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Flixonase Aqueous Nasal Spray

1 NAME OF THE MEDICINAL PRODUCT

Flixonase Aqueous Nasal Spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Aqueous suspension of 0.05% micronised fluticasone propionate. Each actuation contains 50 micrograms of fluticasone propionate.

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Nasal spray, suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis and treatment of seasonal allergic rhinitis including hay fever and perennial rhinitis in adults and children of the age of 4 years and above.

4.2 Posology and method of administration

Flixonase Aqueous Nasal Spray is for administration by the intranasal route only.

Contact with the eyes should be avoided.

Adults and children over 12 years of age:

For the prophylaxis and treatment of seasonal allergic rhinitis and perennial rhinitis. Two sprays into each nostril once a day, preferably in the morning. In some cases two sprays into each nostril twice daily may be required. Once symptoms are under control a maintenance dose of one spray per nostril once a day may be used. If symptoms recur the dosage may be increased accordingly. The minimum dose should be used at which effective control of symptoms is maintained. The maximum daily dose should not exceed four sprays into each nostril.

Elderly patients:

The normal adult dosage is applicable.

Children under 12 years of age:

For the prophylaxis and treatment of seasonal allergic rhinitis and perennial rhinitis in children aged 4-11 years a dose of one spray into each nostril once daily preferably in the morning is recommended. In some cases one spray into each nostril twice daily may be required. The maximum daily dose should not exceed two sprays into each nostril. The minimum dose should be used at which effective control of symptoms is maintained.

Flixonase Aqueous Nasal Spray should not be prescribed for children for a period of more than 1 month.

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 3 to 4 days of treatment.

4.3 Contraindications

Hypersensitivity to fluticasone propionate or any other of the ingredients.

4.4 Special warnings and precautions for use

Treatment should be stopped or the advice of a doctor sought if an improvement is not seen within 7 days. The advice of a doctor or pharmacist should also be sought if symptoms have improved but are not adequately controlled.

This medicine should not be used for more than 3 months continuously without consulting a doctor.

Although fluticasone propionate aqueous nasal spray will control seasonal allergic rhinitis in most cases, an abnormally heavy challenge of summer allergens may in certain instances necessitate appropriate additional therapy.

Medical advice should be sought before using this medicine in the case of;

- concomitant use of other corticosteroid products, such as tablets, creams, ointments, asthma medications, similar nasal sprays or eye/nose drops
- fever or an infection in the nasal passages or sinuses.
- recent injury or surgery to the nose, or problems with ulceration in the nose.

Local infection: infections of the nasal airways should be appropriately treated but do not constitute a specific contraindication to treatment with intranasal fluticasone propionate.

Care must be taken when withdrawing patients from systemic steroid treatment, and commencing therapy with intranasal fluticasone propionate, particularly if there is any reason to suspect that their adrenal function is impaired.

Treatment with higher than recommended doses of nasal corticosteroids may 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.

Significant interactions between fluticasone propionate and potent inhibitors of the cytochrome P450 3A4 system, e.g. ketoconazole and protease inhibitors, such as ritonavir and cobicistat, may occur. This may result in increased systemic exposure to fluticasone propionate.

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. Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children

and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

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.

Flixonase Aqueous Nasal Spray contains benzalkonium chloride which may cause bronchospasm.

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.

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.

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.

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. 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.

4.6 Pregnancy and lactation

There is inadequate evidence of the safety of fluticasone propionate in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development, including cleft palate and intra-uterine growth retardation. There may therefore be a very small risk of such effects in the human foetus. It should be noted however that the foetal changes in animals occur after relatively high systemic exposure; direct intranasal application ensures minimal systemic exposure. As with other drugs the use of this medicine during human pregnancy requires that the possible benefits of the drug be weighed against the possible hazards.

The secretion of fluticasone propionate in human breast milk has not been investigated. Subcutaneous administration of fluticasone propionate to lactating

laboratory rats produced measurable plasma levels and evidence of fluticasone propionate in milk. However, following intranasal administration to primates, no drug was detected in the plasma, and it is therefore unlikely that the drug would be detectable in milk. When this medicine is used in breast feeding mothers the therapeutic benefits must be weighed against the potential hazards to mother and baby.

The label will include a warning that medical opinion should be sought, before using this medicine, in the case of pregnancy or breast feeding.

4.7 Effects on ability to drive and use machines

None reported.

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) 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. In assigning adverse event frequencies, the background rates in placebo groups were not taken into account.

System Organ Class	Adverse Event	Frequency
Immune system disorders	Hypersensitivity reactions, anaphylaxis/anaphylactic reactions, bronchospasm, skin rash, oedema of the face or tongue	Very rare
Nervous system, disorders	Headache, unpleasant taste, unpleasant smell	Common
Eye disorders	Glaucoma, raised intraocular pressure, cataract	Very rare
	Blurred vision	Unknown
Respiratory, thoracic and mediastinal disorders	Epistaxis	Very common
	Nasal dryness, nasal irritation, throat dryness, throat irritation	Common
	Nasal septal perforation	Very rare
	Nasal Ulcers	Unknown

As with other nasal sprays, dryness and irritation of the nose and throat, unpleasant taste and smell, headache and epistaxis have been reported.

Nasal ulceration and nasal septal perforation have been reported following the use of intranasal corticosteroids. usually when there has been previous nasal surgery.

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://forms.gov.il/forms/Resources/DowloadSetup/AGFormsDownloadToolbar.htm?formid=AdversEffectMedic@moh.gov.il).

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

4.9 Overdose

Administration of doses higher than those recommended over a long period of time may lead to temporary suppression of adrenal function.

There are no data available on the effects of acute or chronic overdosage with this medicine. Intranasal administration of fluticasone propionate at 20 times the recommended starting dose in adults (2mg twice daily) for seven days to healthy human volunteers had no effect on hypothalamic-pituitary-adrenal axis function.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids.

ATC Code: R01AD08

Fluticasone propionate is a glucocorticosteroid which has potent anti-inflammatory activity by acting via the glucocorticoid receptor. However, when used at up to four times the recommended daily dose on the nasal mucosa has no detectable systemic activity and causes little or no hypothalamic pituitary adrenal (HPA) axis suppression. Following intranasal dosing of fluticasone propionate, (200 micrograms/day) no significant change in 24h serum cortisol AUC was found compared to placebo (ratio 1.01, 90%CI 0.9-1.14).

Fluticasone propionate has been shown to reduce inflammatory mediators in both the early and late phase reactions of allergic rhinitis.

Once daily dosing with 200µg fluticasone propionate is sufficient to help relieve symptoms (particularly nasal congestion) for up to 24 hours.

5.2 Pharmacokinetic properties

Absorption: Following intranasal dosing of fluticasone propionate, (200 micrograms/day) steady-state maximum plasma concentrations were not quantifiable in most subjects (<0.01ng/mL). The highest Cmax observed was 0.017ng/mL. Direct absorption in the nose is negligible due to the low aqueous solubility with the majority of the dose being eventually swallowed. When administered orally the systemic exposure is <1% due to poor absorption and pre-systemic metabolism. The total systemic absorption arising from both nasal and oral absorption of the swallowed dose is therefore negligible.

Distribution: Fluticasone propionate has a large volume of distribution at steady-state (approximately 318L). Plasma protein binding is moderately high (91%).

Metabolism: Fluticasone propionate is cleared rapidly from the systemic circulation, principally by hepatic metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Swallowed fluticasone propionate is also subject to extensive first pass metabolism. Care should be taken when co-administering potent CYP3A4 inhibitors such as ketoconazole and ritonavir as there is potential for increased systemic exposure to fluticasone propionate.

Elimination: The elimination rate of intravenous administered fluticasone propionate is linear over the 250-1000 micrograms dose range and are characterized by a high plasma clearance (CL=1.1L/min). Peak plasma concentrations are reduced by approximately 98% within 3-4 hours and only low plasma concentrations were associated with the 7.8h terminal half-life. The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% as the carboxylic acid metabolite. The major route of elimination is the excretion of fluticasone propionate and its metabolites in the bile.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in the other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dextrose (anhydrous)

Microcrystalline cellulose and

sodium carboxymethylcellulose

Phenylethyl alcohol

Benzalkonium chloride

Polysorbate 80

Purified water

Dilute hydrochloric acid

6.2 Incompatibilities

None reported

6.3 Shelf life

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

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Amber glass bottle fitted with a metering, atomizing pump.
Each bottle provides approximately 120 metered sprays.

6.6 Special precautions for disposal

No special instructions.

7 MANUFACTURER

Glaxo Wellcome S.A., Burgos, Spain

8 LICENSE HOLDER AND IMPORTER

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

9 LICENSE NUMBER

060-33-26912-00

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