1. NAME OF THE MEDICINAL PRODUCT:
Frinase 0.05% Nasal Spray

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each actuation contains: 50 mcg fluticasone propionate
For excipients, see 6.1.

3. PHARMACEUTIC FORM
Aqueous suspension for intranasal inhalation via metered dose atomizing pump.

4. CLINICAL DATA

4.1. *THERAPEUTIC INDICATIONS*

Frinase is indicated for the prophylaxis and treatment of seasonal allergic rhinitis (including hay fever) and perennial rhinitis. Fluticasone propionate has potent anti-inflammatory activity but when used topically on the nasal mucosa has no detectable systemic activity.

4.2. *POSOLOGY AND METHOD OF ADMINISTRATION*

Frinase is for administration by the intranasal route only.

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 perennal 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.
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 any of its ingredients.

4.4. ***SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE***

Local infections: infections of the nasal airways should be appropriately treated but do not constitute a specific contra-indication to treatment with fluticasone propionate Nasal Spray.

The full benefit of fluticasone propionate Nasal Spray may not be achieved until treatment has been administered for several days.

Care must be taken while transferring patients from systemic steroid treatment to fluticasone propionate Nasal Spray if there is any reason to suppose that their adrenal function is impaired.

Although fluticasone propionate 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.

Systemic effects of nasal corticosteroids may occur particularly at high doses prescribed for prolonged periods. These effects vary between patients and different corticosteroids. 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).

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. 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.

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 (see Section 5.1 for data on intranasal fluticasone propionate).

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

4.5. ***INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS***

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled 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.

In a small study using inhaled fluticasone propionate in healthy volunteers, the slightly less potent CYP3A inhibitor ketoconazole increased the exposure of fluticasone propionate after a single inhalation by 150%. This resulted in a greater reduction of plasma cortisol as compared with fluticasone propionate alone. Co-treatment with other potent CYP3A inhibitors, such as itraconazole, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side-effects. Caution is recommended and long-term treatment with such drugs should if possible be avoided.

4.6. ***USE DURING PREGNANCY AND LACTATION***

There is inadequate evidence of safety 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 fluticasone propionate Nasal Spray 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 the 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 Fluticasone propionate Nasal Spray is used in breast feeding mothers the therapeutic benefits must be weighed against the potential hazards to mother and baby.

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 with the following manifestations:	
	Cutaneous hypersensitivity reactions	Very rare
	Angioedema (mainly facial and oropharyngeal oedema)	Very rare
	Respiratory symptoms (bronchospasm)	Very rare
	Anaphylactic reactions	Very rare
Nervous system disorders	Headache, unpleasant taste, unpleasant smell.	Common
Eye disorders	Glaucoma, raised intraocular pressure, cataract These events have been identified from spontaneous reports following prolonged treatment.	Very rare
Respiratory, Thoracic & Mediastinal disorders	Epistaxis	Very common
	Nasal dryness, nasal irritation, throat dryness, throat irritation.	Common
	Nasal septal perforation.	Very rare

As with other nasal sprays, unpleasant taste and smell and headache have been reported.
As with other nasal sprays, dryness and irritation of the nose and throat, and epistaxis have been reported. Nasal septal perforation has also been reported following the use of intranasal corticosteroids.
Systemic effects of some nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods.

4.9. OVERDOSE

There are no data available on the effects of acute or chronic overdosage with Flixonase Aqueous Nasal Spray. Intranasal administration of 2 mg fluticasone propionate twice daily for seven days to healthy human volunteers has no effect on hypothalamo-pituitary-adrenal (HPA) axis function.
Inhalation or oral administration of high doses of corticosteroids over a long period may lead to suppression of HPA axis function.

5. PHARMACOLOGICAL PROPERTIES

5.1. *PHARMACODYNAMICS PROPERTIES*

Fluticasone propionate causes little or no hypothalamic-pituitary-adrenal axis suppression following intranasal administration.

Following intranasal dosing of fluticasone propionate, (200mcg/day) no significant change in 24h serum cortisol AUC was found compared to placebo (ratio1.01, 90%CI 0.9-1.14).

In a 1-year randomised, double-blind, placebo-controlled, parallel group growth study in pre-pubescent children aged 3 to 9 years (56 patients receiving intranasal fluticasone propionate and 52 receiving placebo,) no statistically significant difference in growth velocity was observed in patients receiving intranasal fluticasone propionate (200 micrograms per day nasal spray) compared to placebo. The estimated growth velocity over one year of treatment was 6.20 cm/year (SE=0.23) in the placebo group and 5.99 cm/year (SE=0.23) in the fluticasone propionate group; the mean difference between treatments in growth velocity after one year was 0.20 cm/year (SE=0.28, 95% CI= -0.35, 0.76). No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.

5.2. PHARMACOKINETIC PROPERTIES

Absorption:

Following intranasal dosing of fluticasone propionate, (200mcg/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 250-1000mcg 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 other sections of the SPC.

6. PHARMACEUTICAL DATA

6.1. LIST OF EXCIPIENTS

Benzyl alcohol
Benzalkonium chloride
Polysorbate 80
Anhydrous dextrose
Sodium chloride
Carbomethylcellulose sodium
Bidistilled water

6.2. INCOMPATIBILITIES

None

6.3. SHELF-LIFE

2 years

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC
Keep out of the reach of children

6.5. NATURE AND CONTENT OF CONTAINER

Frinase Nasal Spray is supplied in an amber glass bottle fitted with a metering, atomizing pump. Pack size of 120 metered sprays.
One amber glass bottle in a carton box including package leaflet.

6.6. INSTRUCTIONS FOR USE AND HANDLING, AND DISPOSAL

Shake gently before use.

7. MARKETING AUTHORIZATION HOLDER

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8. DATA OF REVISION OF THE TEXT :

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9. REFERENCE :

https://www.medicines.org.uk/emc/product/845