FLIXONASE™ AQUEOUS NASAL SPRAY

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.

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.

Reduced growth velocity has been observed in children treated with intranasal corticosteroids. Therefore, children should be maintained on the lowest dose which achieves adequate symptom control.

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*).

Visual disturbance has been reported by patients using systemic and/or topical corticosteroids. If a patient has blurred vision or other visual disturbances, consider evaluation of possible causes which may include cataract, glaucoma or central serous chorioretinopathy.

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.

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 intranasal or inhaled 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.

Pregnancy and Lactation

As with other drugs, the use of intranasal fluticasone propionate during pregnancy and lactation requires that the benefits be weighed against possible risks associated with the product or with any alternative therapy.

There is inadequate evidence of safety in human pregnancy. In animal reproduction studies, adverse effects typical of potent corticosteroids are only seen at high systemic exposure levels; direct intranasal application ensures minimal systemic exposure.

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 (≥1/10), 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.

As with other nasal sprays, unpleasant taste and smell and headache have been reported.

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.

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

Very rare: Nasal septal perforation, nasal ulcers.

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 HPA axis suppression following intranasal administration.

Following intranasal dosing of fluticasone propionate, (200 micrograms/day) no significant change in 24 hour 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 C_{max} 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 hours and only low plasma concentrations were associated with the 7.8 hour 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 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 one of two presentations:

- an amber glass bottle fitted with a metering, atomising pump, nasal adaptor and a dust cover.
- a polypropylene bottle fitted with a metering, atomising pump, nasal adaptor and a dust cover.

Instructions for Use/Handling

The spray has a dust cap which protects the nozzle and keeps it clean. Remember to take this off before using the spray. A new spray (or one that has not been used for a few days), may not work first time so you will need to prepare the nasal spray following the instructions under '**Preparing the nasal spray**'.

Preparing the nasal spray

You must prepare the nasal spray:

- Before you use it for the first time
- If you have not used it for a few days
- If you have just cleaned it following the instructions under 'Cleaning the nasal spray'.

Preparing the nasal spray helps to make sure you always get the full dose of medicine. Follow these steps:

- Shake the nasal spray and remove the dust cap **(picture 1)**
- Hold the nasal spray upright and point the nozzle away from you.
- Put your forefinger and middle finger on the collar either side of the nozzle and put your thumb underneath the bottle. **(picture 2)**
- Keep your thumb still, and press down firmly on the collar with your fingers to release a fine spray into the air. **(picture 2)**
- The nasal spray is now ready for use.
- If you think the nozzle may be blocked, don't use a pin or anything sharp to clear it.
- Try to clean it by following the instructions under **"Cleaning the nasal spray"**.

Pictures for markets taking a glass bottle:

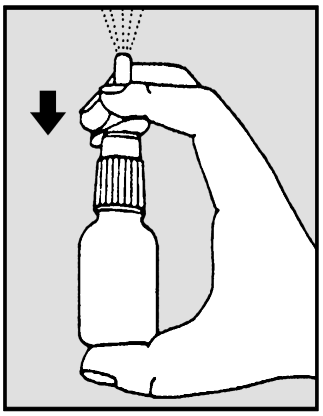
Picture 1

Picture 2

Pictures for markets taking a polypropylene bottle:

Picture 1

Picture 2



Using the nasal spray

1. Shake the nasal spray and remove the dust cap.
2. Blow your nose to clear your nostrils.
3. Close one nostril with your finger and carefully place the nozzle in the other nostril. Tilt your head forward a little bit and hold the nasal spray upright. **(picture 3a and 3b)**
4. As you breathe in through your nose, press down firmly on the collar with your fingers. **(picture 3a and 3b)**
5. Breathe out through your mouth.
6. Repeat steps **3** to **4** for your other nostril.
7. After using your spray, wipe the nozzle carefully with a clean tissue or handkerchief.
8. Replace the dust cap. **(picture 4 *glass bottle only*)**

Pictures for markets taking a glass bottle:

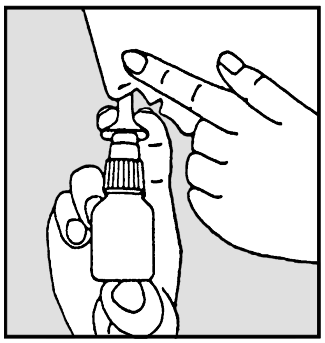
Picture 3a

Picture 3b

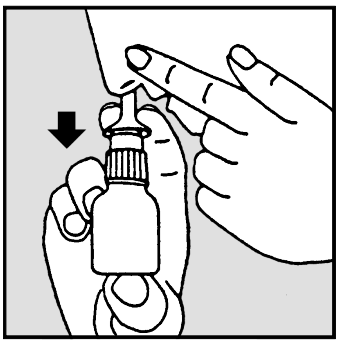
Picture 4

Pictures for markets taking a polypropylene bottle:

Picture 3a



Picture 3b



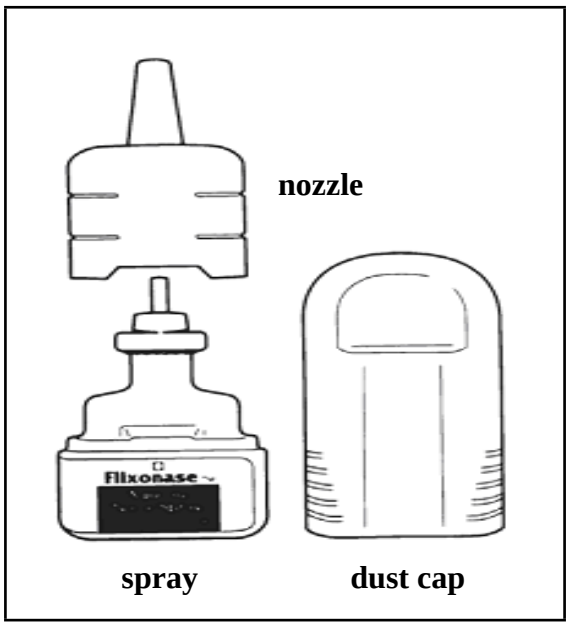
Cleaning the nasal spray

You must clean your nasal spray at least once a week to stop the nozzle from blocking up. Follow these steps:

- Remove the dust cap.
- Remove the nozzle by pulling upwards on the collar. **(picture 5 *glass bottle only*)**
- Soak the nozzle and dust cap in warm water for a few minutes.
- Then rinse under a running tap.
- Shake off the excess water and let them dry in a warm place.
- Put the nozzle back on the spray.
- Prepare the nasal spray following the instructions under **'Preparing the nasal spray'** so that it is ready for use.

Picture for glass bottle only:

Picture 5



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