For the Use of Registered Medicinal Practitioners or a Hospital or a Laboratory only

(Fluticasone Furoate Nasal Spray)

FREEAIR

1. Name of the medicinal product

Freeair

2. Qualitative and quantitative composition

Fluticasone Furoate	0.055 %w/w
Preservative:	
Benzalkonium Chloride IP	0.015 %w/w
Excipients	q.s.

3. Pharmaceutical form

Aqueous intranasal spray

4. Clinical particulars

4.1 Therapeutic indications

FREEAIR Nasal Spray is indicated for the treatment of the symptoms of seasonal and perennial allergic rhinitis in patients aged 2 years and older.

4.2 Posology and method of administration

Adults and Adolescents (12 years of age and older)

The recommended starting dosage is 110 mcg once daily administered as 2 sprays (27.5mcg/spray) in each nostril. When the maximum benefit has been achieved and symptoms have been controlled, reducing the dosage to 55 mcg (1 spray in each nostril) once daily may be effective in maintaining control of allergic rhinitis symptoms.

Children

The recommended starting dosage in children is 55 mcg once daily administered as1 spray (27.5mcg/spray) in each nostril. Children not adequately responding to 55 mcg may use 110 mcg (2 sprays in each nostril) once daily. Once symptoms have been controlled, the dosage may be decreased to 55 mcg once daily.

Method of administration

FREEAIR Nasal Spray is for administration by the intranasal route only.

The intranasal device should be shaken before use. The device is primed by pressing the mist release button for at least six spray actuations (until a fine mist is seen), whilst holding the device upright. Re-priming (approximately 6 sprays until a fine mist is seen) is only necessary if the cap is left off for 5 days or the intranasal device has not been used for 30 days or more. The device should be cleaned after each use and the cap replaced.

4.3 Contraindications

FREEAIR Nasal Spray is contraindicated in patients with a known hypersensitivity to any one of the ingredients.

4.4 Special warnings and precautions for use

Local Nasal Effects

Epistaxis and Nasal Ulceration

In clinical studies of 252 weeks' duration, epistaxis and nasal ulceration were observed more frequently and some epistaxis events were more severe in patients treated with fluticasone furoate nasal spray than those who received placebo.

Candida infection

Patients using fluticasone furoate nasal spray over several months or longer should be examined periodically for Candida infection or other signs of adverse effects on the nasal mucosa.

Nasal Septal Perforation

Instances of nasal septal perforation have been reported in patients following intranasal application of corticosteroids. There were no instances of nasal septal perforation observed in clinical studies with fluticasone furoate nasal spray.

Impaired wound healing

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal ulcers, nasal surgery or nasal trauma should not use fluticasone furoate nasal spray until healing has occurred.

Glaucoma and Cataracts

Nasal and inhaled corticosteroids may result in the development of glaucoma and/or cataracts. Therefore close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma and/or cataracts.

Immunosuppression

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or have not been properly immunized, particular care should be taken to avoid exposure. Corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract, untreated local or Systemic fungal or bacterial infections or ocular herpes simplex because of the potential for worsening of these infections.

Hypothalamic – Pituitary – Adrenal (HPA) Axis Effects

When intranasal steroids are used higher than recommended dosages or in susceptible individuals at recommended dosages, systemic corticosteroid effects such as a hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of fluticasone furoate nasal spray should be discontinued slowly, with accepted procedures for discontinuing oral corticosteroids therapy.

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. In addition, some patients may experience symptoms of corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenalin insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, rapid decreases in systemic corticosteroid dosages may cause a severe exacerbation of their symptoms.

Effect on Growth

Corticosteroids may cause a reduction in growth velocity when administered to paediatric patients. Hence, the growth of paediatric patients receiving fluticasone furoate nasal spray should be routinely monitored. To minimize the systemic effects of intranasal corticosteroids,

including fluticasone furoate nasal spray, each patient's dose should be titrated to the lowest dosage that effectively controls his/her symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

Fluticasone furoate is cleared by extensive first-pass metabolism mediated by the CYP450 isozyme, CYP3A4, Therefore, caution is required with the co-administration of fluticasone furoate nasal spray and ketoconazole or other potent cytochrome CYP3A4 inhibitors, ritonavir is not recommended because of the risk of systemic effect secondary to increased exposure to fluticasone furoate. Enzyme induction and inhibition data suggest that fluticasone furoate is unlikely to significantly alter the CYP450 – mediated metabolism of other compounds at clinically relevant intranasal dosages.

Hepatic impairment

Since fluticasone furoate undergoes extensive first-pass metabolism by the hepatic CYP450 isozyme, CYP3A4, the pharmacokinetics of fluticasone furoate may be altered in patients with hepatic impairment. The systemic exposure would be expected to be higher than that observed had the study been conducted after multiple doses and/or in patients with severe hepatic impairment. Therefore, fluticasone furoate nasal spray should be used with caution in patients with severe hepatic impairment.

Renal impairment

Fluticasone furoate is not detectable in the urine of healthy subjects following intranasal dosing. Less than 1 % of the dose-related material is excreted in the urine. No dosage adjustment is required in patients with renal impairment.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of fluticasone furoate in pregnant women. In animal studies glucocorticoids have been shown to induce malformations including cleft palate and intra-uterine growth retardation. This is not likely to be relevant for humans given recommended nasal doses which results in minimal systemic exposure. Fluticasone furoate should be used in pregnancy only if the benefits to the mother outweigh the potential risks to the foetus or child.

Breast-feeding

It is unknown whether nasal administered fluticasone furoate is excreted in human breast milk.

Administration of fluticasone furoate to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Fertility

There are no fertility data in humans.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during treatment with fluticasone furoate are epistaxis, nasal ulceration and headache. The most serious undesirable effects are rare reports of hypersensitivity reactions, including anaphylaxis (less than 1 case per 1000 patients).

Tabulated list of adverse reactions

There were over 2700 patients treated with fluticasone furoate in safety and efficacy studies for seasonal and perennial allergic rhinitis. Paediatric exposure to fluticasone furoate in safety

and efficacy studies in seasonal and perennial allergic rhinitis included 243 patients 12 to <18 years, 790 patients 6 to <12 years and 241 patients 2 to <6 years.
Data from large clinical trials were used to determine the frequency of adverse reactions.
The following convention has been used for the classification of frequencies: 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.

Immune system disorders	
Rare	Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria.
Nervous system disorders	
Common	Headache.
Eye disorders	
Not known	Transient ocular changes.
Respiratory, thoracic and mediastinal disorders	
Very common	*Epistaxis
Common	Nasal ulceration
Uncommon	Rhinalgia, nasal discomfort (including nasal burning, nasal irritation, and nasal soreness), nasal dryness.
Very rare	Nasal septum perforation
Musculoskeletal and connective tissue disorders (Children)	
Not known	**Growth retardation.

Description of selected adverse reactions
Epistaxis
*Epistaxis was generally mild to moderate in intensity. In adults and adolescents, the incidence of epistaxis was higher in longer-term use (more than 6 weeks) than in short-term use (up to 6 weeks).
Systemic effects
Systemic effects of nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods. Growth retardation has been reported in children receiving nasal corticosteroids.

4.9 Overdose
There are no data on the effects of acute or chronic overdosage with fluticasone furoate nasal spray. Because of low systemic bioavailability and an absence of acute drug-related systemic findings in clinical studies (with dosages of up to 440mcg/day for 2 weeks [4 times the maximum recommended daily dose]), overdose is unlikely to require any therapy other than observation.
Up to 2,640 mcg/day of fluticasone furoate (24 times the recommended adult dose) was administered intranasally to healthy human volunteers for 3 days. Single-and repeat-dose studies with orally inhaled fluticasone furoate doses of 50 to 4,000 mcg have shown decreased mean serum cortisol at doses of 500 mcg or higher. Continual overdosage with any corticosteroids may result in signs and symptoms of hypercorticism.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Fluticasone furoate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. The precise mechanism through which fluticasone furoate affects rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. Specific effects of fluticasone furoate demonstrated in *in vitro* and *in vivo* models included activation of the glucocorticoid response element, inhibition of pro-inflammatory transcription factors such as nuclear factor-kappa B (NFkB), and inhibition of antigen induced lung eosinophilia in sensitized rats.

Fluticasone furoate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor that is approximately 29.9 times that of dexamethasone and 1.7 times that of fluticasone propionate.

5.2 Pharmacokinetic properties

Absorption

Following intranasal administration of fluticasone furoate, most of the dose is eventually swallowed and under goes incomplete absorption and extensive first-pass metabolism in the liver and gut, resulting in negligible systemic exposure. At the highest recommended intranasal dosage of 110 mcg once daily for up to 12 months in adults and up to 12 weeks in children, plasma concentrations of fluticasone furoate are typically not quantifiable despite the use of a sensitive HPLC-MS/MS assay with a lower limit of quantification (LOQ) of 10 pg/mL. However in a 52-week study, fluticasone furoate was detected in high concentrations and above 500 pg/mL in a few isolated cases (<0.3%) and, in a single case the concentration was as high as 1,430 pg/mL. There was no relationship between these concentrations and the cortisol levels in these subjects. The reasons for these high concentrations are unknown.

Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral solution and intravenous dosing of radio-labeled drug have demonstrated that at least 30% of fluticasone furoate is absorbed and then rapidly cleared from plasma. Oral bioavailability is on average 1.26%, and the majority of the circulating radioactivity is due to inactive metabolites.

Distribution

Following intravenous administration, the mean volume of distribution at steady state is 608 L. Binding of fluticasone furoate to human plasma proteins is greater than 99%.

Metabolism

In vivo studies have revealed no evidence of cleavage of the furoate moiety to form fluticasone. Fluticasone furoate is cleared (total plasma clearance of 58.7 L/h) from systemic circulation principally by hepatic metabolism via the cytochrome (CY) P450 isozyme, CYP3A4. The principal route of metabolism is hydrolysis of the S-fluoromethyl carbothioate function to form the inactive 17(beta)-carboxylic acid metabolite.

Elimination

Fluticasone furoate and its metabolites are eliminated primarily in the faeces, accounting for approximately 101% and 90% of the orally and intravenously administered dose, respectively. Urinary excretion accounted for approximately 1% and 2% of the orally and intravenously administered dose, respectively. The elimination phase half-life averaged 15.1 hours following intravenous administration.

5.3 Preclinical safety data

Findings in general toxicology studies were similar to those observed with other glucocorticoids and are associated with exaggerated pharmacological activity. These findings

are not likely to be relevant for humans given recommended nasal doses which results in minimal systemic exposure. No genotoxic effects of fluticasone furoate have been observed in conventional genotoxicity tests. Further, there were no treatment-related increases in the incidence of tumours in two year inhalation studies in rats and mice.

6. Pharmaceutical particulars

6.1 Shelf life

24 months.

6.2 Special precautions for storage

Store in a cool place. Protect from light. Keep out of reach of children. Do not freeze. Shake well before each use. For external use only. For Nasal use only.

6.3 Nature and contents of container

Freeair is available in pack of 120 metered dose.

7. Marketed By

ALKEM

Alkem Laboratories Ltd.
ALKEM HOUSE,
S. B. Road, Lower Parel (West),
Mumbai - 400 013. INDIA.

8. DATE OF REVESION OF TEXT

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