SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

FLIXISONE

2. Qualitative and quantitative composition

Each spray delivers:

Fluticasone Furoate IH ..... 27.5 mcg

Active:

Fluticasone Furoate IH 0.055%w/w

Preservative:

Benzalkonium Chloride Solution BP ..... 0.030% w/w

Excipients ..... q.s

For full list of excipients, see section 6.1.

3. Pharmaceuticals form

Nasal Spray

White to off white aqueous suspension.

4. Clinical particulars

4.1 Therapeutic indication

FLIXISONE is indicated in adults, adolescents and children (6 years and over). FLIXISONE is indicated for the treatment of the symptoms of allergic rhinitis.

4.2 Posology and Method of administration

Posology

Adults and adolescents (12 years and over)

The recommended starting dose is two spray actuations (27.5 micrograms of fluticasone furoate per spray actuation) in each nostril once daily (total daily dose, 110 micrograms).

Once adequate control of symptoms is achieved, dose reduction to one spray actuation in each nostril (total daily dose 55 micrograms) may be effective for maintenance.

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

Children (6 to 11 years of age)

The recommended starting dose is one spray actuation (27.5 micrograms of fluticasone furoate per spray actuation) in each nostril once daily (total daily dose, 55 micrograms).

Patients not adequately responding to one spray actuation in each nostril once daily (total daily dose, 55 micrograms) may use two spray actuations in each nostril once daily (total daily dose, 110 micrograms).

Once adequate control of symptoms is achieved, dose reduction to one spray actuation in each nostril once daily (total daily dose, 55 micrograms) is recommended.

For full therapeutic benefit regular, scheduled usage is recommended. Onset of action has been observed as early as 8 hours after initial administration. However, it may take several days of treatment to achieve maximum benefit, and the patient should be informed that their symptoms will

improve with continuous regular use (see section 5.1). The duration of treatment should be restricted to the period that corresponds to allergenic exposure.

Children under 6 years of age
The safety and efficacy of Flixisone in children under the age of 6 years has not been established. Currently available data are described in section 5.1 and 5.2 but no recommendation on a posology can be made.

Elderly Patients
No dose adjustment is required in this population (see section 5.2).

Renal Impairment
No dose adjustment is required in this population (see section 5.2).

Hepatic Impairment
No dose adjustment is required in patients with hepatic impairment (see section 5.2).

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

4.4 Special warnings and precautions for use
Systemic corticosteroid effects
Systemic effects of nasal corticosteroid 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). Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. If there is evidence for higher than recommended doses being used, then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery. Fluticasone furoate 110 micrograms once daily was not associated with hypothalamic-pituitary-adrenal (HPA) axis suppression in adult, adolescent or paediatric subjects. However the dose of intranasal fluticasone furoate should be reduced to the lowest dose at which effective control of the symptoms of rhinitis is maintained. As

with all intranasal corticosteroids, the total systemic burden of corticosteroids should be considered whenever other forms of corticosteroid treatment are prescribed concurrently.
If there is any reason to believe that adrenal function is impaired, care must be taken when transferring patients from systemic steroid treatment to fluticasone furoate.

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.

Growth retardation
Growth retardation has been reported in children receiving nasal corticosteroids at licensed doses. A reduction in growth velocity has been observed in children treated with fluticasone furoate 110 micrograms daily for one year (see section 4.8 and section 5.1). Therefore, children should be maintained on the lowest possible efficacious dose which delivers adequate symptom control (see section 4.2). It is recommended that the growth of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid if possible, 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 (see section 5.1).

Patients on ritonavir
Concomitant administration with ritonavir is not recommended because of the risk of increased systemic exposure of fluticasone furoate (see section 4.5).

Excipients
This medicinal product contains benzalkonium chloride. Long-term use may cause oedema of the nasal mucosa.

4.5 Interaction with Other Medicinal Products and Other Forms Of Interaction
Interaction with CYP3A inhibitors
Fluticasone furoate is rapidly cleared by extensive first pass metabolism mediated by the cytochrome P450 3A4.
Based on data with another glucocorticoid (fluticasone propionate), that is metabolised by CYP3A4, coadministration with ritonavir is not recommended because of the risk of increased systemic exposure of fluticasone furoate.
Caution is recommended when co-administering fluticasone furoate with potent CYP3A inhibitors including cobicistat-containing products as an increase in the risk of systemic side effects is expected. Co-administration 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 a drug interaction study of intranasal fluticasone furoate with the potent CYP3A4 inhibitor ketoconazole there were more subjects with measurable fluticasone furoate concentrations in the ketoconazole group (6 of the 20 subjects) compared to placebo (1 out of 20 subjects). This small increase in exposure did not result in a statistically significant difference in 24 hour serum cortisol levels between the two groups.

The enzyme induction and inhibition data suggest that there is no theoretical basis for anticipating metabolic interactions between fluticasone furoate and the cytochrome P450 mediated metabolism of other compounds at clinically relevant intranasal doses. Therefore, no clinical studies have been conducted to investigate interactions of fluticasone furoate on other drugs.

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 (see section 5.2). 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

It 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 commo≥n1/10; Common ≥1/100 to <1/10; Uncommon ≥1/1000 to <1/100; Rare ≥1/10,000 to <1/1000; Very rare <1/10,000*;* Not known (cannot be estimated from the available data).

Immune system disorders	
Rare	Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria.
Nervous system disorders	
Common	Headache.
Eye disorders	
Not known	Transient ocular changes (see Clinical experience), vision blurred (see also section 4.4)

Respiratory, thoracic and mediastinal disorders	
Very common	*Epistaxis
Common	Nasal ulceration, dyspnoea**
Uncommon	Rhinalgia, nasal discomfort (including nasal burning, nasal irritation, and nasal soreness), nasal dryness.
Very rare	Nasal septum perforation
Not known	Bronchospasm
Musculoskeletal and connective tissue disorders (Children)	
Not known	***Growth retardation (see Clinical experience).

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 (see section 4.4). Growth retardation has been reported in children receiving nasal corticosteroids.

**Dyspnoea cases were reported in more than 1% of patients during clinical trials with fluticasone furoate; similar rates were also observed in placebo groups.

Paediatric population

The safety in children under 6 years has not been well established. Frequency, type and severity of adverse reactions observed in the paediatric population are similar to those in the adult population.

Epistaxis

*In paediatric clinical studies of up to 12 weeks duration the incidence of epistaxis was similar between patients receiving fluticasone furoate and patients receiving placebo.

Growth retardation

***In a one-year clinical study assessing growth in pre-pubescent children receiving 110 micrograms of fluticasone furoate once daily, an average treatment difference of -0.27 cm per year in growth velocity was observed compared to placebo (see Clinical efficacy and safety).

4.9 Overdose

In a bioavailability study, intranasal doses of up to 2640 micrograms per day were administered over three days with no adverse systemic reactions observed.

Acute overdose is unlikely to require any therapy other than observation.

5 Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nasal preparations, corticosteroids. ATC code: R01AD12

Mechanism of action:

Fluticasone furoate is a synthetic trifluorinated corticosteroid that possesses a very high affinity for the glucocorticoid receptor and has a potent anti-inflammatory action

5.2 Pharmacokinetic properties

Absorption

Fluticasone furoate undergoes incomplete absorption and extensive first-pass metabolism in the liver and gut resulting in negligible systemic exposure. The intranasal dosing of 110 micrograms once daily does not typically result in measurable plasma concentrations (<10 pg/ml). The absolute bioavailability for intranasal fluticasone furoate is 0.50 %, such that less than 1 microgram of fluticasone furoate would be systemically available after administration of 110 micrograms.

Distribution

The plasma protein binding of fluticasone furoate is greater than 99 %. Fluticasone furoate is widely distributed with volume of distribution at steady-state of, on average, 608l.

Biotransformation

Fluticasone furoate is rapidly cleared (total plasma clearance of 58.7 l/h) from systemic circulation principally by hepatic metabolism to an inactive 17β-carboxylic metabolite (GW694301X), by the cytochrome P450 enzyme CYP3A4. The principal route of metabolism was hydrolysis of the S-fluoromethylcarbothioate function to form the 17β-carboxylic acid metabolite. In vivo studies have revealed no evidence of cleavage of the furoate moiety to form fluticasone.

Elimination

Elimination was primarily via the faecal route following oral and intravenous administration indicative of excretion of fluticasone furoate and its metabolites via the bile. Following intravenous administration, the elimination phase half-life averaged 15.1 hours. Urinary excretion accounted for approximately 1 % and 2 % of the orally and intravenously administered dose, respectively.

Paediatric population

In the majority of patients fluticasone furoate is not quantifiable (< 10 pg/ml) following intranasal dosing of 110 micrograms once daily. Quantifiable levels were observed in 15.1 % of paediatric patients following intranasal dosing of 110 micrograms once daily and only 6.8 % of paediatric patients following 55 micrograms once daily. There was no evidence for higher quantifiable levels of fluticasone furoate in younger children (less than 6 years of age). Median fluticasone furoate concentrations in those subjects with quantifiable levels at 55 micrograms were 18.4 pg/ml and 18.9 pg/ml for 2-5 yrs and 6-11 yrs, respectively.

At 110 micrograms, median concentrations in those subjects with quantifiable levels were 14.3 pg/ml and 14.4 pg/ml for 2-5 yrs and 6-11 yrs, respectively. The values are similar to those seen in adults (12+) where median concentrations in those subjects with quantifiable levels were 15.4 pg/ml and 21.8 pg/ml at 55 micrograms and 110 micrograms, respectively.

Elderly

Only a small number of elderly patients≥(65 years, n=23/872; 2.6 %) provided pharmacokinetic data. There was no evidence for a higher incidence of patients with quantifiable fluticasone furoate concentrations in the elderly, when compared with the younger patients.

Renal impairment

Fluticasone furoate is not detectable in urine from healthy volunteers after intranasal dosing. Less than 1 % of dose-related material is excreted in urine and therefore renal impairment would not be expected to affect the pharmacokinetics of fluticasone furoate.

Hepatic impairment

There are no data with intranasal fluticasone furoate in patients with hepatic impairment. Data are available following inhaled administration of fluticasone furoate (as fluticasone furoate or fluticasone furoate/vilanterol) to subjects with hepatic impairment that are also applicable for intranasal dosing. A study of a single 400 microgram dose of orally inhaled fluticasone furoate in patients with moderate hepatic impairment (Child-Pugh B) resulted in increased C_{max} (42 %) and AUC(0-∞) (172 %) and a modest (on average 23 %) decrease in cortisol levels in patients compared to healthy subjects. Following repeat dosing of orally inhaled fluticasone furoate/vilanterol for 7 days, there was an increase in fluticasone furoate systemic exposure (on average two-fold as measured by AUC(0–24)) in subjects with moderate or severe hepatic impairment (Child-Pugh B or C) compared with healthy subjects. The increase in fluticasone furoate systemic exposure in subjects with moderate hepatic impairment (fluticasone furoate/vilanterol 200/25 micrograms) was associated with an average 34% reduction in serum cortisol compared with healthy subjects. There was no effect on serum cortisol in subjects with severe hepatic impairment (fluticasone furoate/vilanterol 100/12.5 micrograms). Based on these findings the average predicted exposure of 110 micrograms of intranasal fluticasone furoate in this patient population would not be expected to result in suppression of cortisol.

6.0 Pharmaceutical particulars

6.1 List of Excipients

Microcrystalline Cellulose & Carboxymethyl Cellulose Sodium (Avicel RC 591) USP, Polysorbate 80 BP, Glycerin BP(Anhyd.), Disodium Edetate BP, Benzalkonium Chloride Solution BP, Distilled Water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Storage

Store at a temperature not exceeding 30˚C, protect from light & moisture.

6.5 Nature and contents of container

6 gm of white to off white aqueous suspension filled in a 15 ml HDPE bottle fitted with metered dose pump, actuator and dust cap.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7.Marketing Authorisation

Biodeal Pharmaceuticals Pvt. Ltd.
Village, Sainimajra, Nalagarh-Ropar Road
Nalagarh-174101, Distt. Solan, H.P, India

8.Marketing Authorisation number

09378/10763/NMR/2023

9.Date of Authorisation

Dec 30, 2023

10. Date of revision of the text
Not Applicable

11. Dosimetry (if applicable)
Not Applicable

12. Instructions for preparation of radiopharmaceuticals (ifApplicable)
Not Applicable