The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in October 2014, was updated according to the guidelines of the Ministry of Health in April 2018

Flixonase Nasule Drops

1. NAME OF THE MEDICINAL PRODUCT

Flixonase Nasule Drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose of Flixonase Nasule Drops contain:
Fluticasone propionate 400 micrograms (1 mg/ml).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal drops

Single dose aqueous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Flixonase Nasule Drops are indicated for the regular treatment of nasal polyps and associated symptoms of nasal obstruction.

4.2 Posology and method of administration

Posology

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

For full therapeutic benefit regular usage is essential. The absence of an immediate effect should be explained to the patient as maximum relief may not be obtained until after several weeks of treatment. However, if no improvement in symptoms is seen after four to six weeks, alternative therapies should be considered.

Unilateral polyposis rarely occurs, and could be indicative of other conditions. Diagnosis should be confirmed by a specialist.

Adults
The contents of one container (400 micrograms) to be instilled once or twice daily. The dose should be divided between the affected nostrils.

Elderly
The normal adult dosage is applicable.

Paediatric population
There are insufficient data at present to recommend the use of fluticasone propionate for the treatment of nasal polyps in children less than 16 years.

Method of administration

Flixonase nasal drops are for administration by the intranasal route only, contact with the eyes should be avoided.

After shaking and opening the container, the patient should adopt one of the positions outlined in the patient information leaflet. The dose should be divided between the nostrils by either counting approximately 6 drops into each nostril or by holding the dimpled sides of the container and squeezing once into each nostril (one squeeze delivers approximately half the dose).

Full instructions for use are given in the patient information leaflet.

4.3 Contraindications

Flixonase Nasule Drops are contra-indicated in patients with a history of hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Local infection: Infections of the nasal airways should be appropriately treated but do not constitute a specific contra-indication to treatment with Flixonase Nasule Drops.

Unilateral polyposis rarely occurs, and could be indicative of other conditions. Diagnosis should be confirmed by a specialist.

Nasal polyps require regular medical assessment to monitor severity of the condition.
Contact with the eyes and broken skin should be avoided.

Care must be taken when withdrawing patients from systemic steroid treatment, and commencing therapy with Flixonase Nasule Drops, particularly if there is any reason to suppose that their adrenal function is impaired.

Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations (see section 5.2). Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses. It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. Therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid, to the lowest dose at which effective control of symptoms is maintained. In addition, consideration should be given to referring the patient to a paediatric specialist, if growth is retarded.

It is possible that long term treatment with higher than recommended doses of nasal corticosteroids could result in clinically significant adrenal suppression. If there is evidence of higher than recommended doses being used then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

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 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 intranasal 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. 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.

Co-treatment with other potent CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects. Other inhibitors of cytochrome CYP 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Care is advised when co-administering cytochrome P450 3A4 inhibitors, especially in long-term use and in case of potent inhibitors, as there is potential for increased systemic exposure to fluticasone propionate.

Intranasal steroids are often used in conjunction with inhaled corticosteroids for concomitant treatment of asthma, commonly seen in patients with an allergic diathesis. In these patients, the cumulative steroid burden is perceived as a potential excess of steroid load which might also affect growth retardation.

4.6 Fertility, pregnancy and lactation

The use of Flixonase Nasule Drops during pregnancy and lactation requires that the benefits be weighed against possible risks associated with the product or with any alternative therapy.

Pregnancy
There is inadequate evidence of safety in human pregnancy. In animal reproduction studies adverse effects typical of potent corticosteroids are only seen at high systemic exposure levels; direct intranasal application ensures minimal systemic exposure.

Breast-feeding
The excretion of fluticasone propionate into human breast milk has not been investigated. Following subcutaneous administration in lactating laboratory rats, there was evidence of fluticasone propionate in the breast milk, however plasma levels in patients following intranasal application of fluticasone propionate at recommended doses are low.

4.7 Effects on ability to drive and use machines

Not relevant.

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) and not known (frequency cannot be estimated from available data). In assigning adverse event frequencies, the background rates in placebo groups in clinical trials were not taken into account, since these rates were generally comparable to or higher than those in the active treatment group.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Event	Frequency	
Immune system disorders	Hypersensitivity reactions, anaphylaxis/ anaphylactic reactions, bronchospasm, rash, oedema of the face and mouth	Very rare (<1/10,000)	
Eye disorders	***Glaucoma, raised intraocular pressure, Cataract	Very rare (<1/10,000)	
	Vision, blurred	Not known (see section 4.4)	
Respiratory, thoracic and mediastinal disorders	Epistaxis	Very common (≥1/10)	
	*Nasal dryness, nasal irritation, throat dryness, throat irritation	Common (≥1/100 to <1/10)	
	**Nasal septal perforation	Very rare (<1/10,000)	
	Nasal ulcers	Not known	

*As with other intranasal products dryness and irritation of the nose and throat, and epistaxis may occur.
**There have also been cases of nasal septal perforation following the use of intranasal corticosteroids.
***These events have been identified from spontaneous reports following prolonged treatment.

Systemic effects of nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods.

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 to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).
Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

There are no data available from patients on the effects of acute or chronic overdosage with Flixonase Nasule Drops.

In healthy volunteers, intranasal administration of 2 milligrams fluticasone propionate twice daily for seven days had no effect on hypothalamic-pituitary-adrenal axis (HPA) function. Administration of doses higher than those recommended over a long period of time may lead to temporary suppression of the adrenal function. In these patients, treatment with fluticasone propionate should be continued at a dose sufficient to control symptoms; the adrenal function will recover in a few days and can be verified by measuring plasma cortisol.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Nasal preparations, Corticosteroids
ATC code: R01AD08

Fluticasone propionate has potent anti-inflammatory activity when used topically on the nasal mucosa. Fluticasone propionate causes little or no HPA axis suppression following intranasal administration.

5.2 Pharmacokinetic properties

Absorption
After recommended doses of intranasal fluticasone propionate plasma levels are low. Systemic bioavailability for the nasal drop formula is extremely low (mean value 0.06 %).
Following intravenous administration the pharmacokinetics of fluticasone propionate are proportional to the dose, and can be described by three exponentials.

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

Distribution
Fluticasone propionate is extensively distributed within the body (Vss is approximately 300 litre). Plasma protein binding is 91 %.

Biotransformation/Elimination
After intravenous administration, fluticasone propionate has a very high clearance (estimated Cl 1.1 litre/min) indicating extensive hepatic extraction. It is extensively metabolised by CYP3A4 enzyme to an inactive carboxylic derivative.

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 as parent compound or as metabolites.

5.3 Preclinical safety data

At doses in excess of those recommended for therapeutic use, only class effects typical of potent corticosteroids have been shown in repeat dose toxicity tests, reproductive toxicology and teratology studies. Fluticasone propionate has no mutagenic effect in vitro or in vivo, no tumorigenic potential in rodents and is non-irritant and non-sensitising in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate, sodium chloride, dibasic sodium phosphate anhydrous, Polysorbate 20, sorbitan laurate, water for injections.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the label and packaging
After removal of foil: 28 days.

6.4 Special precautions for storage

Do not freeze.
Store Flixonase Nasule Drops in the foil wrapper and in the outer carton.
Store upright.
Do not store above 30^{o}C.
Protect from light.

6.5 Nature and contents of container

Strips of polyethylene single dose (400 micrograms) containers, within foil wrapping are available in the following pack sizes:
28 containers (4 strips of 7 Nasules)
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MANUFACTURER

GlaxoSmithKline PTY LTD, Boronia, Australia

8. MARKETING AUTHORISATION HOLDER

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

9. LICENSE NUMBER

115-01-29642

Fli ND DR v4