone propionate or salmeterol-fluticasone propionate 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 fluticasone propionate exposed vs non-fluticasone propionate inhaled corticosteroid exposed women with moderate asthma and 1.2 (95%CI: 0.7 – 2.0) for women with considerable to severe asthma. No difference in the risk of MCMs was identified following first trimester exposure to fluticasone propionate alone versus salmeterol-fluticasone propionate. Absolute risks of MCM across the asthma severity strata ranged from 2.0 to 2.9 per 100 fluticasone propionate-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).

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

### Breast-feeding

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.

### Fertility

There are no data on human fertility. Animal studies indicate no effects of fluticasone propionate on male or female fertility.

#### **4.7 Effects on ability to drive and use machines**

Fluticasone propionate is unlikely to produce an effect.

#### **4.8 Undesirable effects**

##### **Summary of adverse events**

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1000$ ) 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).

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 Section 4.4 Special warnings and precautions for use):

Very rare: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation, decreased bone mineral density, cataract and 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 (see Section 4.4 Special warnings and precautions for use)

## Skin and subcutaneous tissue disorders

Common: Contusions

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: <https://nzphvc.otago.ac.nz/reporting/>.

## **4.9 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

ATC code: Not yet assigned

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.



## 5.2 Pharmacokinetic properties

### 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 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.

### Distribution:

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

### Biotransformation:

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 hours. The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% as the metabolite.

## 5.3 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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

HFA 134a

## **6.2 Incompatibilities**

None reported.

## **6.3 Shelf life**

2 years.

## **6.4 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.

## **6.5 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, 50 mcg, 125 mcg or 250 mcg of fluticasone propionate per actuation, 120 actuations per inhaler.

## **6.6 Special precautions for disposal and other 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.**

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

## **7. MEDICINE SCHEDULE**

Prescription Only Medicine

## 8. SPONSOR

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## 9. DATE OF FIRST APPROVAL

17 July 1997

## 10. DATE OF REVISION OF THE TEXT

3 October 2018

Summary table of changes:

Section changes	Summary of new information
All	Reformat of Data Sheet to SmPC style and minor editorial changes
4.1	Added age range to indication
4.4	Addition of new ocular safety information
4.8	Added reporting of suspected adverse reactions information
6.6	Added instructions on disposal
9	Added date of first approval
	Updated copyright and trademark statement

Version: 7.0

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