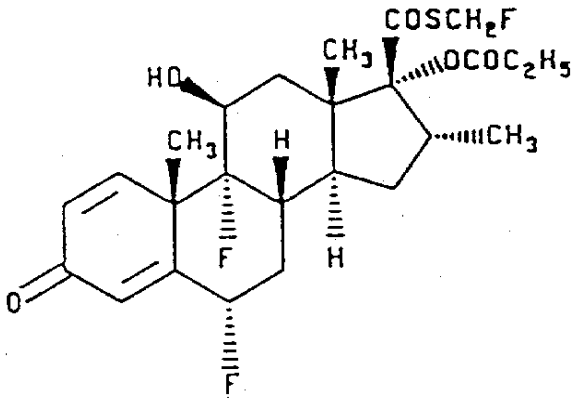
PRODUCT INFORMATION

FLIXONASE® NASULE™ DROPS

NAME OF MEDICINE: Fluticasone propionate

Flixonase Nasule Drops are an aqueous suspension of fluticasone propionate.

The chemical structure of fluticasone propionate is as follows:



CAS NUMBER: 80474-14-2

DESCRIPTION:

The chemical name of fluticasone propionate is S-Fluoromethyl 6α, 9α-difluoro-11ß-hydroxy-16α-methyl-3-oxo-17 α-propionyloxy-androsta-1, 4-diene-17ß-carbothioate. The molecular formula of fluticasone propionate is $C_{25}H_{31}F_3O_5S$.

Flixonase Nasule Drops also contain the following excipients: polysorbate 20, sorbitan monolaurate, sodium phosphate - dibasic dihydrate, sodium phosphate - dibasic anhydrous, sodium chloride, water for injections.

PHARMACOLOGY:

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

Fluticasone propionate causes little or no hypothalamic-pituitary-adrenal (HPA) axis suppression following intranasal or topical (dermal) administration and only causes overt HPA axis suppression after very high oral doses (10mg qds, i.e. 40mg daily, and above).

Pharmacokinetics:

After recommended doses of intranasal fluticasone propionate plasma levels are low. Systemic bioavailability for the nasal drop formula is extremely low (mean value 0.06%).
Following intravenous administration the pharmacokinetics of fluticasone propionate are proportional to the dose, and can be described by three exponentials.

Absolute oral bio-availability is negligible (<1%) due to a combination of incomplete absorption from the gastro-intestinal tract and extensive first pass metabolism.

Fluticasone propionate is extensively distributed within the body (Vss is approximately 300 litre). Plasma protein binding is 91%. After intravenous administration, fluticasone propionate has a very high clearance (estimated Cl 1.1 litre/min) indicating extensive hepatic extraction. It is extensively metabolised by CYP3A4 enzyme to an inactive carboxylic derivative.

Peak plasma concentrations are reduced by approximately 98% within 3-4 hours, and only low plasma concentrations are associated with the terminal half life, which is approximately 8 hours.

Following oral administration of fluticasone propionate, 87-100% of the dose is excreted in the faeces as parent compound or as metabolites.

As fluticasone propionate is given at very low doses, any effect on co-administered drug is unlikely.

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

CLINICAL TRIALS:

The clinical trials program evaluated the efficacy and safety of fluticasone propionate (FP) nasal drops in the treatment of nasal polyposis in patients ≥ 16 years old with mild to moderate polyps. Two main trials were conducted. Both studies were placebo-controlled, and consisted of 12 weeks randomised treatment followed by 12 weeks open treatment.

The first trial (FLTB3045) was double-blind and compared 400 μg fluticasone propionate once daily (od) with placebo for 12 weeks. A total of 104 patients were randomised to treatment, after which all received 400 μg fluticasone propionate od for a further 12 weeks. Six patients (5 from the placebo group) were withdrawn from the randomised phase, while there were no withdrawals during the open label phase. At the end of the treatment period 27% of patients in the FP group showed a reduction in polyp size compared to 16% in the placebo group. This difference was not statistically significant. However, Peak Nasal Inspiratory Flow showed a significant improvement during FP treatment, as did all associated symptoms of rhinitis. The improvement in PNIF is particularly important as relief of nasal obstruction is a main benefit that patients require from treatment with topical steroids.

A second study (FLTB3046) compared 400 μg fluticasone propionate once daily (od) and twice daily (bd) with placebo over 12 weeks, after which most received 400 μg fluticasone propionate od for a further 12 weeks. A total of 142 patients were randomised to treatment, with 16 patients withdrawn after randomisation (10 from the placebo group). 107 patients entered the open label phase. At the end of the 12 week treatment period, 15% of patients in the placebo group showed an improvement in polyp size, 24% in the FP 400 μg od group, and 41% in the 400 μg bd group. The difference in improvement between FP 400 μg bd and placebo was statistically significant. In addition, both doses of FP showed a significant improvement in PNIF, an improvement in the clinical assessment of nasal blockage and rhinitis, and a reduction in nasal discomfort. FP 400 μg bd showed greater improvements than 400 μg od for all symptoms.

In both studies, serum cortisol concentrations were measured at baseline and at the end of the randomised phase to assess effects of treatment on the HPA axis. No significant differences were observed between the fluticasone and placebo groups.

Once daily (400μg/day) and twice daily (800μg/day) dosing has not been studied beyond 24 and 12 weeks respectively.

INDICATIONS:

Flixonase Nasule Drops are indicated for the treatment of mild to moderate nasal polyps and associated symptoms of nasal obstruction in adults and adolescents over 16 years of age.

CONTRAINDICATIONS:

Flixonase Nasule Drops are contraindicated in patients with a history of hypersensitivity to any components of the preparation.

PRECAUTIONS:

Local Infection: Infection of the nasal airways should be appropriately treated but does not constitute a contraindication to treatment with Flixonase Nasule Drops. After nasal surgery, healing must have occurred before use.

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

Systemic effects with 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.

The full benefit of Flixonase Nasule drops may not be achieved until treatment has been administered for several weeks.

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).

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.

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 in

adolescents, may occur with intranasal steroids, particularly at high doses prescribed for prolonged periods of time.

The lowest dose of Flixonase that causes suppression of the HPA axis, effects on bone mineral density or growth retardation has not yet been established. However, the systemic bioavailability of fluticasone propionate is low (estimated at 0.06%) when given as Flixonase Nasal Drops and this limits the potential for systemic side effects. Measurement of serum cortisol concentrations in the clinical studies did not suggest any HPA axis suppression with recommended doses.

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.

A fertility study in rats showed decreased mean fetal weight, retardation of ossification, and decreased postnatal viability at the dose of 50 µg/kg/day SC of fluticasone propionate.

Use in Pregnancy: (Category B3)

There is insufficient evidence of safety of fluticasone propionate in human pregnancy. Systemically absorbed corticosteroids are known to induce fetotoxic 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 fetotoxic and teratogenic effects at SC 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 Nasule Drops 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. As with other drugs, the use of Flixonase Nasule Drops during lactation requires that the benefits be weighed against possible risks associated with the product or with any alternative therapy.

Effects on ability to drive and use machinery:

Fluticasone propionate is unlikely to produce an effect.

INTERACTIONS WITH OTHER MEDICINES:

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 EFFECTS:

The following table lists the drug-related adverse events reported during the randomised treatment phase of the pivotal comparator trials (FLTB3045 and FLTB3046). These adverse events were considered by the investigator to be almost certainly, probably or possibly related to the study drug or of unknown or missing causality:

% Incidence of Drug-Related Adverse Events						
		FLTB3045		FLTB3046		
Disorder classification	Adverse event	PBO 1x daily n=52	FP 400µg 1x daily n=52	PBO n=47	FP 400µg 1x daily n=48	FP 400µg 2x daily n=47
		12 WEEK RANDOMISED PHASE				
Ear, Nose & Throat	Epistaxis	4	19	2	4	6
	Throat irritation	6	2	-	-	-
	Blood in Nasal Mucosa	-	2	-	-	-
	Dryness of nose	-	2	-	-	-
	Nasal Irritation	2	-	-	2	-
Gastrointestinal	Gum signs and symptoms	-	2	-	-	-
	Abdominal distension	-	-	-	-	4
	Nausea and vomiting	-	-	2	-	2
	Gastrointestinal gaseous symptoms	-	-	-	-	2
Neurology	Headaches	8	2	-	-	-
Skin disorders	Scabs	-	2	-	-	-
		12 WEEK OPEN LABEL PHASE				
		FP 400µg 1x daily n=47	FP 400µg 1x daily n=51	FP 400µg 1x daily n=33	FP 400µg 1x daily n=38	FP 400µg 1x daily n=36
Ear, Nose & Throat	Epistaxis	6	4	3	3	-

	Blood in Nasal Mucosa	-	2	-	-	-
	Nasal Irritation	-	-	-	-	3
Gastrointestinal	Gastrointestinal signs & symptoms	-	-	-	-	3
Skin disorders	Scabs	-	2	-	-	-

FP = Fluticasone Propionate Nasal Drops
PBO = placebo
Drug-related = Investigator's opinion of causality of almost certainly, probably or possibly related to the study drug or of unknown or missing causality.

As with other intranasal products, dryness and irritation of the nose and throat may occur.

Unpleasant taste or smell, epistaxis and hypersensitivity reactions, including skin rash and oedema of the face and tongue, have been reported.

Following the use of intranasal corticosteroids there have been rare reports of anaphylaxis/anaphylactoid reactions and bronchospasm. Cases of nasal septal perforation are extremely rare. There have also been very rare reports of glaucoma, raised intraocular pressure and cataract.

DOSAGE AND ADMINISTRATION:

For full therapeutic benefit regular usage is essential. Nasal polyps require regular medical assessment to monitor severity of the condition. The drops should be administered in a 'head down' position (see instructions for use).

Adults and adolescents over 16 years old:

The contents of one container (400μg in 400μl) to be instilled once or twice daily.
The dose should be divided evenly between both affected nostrils.

Unilateral polyposis rarely occurs, and could be indicative of other conditions. Diagnosis should be confirmed by a specialist, and management individualised by them.

Elderly:

The normal adult dosage is applicable.

Children:

There are insufficient data at present to recommend the use of fluticasone propionate for the treatment of nasal polyps in children.

Flixonase Nasule Drops are for administration by the intranasal route only. Contact with the eyes should be avoided.

Instructions for Use:

Gently blow each nostril, in turn, to clear. Open the foil pack by tearing off one side. Detach one Nasule and return the remaining containers, in the foil pack, to the carton. It is important to ensure that the contents of the container are well mixed before use. While holding the container horizontally by the larger tab, 'flick' the other end a few times and shake. Repeat this process several times until the entire contents of the container are completely mixed.

Hold the top of the container and flick or shake downwards with a quick motion. This will remove any liquid from the neck of the container. Hold then lower tab of the container securely and twist to remove the top.

The drops should be administered with the patient in the 'head down' position to ensure the medicine best reaches the affected area, as shown in the 'instructions for use' leaflet inside the pack.
One Nasule holds enough drops for use in both nostrils.

Discard containers after use.

OVERDOSAGE:

There are no data available from patients on the effects of acute or chronic overdosage with Flixonase Nasule Drops. In healthy volunteers, intranasal administration of 2mg fluticasone propionate twice daily for seven days had no effect on hypothalamic-pituitary-adrenal (HPA) axis function. Administration of doses higher than those recommended over a long period of time may lead to temporary suppression of adrenal function. In these patients, treatment with fluticasone propionate should be continued at a reduced dose sufficient to control symptoms; adrenal function generally recovers in a few days and can be verified by measuring plasma cortisol.

PRESENTATION AND STORAGE CONDITIONS:

Flixonase Nasule Drops are packed as strips of seven polyethylene Nasules, each of 400μl, within foil wrapping. Each polyethylene Nasule holds a single 400 μg dose of fluticasone propionate, sufficient for both nostrils. The Nasules are available in 4 x strips of seven units.

SHELF LIFE AND STORAGE CONDITIONS:

Flixonase Nasule Drops should be stored below 30°C.

Condensation may form on the inside of the foil pack during storage, but it is not a cause for concern.

Store upright. Protect from direct sunlight. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR:

GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street
Abbotsford, Victoria 3067

POISON SCHEDULE OF THE MEDICINE: S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 21 September 1999

DATE OF MOST RECENT AMENDMENT: 13 December 2013

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NASULES™ is a trade mark of the GlaxoSmithKline group of companies.

Version 3.0