

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

FLIXOTIDE ACCUHALER, 50 micrograms inhalation powder.

FLIXOTIDE ACCUHALER, 100 micrograms inhalation powder.

FLIXOTIDE ACCUHALER, 250 micrograms inhalation powder.

FLIXOTIDE ACCUHALER, 500 micrograms inhalation powder.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose contains fluticasone propionate (50 mcg, 100 mcg, 250 mcg or 500 mcg).

### Excipient with known effect:

FLIXOTIDE ACCUHALER also contains the excipient lactose monohydrate (which contains milk protein)

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

## 3. PHARMACEUTICAL FORM

Inhalation powder.

FLIXOTIDE ACCUHALER is a moulded plastic device containing a foil strip with 60 regularly placed blisters.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

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 Section 4.2 Dose and method of 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 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 aged 4 years and over who requires preventive asthma medication, including patients not controlled on currently available prophylactic medication.

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

### Dose

FLIXOTIDE ACCUHALER is for inhalation by oral inhalation only.

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.

### *Asthma:*

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.

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 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 device is not recommended for use in children under 4 years of age.

### 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, please refer to Section 6.6 Special precautions for disposal and other handling.

### **4.3 Contraindications**

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

### **4.4 Special warnings and 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.

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 ACCUHALER 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.

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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 during pregnancy should only be considered if the expected benefit to 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 an increased risk of 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 ACCUHALER. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the FLIXOTIDE ACCUHALER.

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 of 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 1000 mcg 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.



## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose (which contains milk protein).

### **6.2 Incompatibilities**

None reported.

### **6.3 Shelf life**

50 mcg: 18 months when stored below 30°C.

100 mcg: 2 years when stored below 30°C.

250 mcg: 3 years when stored below 30°C.

500 mcg: 3 years when stored below 30°C.

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

Store below 30°C.

Store in a dry place.

The ACCUHALER is sealed in a foil overwrap which should only be opened when it is to be used for the first time. Once opened the foil overwrap should be discarded.

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

The powder mix of fluticasone propionate and lactose is filled into a blister strip consisting of a formed base foil with a peelable foil laminate lid.

The foil strip is contained within the ACCUHALER device. The ACCUHALER is packaged within a foil overwrap.

Each ACCUHALER provides 60 doses.

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

#### Disposal

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

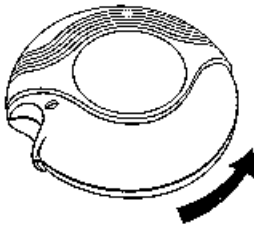
#### Instructions for Use/Handling

##### *About your ACCUHALER*

The ACCUHALER is sealed in a foil overwrap. The overwrap provides moisture protection and should only be opened when you are ready to use it for the first time. Once opened the foil overwrap should be discarded.

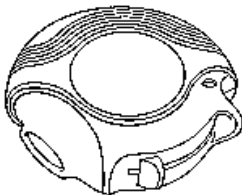
## CLOSED

When you take your ACCUHALER out of its box and remove the foil overwrap, it will be in the closed position.



## OPENED

A new ACCUHALER contains 60 doses of your medicine. The dose indicator tells you how many doses are left.



This ACCUHALER contains 60 individually protected doses of your medicine, in powder form.

Each dose is accurately measured and hygienically protected. It requires no maintenance and no refilling.

The dose indicator on top of your ACCUHALER tells you how many doses are left. Numbers 5 to 0 will appear in RED, to warn you when there are only a few doses left.

The ACCUHALER is easy to use. When you need a dose, just follow the four simple steps illustrated:-

1. Open.

2. Slide.
3. Inhale.
4. Close.

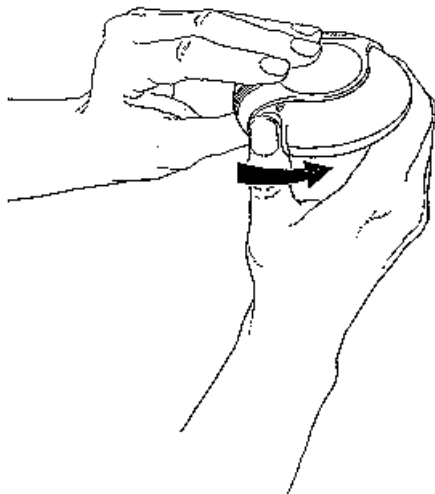
**How your ACCUHALER works:**

Sliding the lever of your ACCUHALER opens a small hole in the mouthpiece and unwraps a dose, ready for you to inhale it. When you close the ACCUHALER, the lever automatically moves back to its original position, ready for your next dose when you need it. The outer case protects your ACCUHALER when it is not in use.

**How to use the ACCUHALER:**

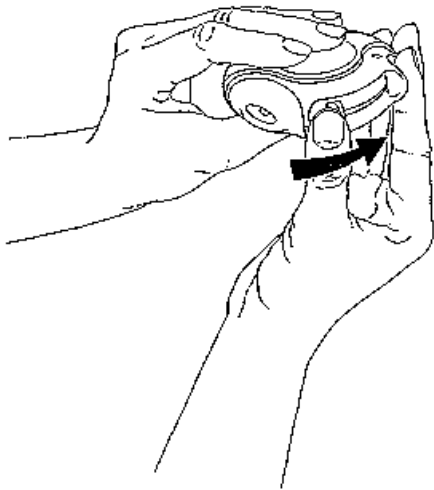
1. Open.

To open your ACCUHALER, hold the outer case in one hand and put the thumb of your other hand on the thumbgrip. Push your thumb away from you as far as it will go.



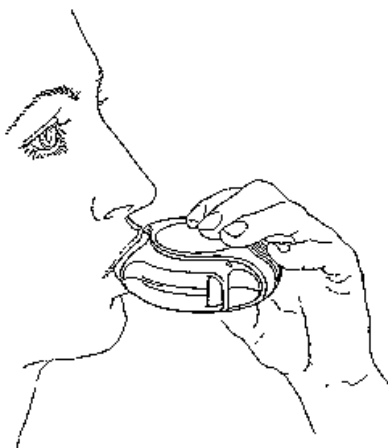
2. Slide.

Hold your ACCUHALER with the mouthpiece towards you. Slide the lever away from you, as far as it will go - until it clicks. Your ACCUHALER is now ready to use. Every time the lever is pushed back, a dose is made available for inhaling. This is shown by the dose counter. Do not play with the lever as this releases doses which will be wasted.



3. Inhale.

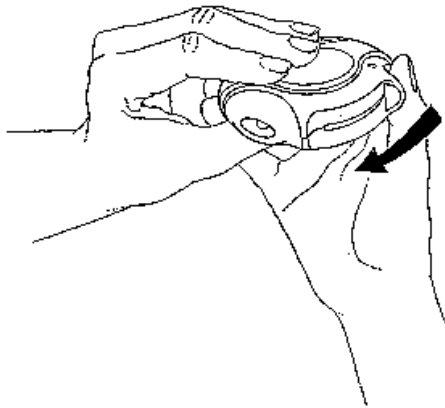
- Before you start to inhale the dose, read through this section carefully.
- Hold the ACCUHALER away from your mouth. Breathe out as far as is comfortable. Remember - never breathe into your ACCUHALER.
- Put the mouthpiece to your lips. Breathe in steadily and deeply - through the ACCUHALER, not through your nose.
- Remove the ACCUHALER from your mouth.
- Hold your breath for about 10 seconds, or for as long as is comfortable.
- Breathe out slowly.



4. Close.

To close your ACCUHALER, put your thumb in the thumbgrip, and slide the thumbgrip back towards you, as far as it will go.

When you close the ACCUHALER, it clicks shut. The lever automatically returns to its original position and is reset. Your ACCUHALER is now ready for you to use again.



If you have been instructed to take two inhalations you must close the ACCUHALER and repeat stages 1 to 4.

**REMEMBER.**

Keep your ACCUHALER dry.

Keep it closed when not in use.

Never breathe into your ACCUHALER.

Only slide the lever when you are ready to take a dose.

Do not exceed the stated dose. Keep out of reach of children.

## **7. MEDICINE SCHEDULE**

Prescription Only Medicine

## 8. SPONSOR

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## 9. DATE OF FIRST APPROVAL

16 May 1996

## 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
4.2	Added subsection on method of administration.
4.4	Addition of new ocular safety information
4.8	Added reporting of suspected adverse reactions information
4.9	Added National Poisons centre information
5.1	New
6.6	Added instructions on disposal
9	Added date of first approval
	Updated copyright and trademark statement

Version 6.0

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