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FLIXOTIDE NEBULES

TITLE

Fluticasone propionate

SCOPE

Trade name

FLIXOTIDE™ NEBULES™ 0.5MG/2ML

FLIXOTIDE™ NEBULES™ 2MG/2ML

Formulation and Strength

Suspension for inhalation by nebulisation

Fluticasone propionate Nebules (plastic ampoules), are intended for nebulisation and contain 0.5mg in 2 ml or 2mg in 2 ml of fluticasone propionate (micronised) as a 2ml buffered isotonic saline suspension.

Excipients

polysorbate 20
sorbitan monolaurate
monosodium phosphate dihydrate
dibasic sodium phosphate
sodium Chloride
water for Injection.

Indications

Adults and adolescents over 16 years of age:

Prophylactic management in severe asthma.
Treatment of acute exacerbation of asthma.

Children and adolescents from 4 to 16 years of age:

Treatment of acute exacerbation 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 and that it should be taken regularly even when they are asymptomatic.

Fluticasone propionate 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 Nebules with ultrasonic nebulisers is not generally recommended.

Fluticasone propionate for nebulisation should not be injected.

Fluticasone propionate for nebulisation is intended for oral inhalation, and use of a mouth piece is recommended. If use of a face mask is necessary, nasal inhalation may occur.

Maximal improvement in asthma may be achieved within 4 to 7 days of starting treatment. However, fluticasone propionate 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 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 Nebules should therefore be administered in a well ventilated room, particularly in hospitals when several patients may be using nebulisers at the same time.

Adults and adolescents over 16 years

500mcg - 2000mcg twice daily.

Children and adolescents from 4 to 16 years

1000 mcg twice daily.

Patients should be given an initial dose of nebulised fluticasone propionate 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 7 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 Nebules are contraindicated in patients with a history of hypersensitivity to any of its components.

Warnings and Precautions

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 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.

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 (see *Overdosage*). 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.

Certain individuals can show greater susceptibility to the effects of inhaled corticosteroid than do most patients.

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.

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 (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*).

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 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

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 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.

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 were 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.

Ability to perform tasks that require judgement, motor or cognitive skills

Fluticasone propionate 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 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 (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 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.

Overdosage

Symptoms and Signs

Acute inhalation of fluticasone propionate 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 overdose therapy may still be continued at a suitable dosage for symptom control.

Treatment

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

Clinical Pharmacology

Pharmacodynamics

Mechanism of Action

Fluticasone propionate 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 has been estimated from within and between study comparisons of inhaled and intravenous pharmacokinetic data. 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 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 h. The renal clearance of fluticasone propionate is negligible (less than 0.2%) and less than 5% as the metabolite.

NON-CLINICAL INFORMATION

Toxicology has shown only those class effects typical of potent corticosteroids, and these only at doses in excess of that 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 INFORMATION

Shelf-Life

3 years

Storage

Fluticasone propionate Nebules should be stored below 30°C

Protect from frost and light.

Do not freeze. Opened Nebules should be refrigerated and used within 12 h of opening.

Store upright.

Nature and Contents of Container

Fluticasone propionate Nebules are presented in 2.5 ml medical grade low density polyethylene containers. Each nebule is individually wrapped in a foil blister; blisters are supplied as packs of 10 in cardboard cartons.

Incompatibilities

None reported.

Use and Handling

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.

Name of Manufacture

GlaxoSmithKline Australia Pty Ltd,1061 Mountain Highway,Boronia, Victoria 3155, Australia

Licence Holder

GlaxoSmithKline (ISRAEL) Ltd.,Israel
25 Basel St. Petach Tikva 49510

Licence Number

FLIXOTIDE NEBULES	0.5mg/2ml	113-87-29613
FLIXOTIDE NEBULES	2mg/2ml	113-88-29614