



Fluticasone propionate

Flixotide[®] Nebules[®]

250mcg/mL Suspension for Inhalation

PRODUCT DESCRIPTION

Each Fluticasone propionate (Flixotide[®]) Nebules[®] 250mcg/mL (plastic ampoules) are intended for nebulisation and contain 0.5 mg of fluticasone propionate (micronised) as a 2 ml buffered isotonic saline suspension.

PHARMACOLOGIC PROPERTIES

Pharmacodynamics

Fluticasone propionate (Flixotide[®]) given by inhalation at recommended doses has a potent glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma.

Pharmacokinetics

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 fluticasone propionate Accuhaler/Diskus (7.8%), fluticasone propionate Diskhaler[®] (9.0%) and fluticasone propionate Evohaler (10.9%) respectively. In patients with asthma or COPD 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%).

Metabolism

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 (less than 0.2%) and less than 5% as the metabolite.

Clinical Studies

Fluticasone propionate containing medications in asthma during pregnancy

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

Within the asthma cohort of 5362 first trimester ICS-exposed pregnancies, 131 diagnosed MCMs were identified; 1612 (30%) were exposed to FP or salmeterol-FP 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 FP exposed vs non-FP ICS 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 FP alone versus salmeterol-FP combination.

Absolute risks of MCM across the asthma severity strata ranged from 2.0 to 2.9 per 100 FP-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).

Pre-clinical 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.

INDICATIONS

ASTHMA

Fluticasone propionate (Flixotide[®]) Nebules[®] has a marked anti-inflammatory effect in the lungs.

It reduces symptoms and exacerbations of asthma in patients previously treated with bronchodilators alone or with other prophylactic therapy.

Relatively brief symptomatic episodes can generally be relieved by the use of fast-acting bronchodilators, but longer lasting exacerbations require, in addition, the use of corticosteroid therapy as soon as possible, to control the inflammation.

- Adults and adolescents over 16 years of age

Prophylactic management in severe asthma (Patients requiring high dose inhaled or oral corticosteroid therapy):

On introduction of inhaled Fluticasone propionate (*Flixotide*[®]) Nebules[®] 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.

Treatment of acute exacerbations of asthma:

Subsequent maintenance dosing may be more conveniently accomplished using a pressurised metered-dose inhaler or powder formulation.

- Children and adolescents from 4 to 16 years of age

Treatment of acute exacerbations of asthma:

Subsequent maintenance dosing may be more conveniently accomplished using a pressurised metered-dose inhaler or powder formulation.

DOSAGE AND ADMINISTRATION

Patients should be made aware of the prophylactic nature of therapy with inhaled Fluticasone propionate (*Flixotide*[®]) Nebules[®] and that it should be taken regularly even when they are asymptomatic.

Fluticasone propionate (*Flixotide*[®]) Nebules[®] should be administered as an aerosol produced by a jet nebuliser, as directed by a physician. As drug delivery can be affected by a wide range of criteria, please refer to the directions recommended by the manufacturer of the nebuliser equipment.

Use of Fluticasone propionate (*Flixotide*[®]) Nebules[®] with ultrasonic nebulisers is not generally recommended.

Fluticasone propionate (*Flixotide*[®]) Nebules[®] for nebulisation should not be injected.

Fluticasone propionate (*Flixotide*[®]) Nebules[®] for nebulisation is intended for oral inhalation, and use of a mouthpiece is recommended. If use of a face mask is necessary, nasal inhalation may occur.

Maximal improvement in asthma may be achieved within four to seven days of starting treatment. However, Fluticasone propionate (*Flixotide*[®]) Nebules[®] has been shown to have a therapeutic effect as soon as 24 hours after starting treatment 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.

To aid administration of small volumes of the suspension, or if a prolonged delivery time is desirable, Fluticasone propionate (*Flixotide*[®]) Nebules[®] suspension for nebulisation may be diluted immediately before use with sodium chloride injection.

As many nebulisers operate on a continuous flow basis, it is likely that nebulised drug will be released in the local environment. Fluticasone propionate (*Flixotide*[®]) Nebules[®] should therefore be administered in a well ventilated room, particularly in hospitals when several patients may be using nebulisers at the same time.

ASTHMA

- Adults and adolescents over 16 years

500 to 2000 micrograms twice daily.

- Children and adolescents from 4 to 16 years of age

1000 micrograms twice daily.

Patients should be given an initial dose of nebulised Fluticasone propionate (*Flixotide*[®]) Nebules[®] which is appropriate for the severity of their disease. The dosage should then be adjusted until control is achieved or reduced to the minimum effective dose according to the individual response.

A dose at the upper end of the range is recommended for the treatment of acute exacerbations of asthma for up to seven days after exacerbation.

Consideration should then be given to reducing the dosage.

- Special patient groups

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

CONTRAINDICATIONS

Fluticasone propionate (*Flixotide*[®]) Nebules[®] are contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS AND PRECAUTIONS

Increasing use of short-acting inhaled beta₂ 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 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 Adverse Reactions). It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored.

Because of the possibility of impaired adrenal response, patients transferring from oral steroid therapy to inhaled Fluticasone propionate (*Flixotide*[®]) Nebules[®] therapy should be treated with special care, and adrenocortical function regularly monitored.

Following introduction of inhaled Fluticasone propionate (*Flixotide*[®]) Nebules[®], 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.

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 Overdose).

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 Fluticasone propionate (*Flixotide*[®]) Nebules[®] should not be stopped abruptly. There have been very rare reports of increases in blood glucose levels (see Adverse Reactions) 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 of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects (see *Interactions*). 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 (*Flixotide*[®]) Nebules[®] should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted. Fluticasone propionate (*Flixotide*[®]) Nebules[®] are not for use alone in the relief of symptoms arising from acute bronchospasm when a short-acting inhaled bronchodilator (e.g. salbutamol) is also required. Fluticasone propionate (*Flixotide*[®]) Nebules[®] are intended for regular daily treatment and as anti-inflammatory therapy in acute exacerbations of asthma.

Severe asthma requires regular medical assessment, as it could be life-threatening. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

Fluticasone propionate (*Flixotide*[®]) Nebules[®] are not a substitute for injectable or oral corticosteroids in an emergency situation.

Patients receiving treatment with nebulised Fluticasone propionate (*Flixotide*[®]) Nebules[®] must be warned that if their clinical condition deteriorates they should not increase the dose or the frequency of administration, but should seek medical advice.

It is advisable to administer the nebulised Fluticasone propionate (*Flixotide*[®]) Nebules[®] via a mouthpiece to avoid the possibility of atrophic changes of facial skin which may occur with prolonged use with a face-mask.

When a face mask is used, the exposed skin should be protected by use of barrier cream or by thorough washing of the face after use.

Prolonged therapy with inhaled Fluticasone propionate (*Flixotide*[®]) Nebules[®] should be reduced gradually, and not be stopped abruptly, other than under medical supervision.

DRUG 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

Fertility

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

Pregnancy

There are limited data in pregnant women. Administration of Fluticasone propionate (*Flixotide*[®]) during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus. Results from a retrospective epidemiological study did not find an increased risk of major congenital malformations (MCMs) following exposure to fluticasone propionate when compared to other inhaled corticosteroids, during the first trimester of pregnancy (see *Clinical Studies*).

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.

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 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.

ADVERSE EFFECTS

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ 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 their medication. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with Fluticasone propionate (*Flixotide*[®]) Nebules[®].

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 Warnings and Precautions):

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 (*Flixotide*[®]) Nebules[®] may cause hoarseness. It may be helpful to rinse out the mouth with water immediately after inhalation.

Very rare: Paradoxical bronchospasm (See Warnings and Precautions).

Skin and subcutaneous tissue disorders

Common: Contusions.

OVERDOSAGE AND TREATMENT

Acute inhalation of Fluticasone propionate (*Flixotide*[®]) Nebules[®] doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function is recovered in a few days, as verified by plasma cortisol measurements. However if higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression may result. Monitoring of adrenal reserve may be necessary. In cases of Fluticasone propionate (*Flixotide*[®]) Nebules[®] overdose, therapy may still be continued at a suitable dosage for symptom control.

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

STORAGE CONDITIONS

Store below 30°C. Protect from frost and light. Do not freeze.

In-use shelf-life:

Once Nebules have been removed from their foil blister or flow wrap pack they should be protected from light and used within 28 days.

Opened nebules should be refrigerated and used within 12 hours of opening. Store upright.

INSTRUCTIONS FOR USE/HANDLING

Instructions for use of your Fluticasone propionate (*Flixotide*[®]) Nebules[®]

Refer to the manufacturer's instructions for nebuliser use.

It is important to ensure the contents of your Nebule are well mixed before use. While holding the Nebule horizontally by the labelled tab, 'flick' the other end a few times and shake. Repeat this process several times until the entire contents of the Nebule are completely mixed.

To open - twist tab at the top of the Nebule.

Dilution:

Dilute with Sodium Chloride Injection, if required.

Discard unused suspension in bowl of nebuliser.

It is advisable to administer via a mouth piece.

If using a face mask, protect the skin with barrier cream, or wash face thoroughly after treatment.

AVAILABILITY

Fluticasone propionate (*Flixotide*[®]) Nebules[®] 250mcg/mL: Each nebule is individually wrapped in a foil blister (Box of 10's)

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Keep all medicines out of reach of children.

FLIXOTIDE, NEBULES and DISKHALER are registered trademarks of the GSK group of companies.

©2015, GlaxoSmithKline. All rights reserved.

Version number: GDS32/IP110

Date of issue: 30 March 2015

Imported by:

GlaxoSmithKline Philippines Inc

2266 Chino Roces Avenue, City of Makati

Tel. 892-0761

Mfd. By:
GlaxoSmithKline Australia Pty Ltd
Boronia, Victoria, Australia