AUSTRALIAN PRODUCT INFORMATION
FLIXONASE ALLERGY & HAYFEVER 24 HOUR

1 NAME OF THE MEDICINE
Fluticasone propionate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredients: 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.

For the full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM
Aqueous suspension of microfine fluticasone propionate. Each 100 mg of spray contains 50 micrograms of fluticasone propionate. Nasal spray, suspension.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF 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.
4.3 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified 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 SECTION 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

**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.

**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.

**Use in hepatic impairment**

No data is available

**Use in renal impairment**

No data is available

**Use in the elderly**

The normal adult dosage is applicable.
Paediatric use

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

Do not use in children under 12 years of age.

**Effects on laboratory tests**

No data available.

4.5 **INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

4.6 **FERTILITY, PREGNANCY AND LACTATION**

**Effects on fertility**

No data available.
Use in pregnancy – 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 mg/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.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (Undesirable effects)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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.
**Not Known:** Vision blurred

**Respiratory, thoracic and mediastinal disorders**

**Very common:** Epistaxis.
**Common:** Nasal dryness, nasal irritation, throat dryness, throat irritation.
**Very rare:** Nasal septal perforation, Nasal ulcer.

### 4.9 OVERDOSE

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 overdosage 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.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 PHARMACODYNAMIC PROPERTIES

**Mechanism of action**

Fluticasone propionate is a glucocorticosteroid 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.

**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).

5.2 PHARMACOKINETIC PROPERTIES

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 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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. There was no evidence of a mutagenic potential in a standard battery of mutagenicity assays.
**Carcinogenicity**

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.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **LIST OF EXCIPIENTS**

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.

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

Contains no sugar, lactose or gluten.

6.2 **INCOMPATIBILITIES**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 **SHELF LIFE**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 **SPECIAL PRECAUTIONS FOR STORAGE**

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

6.5 **NATURE AND CONTENTS OF CONTAINER**

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.

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 **PHYSICOCHEMICAL PROPERTIES**

**Chemical structure**

S-Fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1, 4-diene-17β-carbothioate.
CAS number
Fluticasone Propionate  80474-14-2

Molecular Formula
C_{29}H_{31}F_{3}O_{3}S

7 MEDICINE SCHEDULE (POISONS STANDARD)
S2 (PHARMACY MEDICINE)

8 SPONSOR
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9 DATE OF FIRST APPROVAL
FLIXONASE® ALLERGY & HAYFEVER 24 HOUR
(AUST R 72724) 9th November 2015.

10 DATE OF REVISION
23 July 2019
### SUMMARY TABLE OF CHANGES

<table>
<thead>
<tr>
<th>Section Changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Reformatted Product Information to new form.</td>
</tr>
<tr>
<td>3.0</td>
<td>Addition of statement for <em>pharmaceutical form section</em>.</td>
</tr>
<tr>
<td>4.4</td>
<td>Addition of a statement in <em>precautions sections</em> for visual disturbances.</td>
</tr>
<tr>
<td>4.8</td>
<td>Addition of a statement under <em>Eye disorders</em> for- blurred vision and under <em>Respiratory, thoracic and mediastinal disorders</em>- nasal ulcer.</td>
</tr>
</tbody>
</table>

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