FLIXOTIDE™ NEBULES™

Fluticasone propionate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluticasone propionate 0.5 mg in 2 ml.

FLIXOTIDE NEBULES (plastic ampoules) are intended for nebulisation and contain 0.5 mg of fluticasone propionate (micronised) as a 2 ml buffered isotonic saline suspension.

PHARMACEUTICAL FORM

Suspension for inhalation by nebulisation.

CLINICAL PARTICULARS

Indications

ASTHMA

FLIXOTIDE 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 *FLIXOTIDE* 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 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 *FLIXOTIDE* and that it should be taken regularly even when they are asymptomatic.

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 *FLIXOTIDE* Nebules with ultrasonic nebulisers is not generally recommended.

FLIXOTIDE for nebulisation should not be injected.

FLIXOTIDE 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, *FLIXOTIDE* 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, *FLIXOTIDE* 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. *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 *FLIXOTIDE* 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

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 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 Overdose*). Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and central serous chorioretinopathy. 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 *FLIXOTIDE* therapy should be treated with special care, and adrenocortical function regularly monitored.

Following introduction of inhaled *FLIXOTIDE*, 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 Overdosage*).

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* 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. *FLIXOTIDE* Nebules should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

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. *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.

FLIXOTIDE Nebules are not a substitute for injectable or oral corticosteroids in an emergency situation.

Patients receiving treatment with nebulised *FLIXOTIDE* 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 *FLIXOTIDE* 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 *FLIXOTIDE* Nebules should be reduced gradually, and not be stopped abruptly, other than under medical supervision.

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.

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are co-administered with fluticasone propionate. In a drug interaction study, co-administration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol. In another multiple-dose drug interaction study, co-administration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Pregnancy and Lactation

Fertility

There are no data on human fertility. Animal studies indicate no effects of fluticasone propionate on male or female fertility (see *Pharmacodynamic Properties*).

Pregnancy

There are limited data in pregnant women. Administration of *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.

Effects on Ability to Drive and Use Machines

FLIXOTIDE is unlikely to produce an effect.

Adverse Reactions

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

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 *FLIXOTIDE* 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

Overdose

Acute inhalation of *FLIXOTIDE* 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 *FLIXOTIDE* 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

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. The adjusted odds ratio for MCMs diagnosed by 1 year was 0.9 (95% CI: 0.3-2.9) for FP alone and 1.3 for salmeterol-FP (95% CI: 0.5-3.2) for women with moderate asthma. The adjusted odds ratio for MCMs diagnosed by 1 year was 1.3 (95% CI: 0.6-3.0) for FP alone and 1.1 for salmeterol-FP (95% CI: 0.6-2.0) for women with severe asthma. 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.

Reproductive Toxicology

Fluticasone propionate, administered subcutaneously at doses of up to 50 mcg/kg/day (up to 100 mcg/kg/day in males, prior to Day 36), did not affect the fertility or mating performance of the F0 and F1 generation rats, when given throughout the periods of gametogenesis, mating, gestation, parturition and lactation.

PHARMACEUTICAL PARTICULARS

List of Excipients

Polysorbate 20
Sorbitan monolaurate

Monosodium phosphate dihydrate
Dibasic sodium phosphate anhydrous
Sodium Chloride
Water for Injection

Incompatibilities

None reported.

Shelf Life

The expiry date is indicated on the packaging.

In-use shelf-life:

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

Opened Nebules should be used within 12 hours of opening.

Special Precautions for Storage

FLIXOTIDE Nebules should not be stored above 30°C.

Protect from frost and light.

Do not freeze.

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.

Nature and Contents of Container

FLIXOTIDE Nebules are presented in 2.5 ml medical grade low density polyethylene containers. The Nebules are either individually wrapped in a foil blister or are provided as a strip of Nebules in a foil flow wrap.

Instructions for Use/Handling

Instructions for use of your *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.

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