Flixotide Nebules 2 mg/2 ml

1. NAME OF THE MEDICINAL PRODUCT

Flixotide Nebules 2 mg/2 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Plastic ampoules containing 2 ml of a buffered, isotonic saline suspension containing 2 mg fluticasone propionate.

3. PHARMACEUTICAL FORM

Inhalation suspension for nebulisation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults and adolescents over 16 years Flixotide Nebules can be used:
For prophylactic management of severe chronic asthma in patients requiring high dose inhaled or oral corticosteroid therapy.
It reduces symptoms and exacerbations of asthma in patients previously treated with other prophylactic therapy.

4.2 Posology and method of 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.

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.

Patients should be given an initial dose of nebulised fluticasone propionate which is appropriate for the severity of their disease. The dosage may be increased until control is achieved or reduced to the minimum effective dose according to the individual response.

Adults and adolescents over 16 years: 500-2000 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 100 mcg of fluticasone propionate is approximately equivalent to 200 mcg dose of beclometasone dipropionate (CFC containing) or budesonide.

Prescribers should be aware of the risks of systemic effects when using high doses of corticosteroids (see 4.4 special warnings and precautions for use and 4.8 undesirable effects).

The dose should be titrated down to the lowest dose at which effective control of asthma is maintained.

Children 16 years and under: Flixotide Nebules 2 mg/2 ml are not licensed for use in children under 16 years and therefore should not be used in this patient population. Current clinical data do not allow appropriate dosage recommendations to be made in this patient population.

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

Flixotide Nebules are for inhalation use only. They should be administered as an aerosol produced by a jet nebuliser, as directed by a physician. As drug delivery from nebulisers is variable, the manufacturer's instructions for using the nebuliser must be followed.

Use of Flixotide Nebules with ultrasonic nebulisers is not generally recommended.

Flixotide Nebules should not be injected or administered orally.

It is advisable to administer Flixotide Nebules via a mouthpiece to avoid the possibility of atrophic changes to facial skin, which may occur with prolonged use with a face-mask. When a face-mask is used, the exposed skin should be protected using a barrier cream, or the face should be thoroughly washed after treatment.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The management of asthma should follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

Flixotide Nebules are not designed to relieve acute symptoms for which an inhaled short-acting bronchodilator is required. Patients should be advised to have such rescue medication available. Flixotide Nebules are intended for regular daily prophylactic treatment.

Flixotide Nebules are not a substitute for injectable or oral corticosteroids in an emergency (i.e. life threatening asthma).

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. If patients find that short-acting relief bronchodilator treatment becomes less effective, or they need more inhalations than usual, medical attention must be sought. In this situation patients should be reassessed and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroids or a course of oral corticosteroids). Severe exacerbations of asthma must be treated in the normal way.

There have been very rare reports of increases in blood glucose levels, in patients with or without a history of diabetes mellitus (See section 4.8). This should be considered in particular when prescribing to patients with a history of diabetes mellitus.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. Flixotide Nebules should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral steroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important therefore that the dose of inhaled corticosteroid is

reviewed regularly and reduced to the lowest dose at which effective control of asthma 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 ≥1000 mcg/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 corticosteroids 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.

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

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.

Patients should receive a dose appropriate to the severity of their disease; the dose should be titrated to the lowest dose at which effective control of asthma is maintained. If control cannot be maintained, the use of a systemic steroid and/or an antibiotic may be necessary.

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks 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.

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 section 4.5).

Treatment with Flixotide Nebules should not be stopped abruptly.

For the transfer of patients being treated with oral corticosteroids: The transfer of oral steroid-dependent patients to Flixotide Nebules 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. Dosage reductions should be appropriate to the level of maintenance systemic steroid, and introduced at not less than weekly intervals. In general, for maintenance doses of prednisolone (or equivalent) of 10 mg daily or less, the dosage reductions should not be greater than 1 mg per day, at not less than weekly intervals. For maintenance doses of prednisolone in excess of 10 mg daily, it may be appropriate to employ cautiously, larger reductions 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.

Ritonavir can greatly increase the concentration of fluticasone propionate in plasma. 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 (see section 4.5).

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes, which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

4.5 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.

In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome P450 3A4 inhibitor) 100 mg b.i.d. increased the fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side-effects.

In a small study in healthy volunteers, the slightly less potent CYP3A inhibitor ketoconazole increased the exposure of fluticasone propionate after a single inhalation by 150%. This resulted in a greater reduction of plasma cortisol as compared with fluticasone propionate alone. Co-treatment with other potent CYP3A inhibitors, such as itraconazole, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side-effects. Caution is recommended and long-term treatment with such drugs should if possible be avoided.

Co-treatment with other potent CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. Other inhibitors of cytochrome CYP3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations.

Combinations should be avoided unless the benefit outweighs the potential increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

4.6. Fertility, 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 during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus. It is important, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained. Treatment with fluticasone propionate should not be stopped abruptly.

Results from a retrospective epidemiological study did not find an increased risk of major congenital malformations following exposure to fluticasone propionate when compared to other inhaled corticosteroids, during the first trimester of pregnancy (see Section 5.1).

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. There is inadequate evidence of safety of fluticasone propionate in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development, including cleft palate and intra-uterine growth retardation. There may therefore be a very small risk of such effects in the human fetus. It should be noted, however, that the fetal changes in animals occur after relatively high systemic exposure. Because Flixotide Nebules deliver fluticasone propionate directly to the lungs by the inhaled route the high level of exposure that occurs when corticosteroids are given by systemic routes is avoided. 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 fetus (see Section 5.3).

Breast-feeding

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.

Administration during lactation should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

4.7 Effects on ability to drive and use machines

Fluticasone propionate has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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), very rare (<1/10,000) including isolated reports and not known (cannot be estimated from the available data). Very common, common and uncommon events were generally determined from clinical trial data. Rare and very rare events were generally determined from spontaneous data.

System Organ Class	Adverse Event	Frequency
Infections and Infestations	Candidiasis of the mouth and throat	Very Common
	Pneumonia (in COPD Patients)	Common
	Oesophageal candidiasis	Rare
Immune System Disorders	Hypersensitivity reactions with the following manifestations:	
	Cutaneous hypersensitivity reactions	Uncommon
	Angioedema (mainly facial and oropharyngeal oedema)	Very Rare
	Respiratory symptoms (dyspnoea and/or bronchospasm)	Very Rare
	Anaphylactic reactions	Very Rare
Eye disorders	Vision, blurred (see section 4.4)	Not known

Endocrine Disorders	Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density, cataract, glaucoma	Very Rare
Metabolism and Nutrition Disorders	Hyperglycaemia (see section 4.4)	Very Rare
Psychiatric Disorders	Anxiety, sleep disorders, behavioural changes, including hyperactivity and irritability (predominantly in children) Depression, aggression (predominantly in children)	Very Rare Not known
Respiratory, Thoracic and Mediastinal Disorders	Hoarseness/dysphonia Paradoxical bronchospasm Epistaxis	Common Very Rare Not known
Gastrointestinal Disorders	Dyspepsia	Very Rare
Skin & Subcutaneous Tissue Disorders	Contusions	Common
Musculoskeletal and Connective Tissue Disorders	Arthralgia	Very Rare

Hoarseness and 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 inhalation from the nebuliser. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with Flixotide Nebules.

Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation, decreased bone mineral density, cataract, glaucoma (see section 4.4).

As with other inhalation therapy, paradoxical bronchospasm may occur (see section 4.4). This should be treated immediately with a fast acting inhaled bronchodilators. Flixotide Nebules should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

There was an increased reporting of pneumonia in studies of patients with COPD receiving FLIXOTIDE 500 micrograms. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbation frequently overlap.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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.

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 major congenital malformations following first trimester exposure to inhaled fluticasone propionate alone and salmeterol-fluticasone propionate combination relative to non-fluticasone propionate containing inhaled corticosteroids. No placebo comparator was included in this study.

Within the asthma cohort of 5362 first trimester inhaled corticosteroids-exposed pregnancies, 131 diagnosed major congenital malformations were identified; 1612 (30%) were exposed to fluticasone propionate or salmeterol-fluticasone propionate of which 42 diagnosed major congenital malformations were identified. The adjusted odds ratio for major congenital malformations diagnosed by 1 year was 1.1 (95%CI: 0.5 – 2.3) for fluticasone propionate exposed vs non-fluticasone propionate inhaled corticosteroids 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 major congenital malformations was identified following first trimester exposure to fluticasone propionate alone versus salmeterol-fluticasone propionate combination. Absolute risks of major congenital malformations across the asthma severity strata ranged from 2.0 to 2.9 per 100 fluticasone propionate-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 major congenital malformations events per 100 pregnancies).

5.2 Pharmacokinetic properties

Following inhaled dosing, systemic availability of the nebulised fluticasone propionate in healthy volunteers is estimated at 8% as compared with up to 26% received from the metered dose inhaler presentation. Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the dose may be swallowed.

Absolute oral bioavailability is negligible (<1%) due to a combination of incomplete absorption from the GI tract and extensive first-pass metabolism.

87-100% of an oral dose is excreted in the faeces, up to 75% as parent compound. There is also a non-active major metabolite.

After an intravenous dose, fluticasone propionate is extensively distributed in the body. The very high clearance rate indicates extensive hepatic clearance.

5.3 Preclinical safety data

Toxicology has shown only those class effects typical of potent corticosteroids, and these only at doses greatly 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.

Subcutaneous embryofetal development studies in mouse and rat at 45 and 100 mcg/kg, respectively (approximately equivalent to 4 and 6 times the maximum recommended daily inhaled dose of 500 mcg twice daily in adults based on mouse and rat plasma levels of 486 and 710 pg/mL, respectively) resulted in fetal developmental toxicity characteristic of a potent corticosteroid, including cleft palate and embryonic fetal growth retardation, at doses that caused maternal toxicity. The no effect level for these finding in rat were associated with systemic exposures approximately 3 times the highest clinical exposure based on rat plasma level of 310 pg/mL. In the rabbit, fetal weight reduction and cleft palate occurred at a maternally toxic subcutaneous dose of 4 mcg/kg (less than 1.4 times the maximum recommended inhaled dose of 500 mcg twice daily based on rabbit plasma level of 149 pg/mL). However, fluticasone propionate administered via inhalation to rats did not induce teratogenicity at maternal toxic doses associated with exposures 17 times the human exposure achieved with the maximum recommended daily inhaled dose based on rat plasma level of 1890 pg/mL.

No evidence of impairment of fertility occurred in fertility studies in male and female rats at subcutaneous doses of fluticasone propionate up to 50 mcg/kg/day (approximately 6 times the human exposure associated with the maximum recommended daily inhaled dose of 500 mcg twice daily (110 pg/mL), based on rat plasma levels of approximately 650 pg/mL).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monosodium phosphate dihydrate

Sodium chloride

Dibasic sodium phosphate anhydrous

Polysorbate 20

Sorbitan laurate

Water for injection

6.2 Incompatibilities

None reported.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

In-use shelf-life:

The flow wrap pack should be opened immediately before use. Once Flixotide Nebules have been removed from their flow wrap pack they should be protected from light and used within 28 days.

Once opened, nebules should be used immediately.

6.4 Special precautions for storage

Flixotide Nebules should not be stored above 30ºC. Keep the container in the outer carton in order to protect from light. Do not freeze. Store upright. For storage conditions after first opening of the medicinal product, see section 6.3

6.5 Nature and contents of container

2.5 ml low density polyethylene ampoules provided as a strip of Nebules in a foil flow wrap, in boxes of 10.

Each card of five Flixotide Nebules is wrapped and sealed with a flow wrap foil. The foil is composed of polyester on the outer surface, aluminium as the middle layer and low density polyethylene on the inner surface.

6.6 Special precautions for disposal and other handling

It is important to ensure that the contents of the 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 the Nebule, twist off the tab.

Dilution: Flixotide Nebules may be diluted with Sodium Chloride Injection BP if required, to aid administration of small volumes or if a prolonged delivery time is desirable. Any unused suspension remaining in the nebuliser should be discarded.

For detailed instructions please refer to the Patient Information Leaflet in every pack.

The nebuliser must be used according to the manufacturer's instructions. It is advisable to administer Flixotide Nebules via a mouthpiece (see *Posology and method of administration*).

As many nebulisers operate on a continuous flow basis, it is likely that some nebulised drug will be released into the local environment. Flixotide Nebules should therefore be administered in a well-ventilated room, particularly in hospitals where several patients may be using nebulisers at the same time.

7. MANUFACTURER

GlaxoSmithKline Australia PTY Ltd., Boronia, Australia

8. LICENSE HOLDER AND IMPORTER

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

9. LICENSE NUMBER

113-88-29614

Revised in October 2021 according to MOHs guidelines.

Fli Neb 2 DR v8