

DATA SHEET

FLIXOTIDE[®] Accuhaler[®]

Fluticasone propionate 50, 100, 250 or 500 microgram Accuhalers.

Qualitative and quantitative composition

FLIXOTIDE Accuhaler is a moulded plastic device containing a foil strip with 60 regularly placed blisters each containing a mixture of microfine fluticasone propionate (50mcg, 100mcg, 250mcg or 500mcg) and larger particle size lactose.

Each Accuhaler provides 60 doses.

Pharmaceutical form

Inhalation powder.

Clinical particulars

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 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.

Special patient groups:-

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

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 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 device is not recommended for use in children aged 1 to 4 years, please refer to the FLIXOTIDE Inhaler Data Sheet for dosage recommendations in this age group.

Contra-indications

Hypersensitivity to any ingredient of the preparation (see Pharmaceutical Particulars – List of Excipients).

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 β_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 Accuhaler 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.

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 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 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.

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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 Accuhaler. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the FLIXOTIDE Accuhaler.

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 Warnings 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 Accuhaler 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.

Pharmacological properties

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.

Pharmaceutical particulars

List of excipients

Lactose (which contains milk protein).

Incompatibilities

None reported.

Shelf life

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

100mcg:	24 months when stored below 30°C.
250mcg:	36 months when stored below 30°C.
500mcg:	36 months when stored below 30°C.

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 the foil overwrap is opened, it should be discarded.

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.

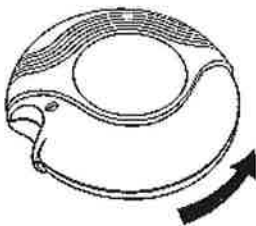
Instructions for Use/Handling

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 the foil overwrap is opened, it 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.

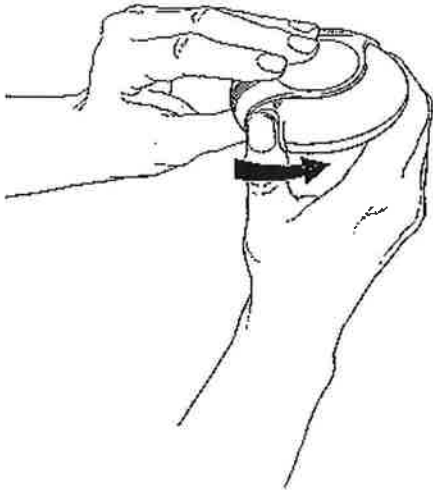
How your Accuhaler works:-

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

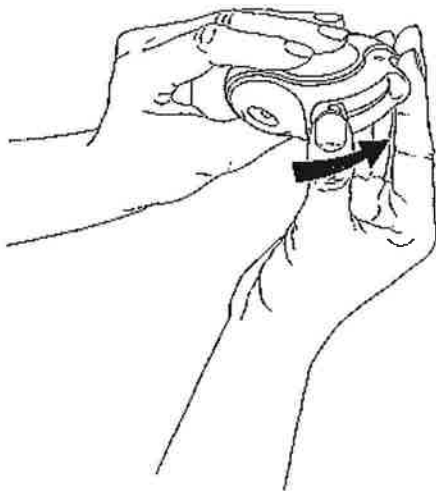
1. Open.

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.

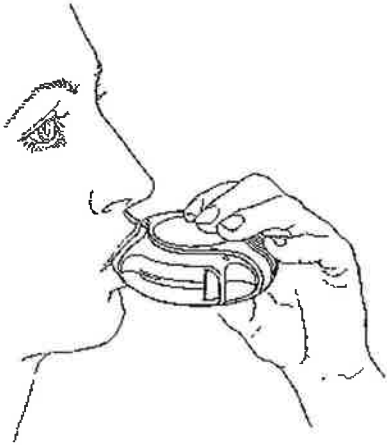
Hold your Accuhaler with the mouthpiece towards you. Slide the lever away from you, as far as it will go - until it clicks. Your Accuhaler is now ready to use. Every time the lever is pushed back, a dose is made available for inhaling. This is shown by the dose counter. Do not play with the lever as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

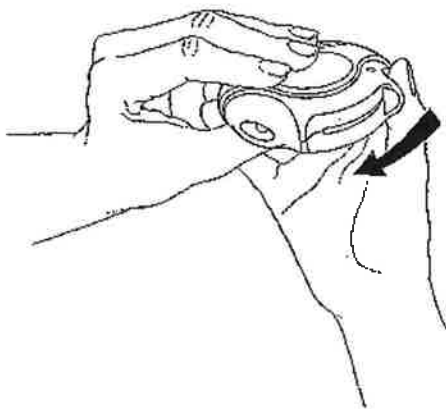
- Remove the Accuhaler from your mouth.
- Hold your breath for about 10 seconds, or for as long as is comfortable.
- Breathe out slowly.



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.

Medicines classification

Prescription Only Medicine

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