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Flixotide™ Diskus™

fluticasone propionate

Qualitative and Quantitative Composition
Flixotide Diskus is a moulded plastic device containing a foil strip with 60 regularly placed blisters each containing a mixture of microfine fluticasone propionate (50 micrograms, 100 micrograms, 250 micrograms or 500 micrograms) and larger particle size lactose.

Pharmaceutical Form
Multi-dose dry powder inhalation device.

Clinical Particulars
Therapeutic Indications
Fluticasone propionate given by inhalation offers preventative treatment for asthma. At recommended doses it has a potent glucocorticoid anti-inflammatory action within the lungs, with a lower incidence and severity of adverse effects than those observed when corticosteroids are administered systemically.
Adults: Prophylactic management in:
Mild asthma: Patients requiring intermittent symptomatic bronchodilator asthma medication on a regular daily basis.
Moderate asthma: Patients with unstable or worsening asthma despite prophylactic therapy or bronchodilator alone.
Severe asthma: Patients with severe chronic asthma and those who are dependent on systemic corticosteroids for adequate control of symptoms. On introduction of inhaled fluticasone propionate many of these patients may be able to reduce significantly, or to eliminate, their requirement for oral corticosteroids.
Children: Any child who requires prophylactic medication, including patients not controlled on currently available prophylactic medication.

Posology and Method of Administration
Flixotide Diskus is for oral inhalation use only. Flixotide Diskus is suitable for many patients, including those who cannot use a metered-dose inhaler successfully.
Patients should be made aware of the prophylactic nature of therapy with Flixotide Diskus and that it should be taken regularly even when they are asymptomatic. The onset of therapeutic effect is within 4 to 7 days.
Adults and children over 16 years: 100 to 1,000 micrograms twice daily.
Prescribers should be aware that fluticasone propionate is as effective as other inhaled steroids approximately at half the microgram daily dose. For example, a 100mcg of fluticasone propionate is approximately equivalent to 200mcg dose of beclometasone dipropionate (CFC containing) or budesonide.
Due to the risk of systemic effects, doses above 500 micrograms twice daily should be prescribed only for adult patients with severe asthma where additional clinical benefit is expected, demonstrated by either an improvement in pulmonary function and/or symptom control, or by a reduction in oral corticosteroid therapy.
Patients should be given a starting dose of inhaled fluticasone propionate which is appropriate to the severity of their disease.

Typical Adult Starting Doses:
For patients with mild asthma, a typical starting dose is 100 micrograms twice daily. In moderate and more severe asthma, starting doses may need to be 250 to 500 micrograms twice daily. Where additional clinical benefit is expected, doses of up to 1000 micrograms twice daily may be used. Initiation of such doses should be prescribed only by a specialist in the management of asthma (such as a consultant physician or general practitioner with appropriate experience).
The dose should be titrated down to the lowest dose at which effective control of asthma is maintained.

Typical starting doses for children over 4 years of age:
50 to 100 micrograms twice daily.
Many children's asthma will be well controlled using the 50 to100 microgram 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 micrograms twice daily. **The maximum licensed dose in children is 200 micrograms twice daily.**
The starting dose should be appropriate to the severity of the disease.
The dose should be titrated down to the lowest dose at which effective control of asthma is maintained.

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

Contraindications
Hypersensitivity to any ingredient of the preparation.

Warnings and Precautions
Severe asthma requires regular medical assessment, including lung-function testing, as patients are at risk of severe attacks and even death. Increasing use of short-acting inhaled β_2-agonists to relieve symptoms indicates deterioration of asthma control.
Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to increasing corticosteroid dosage.
As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. Flixotide Diskus should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.
Fluticasone propionate 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. 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 reviewed regularly and titrated to the lowest dose at which effective control is maintained.
Prolonged treatment with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children aged < 16 years taking higher than licensed doses of fluticasone (typically ≥1000mcg/day) may be at particular risk. Situations, which could potentially trigger acute adrenal crisis, include trauma, surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.
When changing from a dry powder inhaler to a metered dose inhaler, administration of high doses, above 1000 mcg daily, is recommended through a spacer to reduce side effects in the mouth and throat. However, this may increase drug delivery to the lungs. As systemic absorption is largely through the lungs, there may be an increase in the risk of systemic adverse effects. A lower dose may be required.
The benefits of inhaled fluticasone propionate should minimise the need for oral steroids. However, patients transferred from oral steroids, remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled fluticasone propionate. The possibility of adverse effects may persist for some time. These patients may require specialised advice to determine the extent of adrenal impairment before elective procedures. The possibility of residual impaired adrenal response should always be considered in emergency (medical or surgical) and elective situations likely to produce stress, and appropriate corticosteroid treatment considered.
For the transfer of patients being treated with oral corticosteroids: The transfer of oral steroid-dependent patients to Flixotide Diskus and their subsequent management needs special care as recovery from impaired adrenocortical function, caused by prolonged systemic steroid therapy, may take a considerable time.
Patients who have been treated with systemic steroids for long periods of time or at a high dose may have adrenocortical suppression. With these patients adrenocortical function should be monitored regularly and their dose of systemic steroid reduced cautiously.
After approximately a week, gradual withdrawal of the systemic steroid is commenced. Decrements in dosages should be appropriate to the level of maintenance systemic steroid, and introduced at not less than weekly intervals. For maintenance doses of prednisolone (or equivalent) of 10mg daily or less, the decrements in dose should not be greater than 1mg per day, at not less than weekly intervals. For maintenance doses of prednisolone in excess of 10mg daily, it may be appropriate to employ cautiously, larger decrements in dose at weekly intervals.
Some patients feel unwell in a non-specific way during the withdrawal phase despite maintenance or even improvement of the respiratory function. They should be encouraged to persevere with inhaled fluticasone propionate and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency.
Patients weaned off oral steroids whose adrenocortical function is still impaired should carry a steroid warning card indicating that they need supplementary systemic steroid during periods of stress, e.g. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.
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.
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 fluticasone propionate should not be stopped abruptly.
There have been very rare reports of increases in blood glucose levels, in patients with or without a history of diabetes mellitus and this should be considered when prescribing to patients with a history of diabetes mellitus.
As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis.
During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects. There is also an increased risk of systemic side effects when combining fluticasone propionate with other potent CYP3A inhibitors.
The possibility of impaired adrenal response should always be borne in mind in emergency situations, including surgery, and elective situations likely to produce stress and appropriate corticosteroid treatment must be considered.

Interactions
Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.
A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects.
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.

Pregnancy and Lactation
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 exposures in excess of those seen at the recommended inhaled therapeutic dose. Tests for genotoxicity have shown no mutagenic potential.
However, as with other drugs 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.
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.

Adverse Reactions
Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥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 their medication.
Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with fluticasone propionate.

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:
Very rare: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, 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/dysphonia.
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.

Fluticasone propionate should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

Skin and subcutaneous tissue disorders
Common: Contusions

Gastrointestinal Disorders
Very Rare: Dyspepsia

Musculoskeletal & Connective Tissue Disorders
Very Rare: Arthralgia

Overdosage

Symptoms and Signs
Acute inhalation of fluticasone propionate doses in excess of those approved may lead to temporary suppression of the hypothalamic-pituitary-adrenal axis. This does not usually require emergency action, as normal adrenal function typically recovers within a few days.
If higher than approved doses are continued over prolonged periods, significant adrenocortical suppression is possible. There have been very rare reports of acute adrenal crisis occurring in children exposed to higher than approved doses (typically 1000 micrograms daily and above), over prolonged periods (several months or years); observed features included hypoglycaemia and sequelae of decreased consciousness and/or convulsions. Situations which could potentially trigger acute adrenal crisis include exposure to trauma, surgery, infection or any rapid reduction in dosage.

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

List of Excipients
Lactose (which contains milk protein)

Shelf Life
Shelf Life is indicated on the outer packaging.

Special Precautions for Storage
Do not store above 30°C. Store in the original package.

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 Diskus device.

Instructions for Use/Handling
The powdered medicine is inhaled through the mouth into the lungs.
The Diskus device contains the medicine in individual blisters which are opened as the device is manipulated.
For detailed instructions for use refer to the Patient Information Leaflet in every pack.

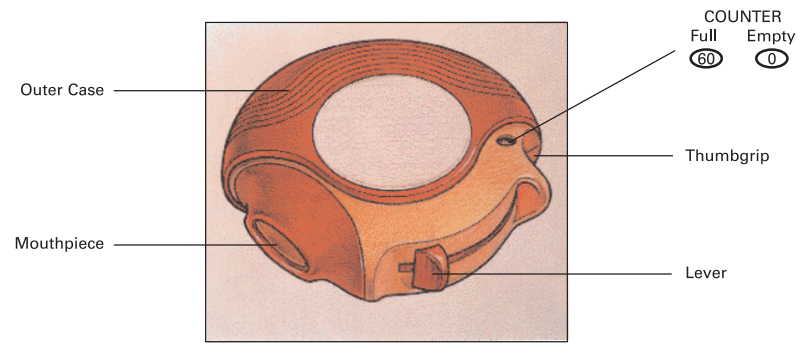
GDS Version Number: 26, **Version Date**: 11 January 2008

Manufactured by: Glaxo Operations UK Limited*, Ware, UK
* Member of the GlaxoSmithKline group of companies

THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists.

Flixotide™ Diskus™



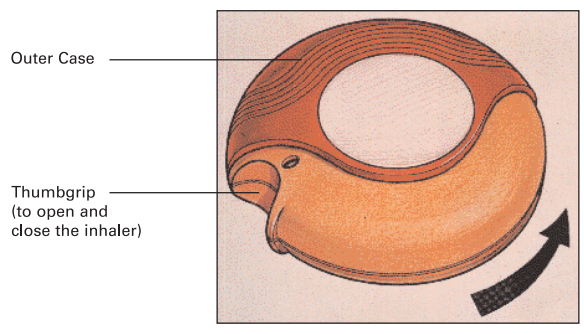
WHAT YOU SHOULD KNOW ABOUT FLIXOTIDE DISKUS
This leaflet refers only to Flixotide Diskus. Please read it carefully before you start to take your medicine. It tells you the main points about your medicine. For more information or advice ask your doctor or pharmacist.

THE NAME OF YOUR MEDICINE
The name of your medicine is Flixotide (fluticasone propionate) Diskus.

WHAT IS FLIXOTIDE DISKUS?
Flixotide Diskus is a plastic inhaler device containing a foil strip with 60 blisters. Each blister contains 50, 100, 250 or 500 micrograms of the active ingredient fluticasone propionate and lactose, which acts as a 'carrier'. The blisters protect the powder for inhalation from the effects of the atmosphere. The device has a dose counter which tells you the number of doses remaining. It counts down from 60 to 0. To show when the last five doses have been reached the numbers appear in red.

HOW TO USE YOUR DISKUS INHALER
When you take your Diskus out of its box, your Diskus will be in the closed position.

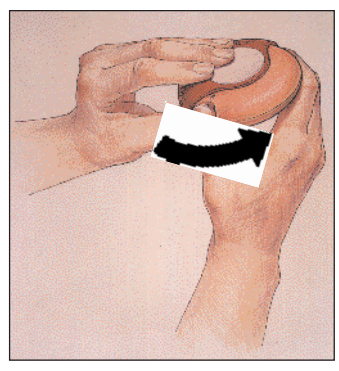
CLOSED



The inhaler opens in this direction

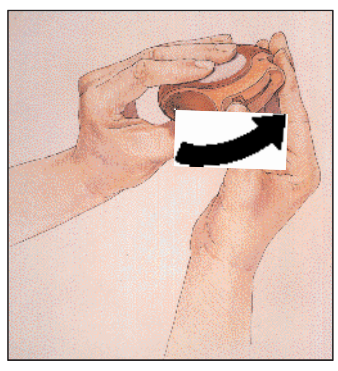
A new Diskus contains 60 individual blisters containing your medicine in powder form.
The contents of each blister are **accurately measured** and **hygienically protected**. The Diskus requires **no maintenance** and **no refilling**.
The counter on the top of your Diskus tells you how many blisters are left. Numbers 5 to 0 will appear in **RED**, to warn you when there are only a few blisters left.

HOW YOUR DISKUS WORKS
Sliding the lever of your Diskus opens a small hole in the mouthpiece and opens a blister in a foil strip, ready for you to inhale the powder.
When you close the Diskus, the lever automatically moves back to its original position. The outer case protects your Diskus when it is not in use.
The Diskus is **easy to use**. When you need to use it, just follow these four simple steps:
1 **OPEN** 2 **SLIDE** 3 **INHALE** 4 **CLOSE**



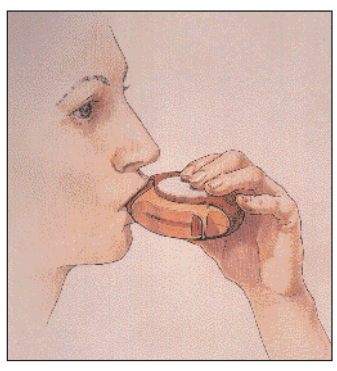
1 OPEN

To open your Diskus 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 until you hear a click.



2 SLIDE

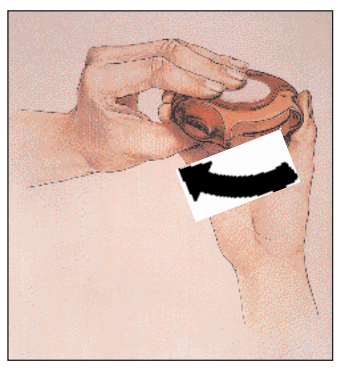
Hold your Diskus with the mouthpiece towards you. You can hold it in either your right or left hand. Slide the lever away from you, as far as it will go - until it clicks. Your Diskus is now ready to use. Every time the lever is pushed back a blister is opened and the powder made available for inhaling. This is shown by the counter. Do not play with the lever because this opens the blisters and wastes the medicine.



3 INHALE

BEFORE YOU START TO INHALE READ THROUGH THIS SECTION CAREFULLY.

- Hold the Diskus away from your mouth. Breathe out as far as is comfortable.
  Remember - never breathe **into** your Diskus.
- Put the mouthpiece to your lips. Suck in steadily and deeply through the Diskus.
- Remove the Diskus from your mouth.
- Hold your breath for about 10 seconds, or as long as is comfortable.
- Breathe out slowly.



4 CLOSE

To close your Diskus, put your thumb in the thumbgrip, and slide the thumbgrip back towards you, as far as it will go. When you close the Diskus, it clicks shut. The lever automatically returns to its original position and is reset. Your Diskus is now ready for you to use again. If you have been instructed to take two blisters you must close the Diskus and repeat steps 1 to 4.

CLEANING
Wipe the mouthpiece of the Diskus with a dry tissue to clean it.

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