PRODUCT INFORMATION

FLIXONASE ALLERGY & HAYFEVER 24 HOUR

NAME
Fluticasone propionate

DESCRIPTION
FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Aqueous Nasal Spray (0.05% w/w) is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomising spray pump. Each 100 mg of spray delivered by the nasal adaptor contains 50 µg of fluticasone propionate.

FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Aqueous Nasal Spray also contains the following excipients: anhydrous glucose, cellulose - dispersible, sodium carboxymethylcellulose, phenethyl alcohol, benzalkonium chloride solution, polysorbate 80, hydrochloric acid, water - purified.

CHEMICAL NAME
S-Fluoromethyl 6α, 9α-difluoro-11ß-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1, 4-diene-17ß-carbothioate.

STRUCTURE

![Chemical Structure](image)

CAS: 80474-14-2

MOLECULAR FORMULA: C_{25}H_{31}F_{3}O_{5}S
PHARMACOLOGY

Fluticasone propionate has potent anti-inflammatory activity but when used topically on the nasal mucosa at recommended doses has little or no detectable systemic activity.

Fluticasone propionate causes little or no hypothalamic-pituitary-adrenal axis suppression following intranasal administration. Following intranasal dosing of fluticasone propionate at the recommended dose (200 µg /day) no significant change in 24 h serum cortisol AUC was found compared to placebo (ratio 1.01, 90% CI 0.9-1.14). After intranasal administration of high dose FP (2,400 µg /day ie 12 times the recommended dose) a small change in 24 h serum cortisol AUC was found compared to placebo (ratio 0.79, 90% CI 0.71-0.89).

The effects of BKC on nasal mucosa and ciliary function have been examined, and no damaging effects have been observed in clinical studies of up to 1 year duration.

PHARMACOKINETICS

The data for paediatric pharmacokinetics show consistency with the adult findings.

Absorption
Following intranasal dosing of fluticasone propionate, (200 µg /day) steady-state maximum plasma concentrations were not quantifiable in most subjects (<0.01 ng/mL). The highest $C_{\text{max}}$ observed was 0.017 ng/mL. Following the recommended dose of 200 µg /day, the bioavailability could not be quantified in most subjects and the highest reported value was 1%. The amount of direct absorption in the nose is unknown but appears to be low 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 absolute bioavailability of intranasal FP at high doses (2,400 µg /day ie 12 times the recommended dose) is estimated as 1.26% (90% CI 0.85, 1.86).

Distribution
Fluticasone propionate has a large volume of distribution at steady-state (approximately 318 L). 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 250-1,000 µg dose range and are characterized by a high plasma clearance (CL=1.1 L/min). Peak plasma concentrations are reduced by approximately 98% within 3-4 hours and only low plasma concentrations were associated with the 7.8 h 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.
CLINICAL TRIALS

Rhinitis
Clinical Trials aimed to establish the efficacy of Fluticasone Propionate Aqueous Nasal Spray (FPANS) 200 µg once daily (od) in adults with seasonal or perennial rhinitis. To determine that these dosages were optimal for treating adults and to compare the efficacy of FPANS 200 µg od with that of the standard therapy, beclomethasone dipropionate aqueous nasal spray (BDPANS) 200 µg was used twice daily (bd). Clinical trial data is available from over 4,000 patients. Efficacy determination included daily symptom assessments.

Dose-ranging studies showed FPANS to be significantly superior to placebo in the relief of symptoms of rhinitis, even at very low doses (25 µg twice daily), although higher doses (eg 200 µg daily) provided significant improvements more rapidly.

Once daily doses of 200 µg FPANS have been shown to be efficacious in patients with seasonal rhinitis. For the relief of adult perennial rhinitis, 200 µg once daily was as effective as 100 µg twice daily.

Sinus pain & pressure
In patients with allergic rhinitis, fluticasone propionate aqueous nasal spray has also been shown to be of benefit for the management of associated sinus pain and pressure.

Two 14 days, randomised, double blind, parallel group clinical studies were performed in 401 adult and adolescent patients aged ≥12 years. Both studies compared FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Nasal Spray 200 µg once daily, administered as two 50 µg sprays per nostril, with placebo. The primary endpoint for both studies was the mean change from baseline in the patient-rated sinus pain and pressure score at week 2. In both studies, FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Nasal Spray provided significantly greater improvement compared with placebo for the primary endpoint (p<0.05). The magnitude of the improvement was 10 points compared to placebo and approximately 35 points from baseline (baseline score for this symptom was 75 on a 0-100 scale). The sinus pain and pressure score was also significantly decreased in the FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Nasal Spray treated group over the entire 2 week study period (p<0.05).

Treatment with FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Nasal Spray provided significantly greater improvement in symptoms of nasal congestion during week 1, 2 and overall during the 2 week study period (p<0.05). The overall improvement in congestion compared to placebo was 10 points and approximately 37 points from baseline (baseline score for this symptom was 78 on a 0-100 scale).

INDICATIONS
Fluticasone Propionate Aqueous Nasal Spray is indicated for the short-term (3 – 6 months) prevention or treatment of seasonal allergic rhinitis and perennial rhinitis in adults and children over 12 years old.
CONTRAINDICATIONS

Fluticasone Propionate Aqueous Nasal Spray is contraindicated in patients with a hypersensitivity to any of its ingredients, or a history of allergic reaction to other corticosteroid medicines.

PRECAUTIONS

Local infection: Infections of the nasal airways should be appropriately treated but do not constitute a specific contra-indication to treatment with Fluticasone Propionate Aqueous Nasal Spray.

Although some beneficial effects of Fluticasone Propionate Aqueous Nasal Spray may be observed within 24 hours, the full benefit of Fluticasone Propionate Aqueous 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 Aqueous Nasal Spray if there is any reason to suppose that their adrenal function is impaired.

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, particularly to control eye symptoms.

Rare instances of glaucoma and increased intra-ocular pressure have been reported following administration of intranasal corticosteroids, as a class effect.

Candidiasis of the throat can occur in patients treated with intranasal steroids. Special care should be taken when treating patients who may be susceptible to candida infections (eg diabetics).

Because of the inhibitory effect of these drugs on wound healing, patients with recent nasal septal ulcers, nasal surgery or nasal trauma should not use intranasal corticosteroids until healing has occurred.

Adrenocortical function

Intranasal steroid products are designed to deliver drug directly to the nasal mucosa in order to minimise overall systemic glucocorticoid exposure and side effects. However systemic effects such as HPA axis suppression, reduction of bone density and retardation of growth rate in children may occur with intranasal steroids, particularly at high doses prescribed for prolonged periods of time.

The lowest dose of FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Nasal Spray that causes suppression of the HPA axis or effects on bone mineral density or growth retardation has not yet been established. However, the systemic bioavailability of fluticasone propionate is low (estimated at 1.26% using high doses), when given as FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Aqueous Nasal Spray, and this limits the potential for such systemic side effects. Measurement of serum cortisol and 24 hour urinary cortisol in the clinical studies in adults did not suggest any HPA axis suppression with recommended doses. Studies of effects on the HPA axis in children have not been conducted.
Carcinogenicity, Mutagenicity and Impairment of Fertility
Fluticasone propionate has no mutagenic effect in vivo or in vitro, no tumorigenic potential in rodents and is non-irritant and non-sensitising in animal models.

No evidence of a tumorigenic effect was observed in either a 2 year study in rats receiving doses of fluticasone propionate up to 57 µg /kg/day by inhalation or in an 18 month study in mice receiving oral doses of fluticasone propionate up to 1 mg/kg/day. There was no evidence of a mutagenic potential in a standard battery of mutagenicity assays.

Use in Pregnancy: (Category B3)
There is insufficient evidence of safety of fluticasone propionate in human pregnancy. Systemically absorbed corticosteroids are known to induce foetotoxic and teratogenic effects in rodent studies. However, equivalent effects have not been reported when these compounds have been given to humans during pregnancy. Reproductive toxicity studies with fluticasone propionate in mice and rats have shown the expected foetotoxic and teratogenic effects at subcutaneous doses of 100 to 150 µg /kg/day and above. As with previous compounds of this class, these effects are unlikely to be relevant to human therapy. Direct intranasal application ensures minimal systemic exposure. As with other drugs, the use of FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Aqueous Nasal Spray during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Use in Lactation
The excretion of fluticasone propionate into human breast milk has not been investigated. Subcutaneous administration of tritiated drug to lactating rats resulted in measurable radioactivity in both plasma and milk (levels in milk were 3-7 times plasma levels) 1-8 hours post-dosing. However plasma levels in patients following intranasal application of fluticasone propionate at recommended doses are low and the amount of fluticasone ingested by the newborn is estimated to be very small as a consequence of very low maternal plasma concentration.

Effects on ability to drive and use machinery
Fluticasone propionate is unlikely to affect the ability to drive or use machinery.

INTERACTIONS
Care should be taken when co-administering known, strong CYP3A4 inhibitors, eg. Ritonavir and ketoconazole, as there is potential for increased systemic exposure to fluticasone propionate.

ADVERSE REACTIONS
Adverse reactions in controlled clinical studies with FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Nasal Spray have been primarily associated with irritation of the nasal mucous membranes and are consistent with those expected from application of a topical medication to an already inflamed membrane. The adverse reactions reported by patients treated with FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Nasal Spray were similar to those reported by patients receiving placebo.

The most frequently reported adverse reactions (>1% in any treatment group) considered by the investigator to be potentially related to FLIXONASE ALLERGY & HAYFEVER 24
HOUR Fluticasone Nasal Spray or placebo in trials of seasonal allergic rhinitis are listed below. These studies conducted in 948 adults and in 499 children evaluated 14-28 days of treatment with recommended doses of FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Nasal Spray compared with placebo.

**Adverse Reactions Reported Most Frequently in Clinical Trials of Seasonal Allergic Rhinitis**

<table>
<thead>
<tr>
<th></th>
<th>Adults (age &gt; 12 years)</th>
<th>Children (age 4-11 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FANS 100 µg bd (n=312)</td>
<td>Placebo (n=314)</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Nasal burning</td>
<td>2.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1.3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Runny nose</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Blood in nasal mucus</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1.6</td>
<td>3.0</td>
</tr>
<tr>
<td>Sneezing</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Crusting in nostrils</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>0</td>
<td>1.2</td>
</tr>
<tr>
<td>Nasal ulcer</td>
<td>&lt;1</td>
<td>1.2</td>
</tr>
<tr>
<td>Headache</td>
<td>1.3</td>
<td>1.2</td>
</tr>
</tbody>
</table>

|                          | FANS 200 µg od (n=322) | Placebo (n=167) |
|                          | %                       | %               |
| Nasal burning            | 3.4                     | 2.4            |
| Pharyngitis              | 1.6                     | <1             |
| Runny nose               | 1.6                     | <1             |
| Blood in nasal mucus     | 1.6                     | 0              |
| Epistaxis                | 2.8                     | 3.7            |
| Sneezing                 | 1.2                     | <1             |
| Crusting in nostrils      | 0                       | 0              |
| Nasal congestion         | 0                       | 0              |
| Nasal ulcer              | 0                       | 1.2            |
| Headache                 | 2.5                     | 1.2            |

|                          | FANS 200 µg od (n=164) | Placebo (n=168) |
|                          | %                       | %               |
| Nasal burning            | 1.8                     | 1.2            |
| Pharyngitis              | <1                      | 0              |
| Runny nose               | <1                      | <1             |
| Blood in nasal mucus     | <1                      | <1             |
| Epistaxis                | 2.2                     | 3.6            |
| Sneezing                 | 2.2                     | 0              |
| Crusting in nostrils      | 0                       | 0              |
| Nasal congestion         | 0                       | 1.2            |
| Nasal ulcer              | 0                       | 1.2            |
| Headache                 | 1.9                     | 1.2            |

FANS: FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Aqueous Nasal Spray

In two 6 month trials involving 831 patients aged 12-75 years with perennial allergic rhinitis, the adverse reactions reported by patients treated with FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Nasal Spray were similar in type and incidence to those reported in seasonal trials, with the exception of epistaxis (≤13.3%) and blood in nasal mucus (≤8.3%). In addition to the events reported most frequently in the seasonal trials, patients receiving FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Nasal Spray in the 6 month trials reported nasal soreness (≤2.5%), nasal excoriation (≤2.0%), sinusitis (≤1.6%) and nasal dryness (≤1.3%).

Infrequent adverse reactions (incidence of 0.1%-1% and greater than placebo) reported by patients receiving fluticasone propionate aqueous nasal spray at the recommended daily dose of 200 µg (or 100 µg per day for children 4-11 years of age) in the aforementioned clinical trials included pharyngeal irritation, nasal stinging, nausea and vomiting, unpleasant smell and taste, and sinus headache (0.3%); lacrimation, eye irritation, xerostomia, cough, urticaria and rash (0.2%); and nasal septum perforation (0.1%).

In two clinical trials that investigated FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Nasal Spray in the management of the symptoms of sinus pain and pressure associated with allergic rhinitis, the adverse reactions considered by the investigator to be potentially drug related were similar in type to those reported in the seasonal trials. The more frequently reported drug related adverse reactions (≥1% in any treatment group) was epistaxis (2%), nasal burning (1%), blood in nasal mucus (1%) and sore throat (1%). The studies were conducted in 401 patients aged 12-74 years and evaluated 14 days of treatment with recommended doses of FLIXONASE ALLERGY & HAYFEVER 24 HOUR Fluticasone Nasal Spray compared with placebo.
Post-Marketing Surveillance
In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of fluticasone propionate in clinical practice.

General
Hypersensitivity reactions including angioedema, skin rash, oedema of the face or tongue, pruritis, wheezing, dyspnoea and rarely, bronchospasm and anaphylaxis/anaphylactic reactions have been reported.

Ear, Nose and Throat
Alteration or loss in sense of taste and/or smell, sore throat, throat irritation and dryness, hoarseness, and voice changes.

Eye
Dryness and irritation of the eyes, conjunctivitis and blurred vision. There have been very rare reports of glaucoma, raised intraocular pressure and cataracts.

DOSAGE AND ADMINISTRATION
Fluticasone propionate is for administration by the intranasal route only. Although some beneficial effects may be seen within 24 hours, 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.

When symptoms are under control, a maintenance dose of one spray into each nostril once a day may be used. If symptoms reoccur the dosage may be increased accordingly. The minimum dose at which effective control of symptoms is maintained should be used.

Shake gently before use.

It is necessary to prime the pump before first use or after a period of non-use (1 week or more). After initial priming (a few sprays/actuations), each actuation delivers 50 µg of fluticasone propionate in 100 mg of formulation through the nasal adapter.

For the treatment of seasonal allergic rhinitis and perennial rhinitis in adults and children over 12 years old
Two sprays into each nostril once a day, preferably in the morning. The maximum daily dose should not exceed 200 µg (4 sprays) per day.

Elderly
The normal adult dosage is applicable.

OVERDOSAGE
There are no data available on the effects of acute or chronic overdosage with Fluticasone Propionate Aqueous Nasal Spray. Intra-nasal administration of 2,400 µg fluticasone per day (ie 12 times the recommended dose) for four days to healthy human volunteers caused a small degree of suppression of adrenal steroid production.
Suppression of adrenal steroid production may give rise to typical signs and symptoms of Cushing’s disease, such as buffalo hump, puffiness of face, hypertension and elevated blood glucose. If such a condition were to occur, care should be taken to wean the patient slowly off the steroid due to the probability of adrenal impairment. Recovery from impaired adrenocortical function caused by prolonged steroid therapy is usually slow and has been known to last up to 12 months.

PRESENTATION

Fluticasone Propionate Aqueous Nasal Spray is supplied in an amber glass bottle fitted with a metering, atomising pump, nasal adaptor and a dust cover. Bottles of approximately 60 or approximately 120 metered sprays, when used as recommended.

Fluticasone Propionate Aqueous Nasal Spray contains the antimicrobial preservatives benzalkonium chloride (BKC) and phenethyl alcohol.

STORAGE CONDITIONS

Fluticasone Propionate Aqueous Nasal Spray should be stored below 30°C. Protect from light. Do not refrigerate.

POISON SCHEDULE: S2 (PHARMACY MEDICINE)

SPONSOR

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