

PRODUCT INFORMATION

FLIXONASE ALLERGY & HAYFEVER 24 HOUR

NAME

Fluticasone propionate

DESCRIPTION

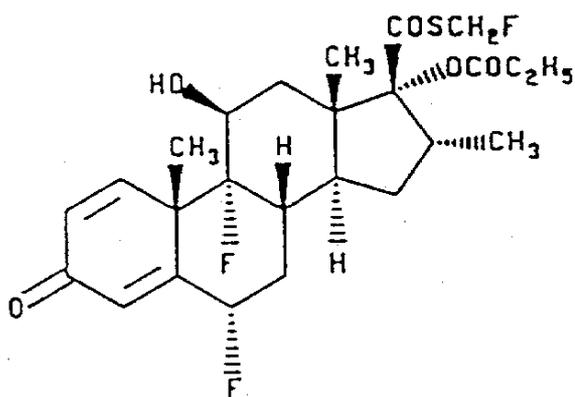
FLIXONASE ALLERGY & HAYFEVER 24 HOUR Nasal Spray (0.05% w/w) is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomising spray pump. Each 100 mg of spray delivered by the nasal adaptor contains 50 µg of fluticasone propionate.

FLIXONASE ALLERGY & HAYFEVER 24 HOUR 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 6 α , 9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy-androsta-1, 4-diene-17 β -carbothioate.

STRUCTURE



CAS: 80474-14-2

MOLECULAR FORMULA: C₂₅H₃₁F₃O₅S

PHARMACOLOGY

Mechanism of Action

Fluticasone propionate is a glucocorticoid steroid which has potent anti-inflammatory activity by acting via the glucocorticoid receptor. 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 (HPA) axis suppression following intranasal administration. Following intranasal dosing of fluticasone propionate at the recommended dose (200 µg /day) no significant change in 24 hour serum cortisol AUC was found compared to placebo (ratio 1.01, 90% CI 0.9-1.14). After intranasal administration of high dose –fluticasone propionate (2,400 µg /day i.e. 12 times the recommended dose) a small change in 24 hour 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.

Pharmacodynamic Effects

Fluticasone propionate has been shown to significantly reduce inflammatory mediators in both the early and late phase reactions of allergic rhinitis.

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_{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 total systemic absorption arising from both nasal and oral absorption of the swallowed dose is therefore negligible. The absolute bioavailability of intranasal fluticasone propionate at high doses (2,400 µg /day i.e. 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 intravenously 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 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 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 Nasal Spray treated group over the entire 2 week study period ($p < 0.05$).

Treatment with FLIXONASE ALLERGY & HAYFEVER 24 HOUR 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

FLIXONASE ALLERGY & HAYFEVER 24 HOUR Nasal Spray is indicated for the prophylaxis and treatment of allergic rhinitis for up to 6 months in adults 18 years and over.

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

If improvement is not seen within 7 days of continuous use treatment should be stopped and the advice of a doctor sought.

If after 7 days of continuous use, symptoms have improved but are not adequately controlled then the advice of a pharmacist or doctor should be sought.

The nasal spray should not be used for more than 6 months continuously without consulting a doctor.

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.

Care must be taken when withdrawing patients from systemic steroid treatment, and commencing therapy with intranasal fluticasone propionate, particularly if there is any reason to suspect that their adrenal function is impaired.

Systemic effects of nasal corticosteroids have been reported, 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.

Reduced growth velocity has been observed in children treated with intranasal corticosteroids.

Medical advice should be sought before using Flixonase Allergy & Hayfever 24 Hour in the case of:

- Concomitant use of other corticosteroid products, such as tablets, creams, ointments, asthma medications, similar nasal sprays or eye/nose drops.
- Fever or an infection in the nasal passages or sinuses.
- Recent injury or surgery to the nose, or problems with ulceration in the nose.

During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects (*see Interactions*).

The full benefit of Fluticasone Propionate Aqueous Nasal Spray may not be achieved until treatment has been administered for several days.

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 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 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)

The use of intranasal fluticasone propionate during pregnancy requires that the benefits be weighed against possible risks associated with the product or with any alternate therapy.

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.

The use of FLIXONASE ALLERGY & HAYFEVER 24 HOUR Nasal Spray during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus. Medical advice should be sought before use if pregnant.

Use in Lactation

The use of intranasal fluticasone propionate during lactation requires that the benefits be weighed against possible risks associated with the product or with any alternate therapy.

The excretion of fluticasone propionate into human breast milk has not been investigated. Subcutaneous administration of titrated 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.

Medical advice should be sought before use if breast-feeding.

Effects on ability to drive and use machinery

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

INTERACTIONS

Under normal circumstances, very 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.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects.

Studies have shown that 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. Nevertheless, care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole), as there is potential for increased systemic exposure to fluticasone propionate.

ADVERSE REACTIONS

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, since these rates were generally comparable to those in the active treatment group.

Immune system disorders

Very rare: Hypersensitivity reactions, anaphylaxis/anaphylactic reactions, bronchospasm, skin rash, oedema of the face or tongue.

Nervous system disorders

Common: Headache, unpleasant taste, unpleasant smell.

Eye disorders

Very rare: Glaucoma, raised intraocular pressure, cataract.

Respiratory, thoracic and mediastinal disorders

Very common: Epistaxis.

Common: Nasal dryness, nasal irritation, throat dryness, throat irritation.

Very rare: Nasal septal perforation.

DOSAGE AND ADMINISTRATION

Flixonase Allergy & Hayfever 24 Hour is for administration by the intranasal route only.

Adults 18 years and over: For the prophylaxis and treatment of seasonal allergic rhinitis and perennial rhinitis:-

The recommended dose is two sprays into each nostril once a day (200 micrograms per day), preferably in the morning. Once control is achieved the dose should be titrated down to one spray in each nostril once a day (100 micrograms per day).

Although some beneficial effects may be seen within 24 hours, for full therapeutic benefit daily 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.

The maximum daily dose should not exceed four sprays (200mcg) into each nostril.

Prophylaxis of allergic rhinitis requires treatment before contact with allergen.

For full therapeutic benefit regular usage is essential.

Adolescents 12-17 years: Use only on medical advice.

Do not use in children under 12 years of age.

Elderly:-

The normal adult dosage is applicable.

OVERDOSAGE

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 from patients available on the effects of acute or chronic overdose with intranasal fluticasone propionate. 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 a polypropylene bottle fitted with a metering, atomising pump, nasal adaptor and a dust cover. It contains approximately 60 or 120 metered sprays, when used as recommended.

Not all packs may be marketed.

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

STORAGE CONDITIONS

FLIXONASE ALLERGY & HAYFEVER 24 HOUR Nasal Spray should be stored below 30°C. Protect from light. Do not freeze.

POISON SCHEDULE: S2 (PHARMACY MEDICINE)

SPONSOR

GlaxoSmithKline Consumer Healthcare.
82 Hughes Avenue
Ermington NSW 2115.

DATE OF TGA APPROVAL: 9th November 2015.

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