Fluticasone-propionate

QUALITATIVE AND QUANTITATIVE COMPOSITION
FLIXONASE 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 micrograms of fluticasone propionate.

PHARMACEUTICAL FORM
Nasal spray, suspension.

CLINICAL PARTICULARS
Indications
FLIXONASE Aqueous Nasal Spray is indicated for the prophylaxis and treatment of seasonal allergic rhinitis including hay fever, and perennial rhinitis. In patients with allergic rhinitis, FLIXONASE Aqueous Nasal Spray is also indicated for the management of associated sinus pain and pressure. Fluticasone propionate has potent anti-inflammatory activity but when used topically on the nasal mucosa has no detectable systemic activity.

Dosage and Administration
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 three to four days of treatment. FLIXONASE Aqueous Nasal Spray is for administration by the intranasal route only.
For the prophylaxis and treatment of seasonal allergic rhinitis and perennial rhinitis:

• Adults and children over 12 years of age
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. The maximum daily dose should not exceed four sprays into each nostril.

• Children aged 4 to 11 years
One spray into each nostril once a day, preferably in the morning. 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.

• Elderly
The normal adult dosage is applicable.

Contraindications
FLIXONASE Aqueous Nasal Spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

Warnings and Precautions
Local infection: Infections of the nasal airways should be appropriately treated but do not constitute a specific contraindication to treatment with intranasal fluticasone propionate.
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.
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 FLIXONASE Aqueous Nasal Spray may not be achieved until treatment has been administered for several days.
Although FLIXONASE 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.
The excretion of fluticasone propionate into human breast milk has not been investigated. When measurable plasma levels were obtained in lactating laboratory rats following subcutaneous administration, there was evidence of fluticasone propionate in the breast milk. However, plasma levels in patients following intranasal application of fluticasone propionate at recommended doses are likely to be low.

Effects on Ability to Drive and Use Machines
Fluticasone propionate is unlikely to produce an effect.

Adverse Reactions
Adverse events are listed below by system organ class and frequency. Frequencies are defined as:

- **very common**: ≥1 in 10
- **common**: ≥1 in 100 and <1 in 10
- **uncommon**: ≥1 in 1,000 and <1 in 100
- **rare**: ≥1 in 10,000 and <1 in 1,000
- **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.
As with other nasal sprays, unpleasant taste and smell and headache have been reported.

Eye disorders
Very rare: Glaucoma, raised intraocular pressure, cataract.
A very small number of spontaneous reports have been identified following prolonged treatment. However, clinical trials of up to one year duration have shown that intranasal fluticasone propionate is not associated with an increased incidence of ocular events including cataract, increased intraocular pressure or glaucoma.

Respiratory, thoracic and mediastinal disorders
Very common: Epistaxis.

Common: Nasal dryness, nasal irritation, throat dryness, throat irritation. As with other intranasal products, dryness and irritation of the nose and throat, and epistaxis have been reported.

Very rare: Nasal septal perforation. Nasal septal perforation has been reported following the use of intranasal corticosteroids.

Overdose
There are no data from patients available on the effects of acute or chronic overdosage with intranasal fluticasone propionate. In healthy volunteers, intranasal administration of 2 mg 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 dose sufficient to control symptoms; adrenal function will recover in a few days and can be monitored by measuring plasma cortisol.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics
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 axis suppression following intranasal administration.

Following intranasal dosing of fluticasone propionate, (200 micrograms/day) no significant change in 24 h serum cortisol AUC was found compared to placebo (ratio: 1.01, 90% CI 0.9 to 1.14).

Pharmacokinetics
Absorption
Following intranasal dosing of fluticasone propionate (200 micrograms/day), steady-state maximum plasma concentrations were not quantifiable in most subjects (less than 0.01 nanograms/ml). The highest Cmax observed was 0.017 nanograms/ml. Direct absorption in the nose is negligible due to the low aqueous solubility with the majority of the dose being eventually swallowed. Absolute oral bioavailability is negligible (less than 1%) due to a combination of incomplete absorption from the gastro-intestinal tract and extensive first pass 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 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 i.v. administered fluticasone propionate is linear over the 250 to 1000 micrograms dose range and is characterised by a high plasma clearance (CL=1.1 l/min). Peak plasma concentrations are reduced by approximately 98% within 3 to 4 h and only low plasma concentrations were associated with the 7.8 h terminal half-life. The renal clearance of fluticasone propionate is negligible (less than 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.
Pre-clinical Safety Data
Toxicology has shown only those class effects typical of a potent corticosteroid, and these only at doses greatly in excess of those proposed for therapeutic use. No novel effects were identified in repeat dose toxicity tests, reproductive toxicology studies or teratology studies.

Fluticasone propionate is devoid of mutagenic activity in vitro and in vivo and showed no tumorigenic potential in rodents. It is both non-irritant and non-sensitising in animal models.

PHARMACEUTICAL PARTICULARS

List of Excipients
Dextrose (anhydrous)
Microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC591)
Phenylethyl alcohol
Benzalkonium chloride
Polysorbate 80
Dilute hydrochloric acid
Purified water.

Incompatibilities
None reported.

Shelf Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
Store below 30°C.

Nature and Contents of Container
FLIXONASE Aqueous Nasal Spray is supplied in an amber glass bottle fitted with a metering, atomising pump, nasal adaptor and a dust cover. Each bottle provides approximately 120 metered sprays, when used as recommended.

Instructions for Use/Handling
Shake gently before use.
Before using FLIXONASE Aqueous Nasal Spray you must wash your hands and remove the dust cap on the spray.

PRIMING THE SPRAY
If it is a new bottle, or hasn’t been used for a few days, you will need to “prime” the spray so that it works properly.

• Holding the bottle upright put your thumb on the base of the bottle and a finger on each side of the spray nozzle.
• Continue to hold the bottle upright, but point the spray away from you.
• Press down with your fingers keeping your thumb steady. The spray should come out in a fine mist.

If it works: go to the section called “USING THE SPRAY”
If the spray doesn’t work: or if you think it may be blocked, go to the section called “ CLEANING THE SPRAY”. DO NOT use a pin or anything sharp to try to unblock the spray or make the spray hole bigger. It will break the spray mechanism.

USING THE SPRAY (Follow these instructions carefully)
1. Shake the bottle gently.
2. Gently blow your nose to clear.
3. Holding the spray upright put your thumb on the base of the bottle and a finger on each side of the spray nozzle.
4. Close off one nostril with a finger and put the spray nozzle into the open nostril.
5. Tilt your head forward slightly to keep the bottle upright. Start to breathe in through your nose and press down with your fingers. Leave the spray in your nostril while breathing out through your mouth.
6. Take a second spray into the same nostril by repeating step 5 above.
7. Take the spray out and repeat steps 3 to 6 in the other nostril.
8. After using the spray, wipe the nozzle with a clean tissue and replace the dust cap.

CLEANING THE SPRAY
• Your nasal spray should be cleaned at least once a week.
• Remove the dust cap and then gently pull upwards to remove the spray nozzle.
• Wash the nozzle and dust cap under warm tap water. Allow to dry at room temperature, then place the nozzle and dust cap back on the bottle.
• If the nozzle becomes blocked, it can be removed as above and left to soak in warm water. Rinse with cold tap water, dry and refit.
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