SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluticasone propionate 50 micrograms/actuation nasal spray, suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Aqueous suspension of 0.5 mg (500 micrograms)/ml fluticasone propionate.

Each actuation delivers 100 mg suspension containing 50 micrograms of fluticasone propionate as a delivered dose.

Excipient(s) with known effect:

This medicine contains 0.02 mg benzalkonium chloride in one dose of spray solution which is equivalent to 0.2 mg of benzalkonium chloride each 1 ml of solution.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Nasal spray, suspension.

A white opaque, aqueous suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluticasone propionate is indicated in adults aged 18 years and over.

This medicine provides symptomatic treatment of allergic rhinitis due to hay fever or other airborne allergens (such as dust mites, mould spores, or animal dander).

4.2 Posology and method of administration

Posology

Adults aged 18 years and over:

The recommended dose is two actuations into each nostril once a day (200 micrograms fluticasone propionate), preferably in the morning. In cases of severe symptoms two actuations into each nostril twice daily may be required but only for short term use. Once symptoms are under control a maintenance dose of one actuation per nostril once a day may be used. If symptoms recur the dosage may be increased accordingly. The minimum dose at which effective control of symptoms is maintained should be used.

The maximum daily dose should not exceed four actuations into each nostril.

In some patients full benefit of treatment may not be achieved in the first few days and therefore treatment of patients with a history of seasonal allergic rhinitis may need to be initiated some days before the expected start of the pollen season to help prevent symptoms from occurring. For full therapeutic benefit regular usage is recommended. Treatment should not exceed the period of allergen exposure.

Maximum benefit may require 3-4 days of continuous treatment in some people.

Elderly: The normal adult dosage is applicable.

Paediatric population

The nasal spray should not be used in children and adolescents under 18 years of age due to a lack of experience.

Method of administration

For administration by the intranasal route only. Not to be used in the eyes or mouth.

Shake gently before use.

Before first use of a new bottle, or if the bottle has not been used for some time, the bottle needs to be primed by pumping until a fine spray is produced.

To use the spray, place the nozzle in one nostril whilst the other is closed ensuring the nozzle is aimed away from the nasal septum. Spray into the nostril whilst breathing in and then breathe out through the mouth.

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

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 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.

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.
- an infection in the nasal passages or sinuses.
- recent injury or surgery to the nose, or problems with ulceration in the nose.

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 (see section 4.5).

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 and more rarely bone mineral density reduction, effects on glucose metabolism and 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.

Benzalkonium chloride may cause irritation or swelling inside the nose, especially if used for a long time. (see section 5.3).

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 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 Fertility, Pregnancy and lactation

Pregnancy

There is inadequate evidence of the 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; direct intranasal application ensures minimal systemic exposure (see Section 5.3).

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. Therefore medical advice should be sought before use if pregnant.

Breast-feeding

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. Therefore medical advice should be sought before use if breast-feeding.

Fertility

There are no data on the effects of fluticasone on human fertility.

4.7 Effects on ability to drive and use machines

No or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most common event experienced after administration is epistaxis; however most cases are non-serious in nature and self-limiting. The most serious events are anaphylaxis/anaphylactic reactions, bronchospasm and nasal septal perforation.
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 ulcer	Unknown

Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed 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 via the national reporting system listed in Appendix V.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nasal preparations, corticosteroids, ATC code: R01AD08

Mechanism of action

Fluticasone propionate is a glucocorticosteroid which has potent anti-inflammatory activity by acting via the glucocorticoid receptor.

Pharmacodynamic effects

Following intranasal dosing of fluticasone propionate (200 micrograms/day), no significant change in 24 hour serum cortisol AUC was found compared to placebo (ratio 1.01, 90% CI 0.9-1.14).

Clinical efficacy and safety

Multiple randomised, double-blind, placebo-controlled clinical trials were conducted to investigate the use of fluticasone propionate nasal spray (200 micrograms once daily) in adult patients with SAR or PAR and two studies investigated sinus discomfort and pressure associated with AR nasal congestion in patients ≥ 12 years. Compared with placebo, fluticasone propionate nasal spray significantly improved nasal (comprising rhinorrhoea, nasal congestion, sneezing and nasal itching) and ocular (ocular itching, tearing and redness) symptoms ($p<0.05$). Efficacy was maintained over the full 24 hour dosing interval. Sinus pain and pressure scores were significantly reduced versus placebo during the 2nd week of treatment in both studies and during the 1st week of treatment in one of the studies ($p<0.05$).

A post-hoc analyses of 22 clinical studies with fluticasone propionate nasal spray showed that the onset of therapeutic effect occurs within 12 hours, and as early as 2 to 4 hours in some patients, after initial administration of fluticasone propionate nasal spray.

The prevention of onset of SAR symptoms has been evaluated in two studies for fluticasone propionate nasal spray (200 micrograms once daily) in patients ≥ 12 years. Fluticasone propionate nasal spray was compared to disodium cromoglycate 2% aqueous nasal spray (study 1) or to the combination of fluticasone propionate nasal spray and oral cetirizine (10 mg daily) (study 2). Both were double-blind, and parallel-group studies. Patients treated with fluticasone propionate had significantly more symptom-free days (i.e. free of sneezing, rhinorrhea, congestion, and itching) compared to disodium cromoglycate treatment ($p<0.01$). There was no difference in ocular symptoms relief between the two treatment groups. No significant differences between fluticasone propionate nasal spray plus oral cetirizine versus fluticasone propionate nasal spray alone were observed.

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 (<0.01 ng/mL). The highest C_{max} observed was 0.017 ng/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%).

Biotransformation

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

Toxicology studies in animals, including reproductive and development toxicology studies, have shown class effects typical of a potent corticosteroid, and these only at doses greatly in excess of those proposed for therapeutic use. No novel effects were identified in repeat dose toxicity tests. Fluticasone proprionate is devoid of mutagenic activity *in vitro* and *in vivo* and showed no tumorigenic potential in rodents. It is both non-irritating and non-sensitising in animal models.

The available nonclinical animal data indicate that at doses exceeding the clinical therapeutic dose, repeated intranasal administration of benzalkonium chloride can induce squamous cell metaplasia, decrease the number of cilia and goblet cells and reduce mucus secretion, primarily in areas of the nasal mucosa where the concentration of the topically applied substance was greatest. Additionally, the collective clinical data indicate that short-term inhalation of benzalkonium chloride can induce bronchoconstriction in asthmatics and paradoxic bronchoconstriction with repeated use by patients with severe asthma. However, adverse effects on nasal cilia and mucosa have not been demonstrated in the reported clinical studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose, anhydrous

Microcrystalline cellulose

Carmellose sodium

Phenylethyl alcohol

Benzalkonium chloride

Polysorbate 80

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years for 120 dose

2 years for 60 dose

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

An amber glass bottle fitted with a metering pump comprised of plastic, rubber and metal components, a polypropylene nasal applicator and a polypropylene dust cover.

Each bottle provides 60 metered sprays, with total content not less than 7.0 g or 120 sprays with a total content not less than 14.0g.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Haleon Ireland Dungarvan Limited,

Knockbrack,

Dungarvan,

Co. Waterford,

Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 44673/0102

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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