Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flixotide Nebules 0.5 mg/ 2ml Nebuliser Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each nebule contains 0.5mg Fluticasone propionate in a 2ml suspension.
Each ml of suspension contains 0.25mg Fluticasone propionate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Nebuliser Suspension (Nebuliser Liquid)
A white, opaque suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults and adolescents over 16 years of age:

- Prophylactic management in severe asthma (patients requiring high dose inhaled or oral corticosteroid therapy).
- Treatment of acute exacerbations of asthma.

Children and adolescents from 4 to 16 years of age:

- Treatment of acute exacerbations of asthma.

4.2 Posology and method of administration

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.

Fluticasone propionate for nebulisation should not be injected.

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

Fluticasone propionate 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.

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. 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 BP.

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.

Dosage:

Adults and adolescents over 16 years: For the prophylactic management and treatment of acute exacerbations of asthma, take 500-2000 mcg twice daily.

Children and adolescents from 4 to 16 years: For the treatment of acute exacerbations of asthma only, take 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 for nebulisation should not be injected.

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.

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.

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 section 4.9). 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 reduced to the lowest dose at which effective control of asthma is maintained (see section 4.8).

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 are encouraged to carry steroid warning cards 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 section 4.8) 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 4.5 *Interaction with Other Medicinal Products and Other Forms of Interaction*).

Adrenal function and adrenal reserve usually remain within the normal range on recommended doses of fluticasone propionate therapy. The benefits of inhaled fluticasone propionate therapy should minimise the need for oral steroids. However, the possibility of adverse effects in patients, resulting from prior or intermittent administration of oral steroids, may persist for some time. The extent of the adrenal impairment may require specialist advice before elective procedures. The possibility of impaired adrenal response should always be borne in mind in emergency situations, including surgery, which are likely to produce stress and appropriate corticosteroid treatment must be considered.

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.

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

Patients receiving treatment with nebulised fluticasone propionate 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 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.

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 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.

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

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 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 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.

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 is unlikely to produce an effect.

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 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <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.

Infections and

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 nebulised fluticasone propionate.

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

Possible systemic effects (see section 4.4) include:

Very rare: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density, cataract, glaucoma.

Eye disorders

Not Known: Vision, blurred (see section 4.4)

Metabolism and nutrition disorders

Very rare: Hyperglycaemia.

Psychiatric disorders

Very rare: Anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children).

Not known: Depression, aggression (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 (see section 4.4)

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.

Not known: Epistaxis

Skin and subcutaneous tissue disorders

Common: Contusions

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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.

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, resulting in reduced symptoms and exacerbations of asthma, without the adverse effects observed when corticosteroids are administered systemically.

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 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).

5.2 Pharmacokinetic properties

Following intravenous administration the pharmacokinetics of fluticasone propionate are proportional to the dose, and can be described by three exponentials. Fluticasone propionate is extensively distributed within the body (Vss is approximately 300L) and has a very high clearance (estimated to be Cl 1.1L/min) indicating extensive hepatic extraction. Peak plasma concentrations are reduced by approximately 98% within 3-4 hours, and only low plasma concentrations are associated with the terminal half-life, which is approximately 8 hours.

Following oral administration of fluticasone propionate, 87-100% of the dose is excreted in the faeces. Following doses of either 1 or 16 mg, up to 20% and 75% respectively, is excreted in the faeces as parent compound. Absolute oral bioavailability is negligible (<1%) due to a combination of incomplete absorption from the gastro-intestinal tract and extensive first pass metabolism.

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

Plasma binding is 91%. Fluticasone propionate is extensively metabolised by CYP3A4 enzyme to an inactive carboxylic acid derivative. As fluticasone propionate is given at very low doses, any effect on co-administered drugs is unlikely. In clinical programmes, there were no reports of suspected drug interactions whilst patients were on inhaled fluticasone propionate therapy.

The limited data for paediatric pharmacokinetics show consistency with the adult findings.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20
Sorbitan monolaurate
Monosodium Phosphate Dihydrate
Dibasic Sodium Phosphate Anhydrous
Sodium Chloride
Water for Injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except these mentioned in section 6.6.

6.3 Shelf life

Unopened: 3 years.
Once Nebules have been removed from their foil flow wrap pack, they should be used within 28 days.
Opened Nebules should be used immediately.
If diluted with sodium chloride injection, use immediatley (see section 4.2 and 6.6)

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original container to protect from light.
Do not freeze.
Once Nebules have been removed from their foil flow wrap pack, they should be protected from light and used within 28 days.
Opened Nebules should be used immediately.
Store upright.

6.5 Nature and contents of container

Flixotide Nebules are presented in 2.5 ml medical grade low density polythene containers. Each nebule contains 2 ml of solution. Each cardboard carton contains two foil flow wrap packs. Each foil flow wrap pack contains a strip of five Nebules.

6.6 Special precautions for disposal and other 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.

Shake gently before use.

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

Dilution:
Dilute with Sodium Chloride Injection BP immediately before use, if required. The diluted product should be a white semi-opaque suspension.

Do not use the product if discoloured.

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.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1077/044/016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 10th October 2008

10 DATE OF REVISION OF THE TEXT

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