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IMPORTANT SAFETY INFORMATION FOR HEALTHCARE PROFESSIONALS

Flixonase Allergy Relief – restriction of use to adults (aged over 18 years) only due to growth velocity reduction concerns in children

Date: 20 November 2013

Dear Healthcare Professional,

GlaxoSmithKline Consumer Healthcare (GSK), with the agreement of the Irish Medicines Board, wishes to inform you about GSK's decision to change the minimum age of patients for whom use of Flixonase Allergy Relief (fluticasone propionate nasal spray) without medical supervision is approved.

Summary:

Several clinical trials have shown that young children who use intranasal corticosteroids (including Flixonase Allergy Relief) daily for 1 year experienced a reduction in their rate of growth. In some of these trials, the mean difference in height was small yet significant. It is not known how intermittent use of intranasal corticosteroids might affect growth.

Flixonase Allergy Relief should be used in adults only (aged over 18 years).

Children or adolescents under 18 years of age who are currently using Flixonase Allergy Relief must see their doctor to discuss treatment options for their allergic rhinitis symptoms.

It is GSK's view that intranasal fluticasone for prophylaxis and treatment of allergic rhinitis should not be used in children without medical supervision.

Further information

Flixonase Allergy Relief is an intranasal corticosteroid spray indicated for prophylaxis and treatment of allergic rhinitis.

Please note that this change only refers to Flixonase Allergy Relief. There are currently other fluticasone propionate nasal spray products licensed for use in children under medical supervision.

Call for reporting

Suspected adverse reactions should be reported to the IMB using a Yellow Card obtained either from the IMB or electronically via the website at www.imb.ie. Adverse reactions can also be reported to the IMB by calling 01 676 4971.

Suspected adverse reactions with Flixonase Allergy Relief can also be reported to GSK at 01 495 5511.

For the complete prescribing and safety information, I am attaching the updated Summary of Product Characteristics for Flixonase Allergy Relief.

If you have questions about Flixonase Allergy Relief, please contact us at 01 495 5000.

Yours sincerely,

Dr Simon Arnold
Medical Director, Europe

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Flixonase Allergy Relief 50 micrograms per dose Nasal Spray

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each actuation delivers 100mg of suspension containing 50 micrograms of fluticasone propionate.

Excipients: also includes 20 micrograms of Benzalkonium Chloride per spray.

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, suspension
A white, opaque aqueous suspension intended for intranasal administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Flixonase Allergy Relief is indicated for the prophylaxis and treatment of allergic rhinitis, including hayfever and that caused by other airborne allergens such as house dust mite and animal dander.

4.2 Posology and method of administration

Flixonase Allergy Relief is for administration by the intranasal route only.

Adults 18 years and over: for the prophylaxis and treatment of allergic rhinitis:
Two sprays into each nostril once a day, preferably in the morning. Once control is achieved the dose should be titrated down to the lowest effective dose of one spray in each nostril once a day (100 micrograms per day).

In some cases two sprays into each nostril twice daily may be required for short periods to achieve control of symptoms, after which the dose should be titrated down to the lowest effective dose (see above).

The maximum daily dose should not exceed four sprays into each nostril.

Elderly patients:
The normal adult dosage is applicable.

Children and adolescents under 18 years of age:
Do not use in those under 18 years of age.

Onset of action in the treatment of allergic rhinitis has been observed in some patients as early as 2-4 hours after use, with most users achieving symptomatic relief within 12 hours of treatment.

Prophylaxis of allergic rhinitis requires treatment before contact with allergen.

For full therapeutic benefit regular usage is recommended.

Maximum benefit may require 3-4 days of continuous treatment in some people (see section 5.1 *Pharmacodynamic Properties*).

When Flixonase Allergy Relief is discontinued, it may be several days before symptoms recur.

4.3 Contraindications

Flixonase Allergy Relief is contra-indicated in patients with a hypersensitivity to any of its ingredients.

4.4 Special warnings and precautions for use

The full benefit of fluticasone propionate aqueous nasal spray may not be achieved until treatment has been administered for several days.

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 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 of nasal corticosteroids (such as Cushing's syndrome, hypertension, adrenal suppression) may occur, 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 Relief 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Under normal circumstances, very low plasma concentrations of flucticasone 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 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.

Pregnancy
There is inadequate evidence of the safety of fluticasone propionate 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 use of Flixonase Allergy Relief should be avoided during pregnancy unless thought essential by the doctor. Medical advice should be sought before use if pregnant.

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

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 very low.

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

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 are 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.
Very rare: Nasal septal perforation.

As with other nasal sprays, dryness and irritation of the nose and throat and epistaxis have been reported. Nasal septal perforation has also been reported following the use of intranasal corticosteroids.

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 is no data available on the effects of acute or chronic overdosage with Flixonase Allergy Relief. Intranasal administration of fluticasone propionate at 20 times the recommended dose in adults (2mg twice daily) for seven days to healthy human volunteers had no effect on hypothalamic-pituitary-adrenal axis function.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Fluticasone propionate is a glucocorticosteroid, which has potent anti-inflammatory activity by acting via the glucocorticoid receptor. However, when used at up to four times the recommended daily dose on the nasal mucosa, has no detectable systemic activity and causes little or no hypothalamic pituitary adrenal (HPA) axis suppression. Following intranasal dosing of fluticasone propionate, (200mcg/day) no significant change in 24h serum cortisol AUC was found compared to placebo (ratio1.01, 90%CI 0.9-1.14).

Fluticasone propionate has been shown to significantly reduce inflammatory mediators in both the early and late phase reactions of allergic rhinitis. Placebo-controlled clinical studies have demonstrated that intranasal fluticasone propionate significantly reduces the symptoms of allergic rhinitis.

In addition, comparator studies have shown that intranasal fluticasone propionate is more effective in treating nasal symptoms of allergic rhinitis than anti-histamines, but with a similar beneficial effect on eye symptoms.

As with other aqueous nasal sprays, fluticasone propionate has an immediate cooling, lavage effect in the nose, and onset of action has been observed in clinical trials to be as early as 2-4 hours after use. However, most users experience symptomatic relief within 12 hours of starting treatment. Maximum relief may require 3-4 days of continuous treatment in some people.

Quality of life studies have shown fluticasone propionate, when compared with placebo and antihistamine, to improve patient's routine functioning, including physical and social functioning, and sense of well-being as exemplified by effects on indicators of emotional health, mental health, and energy. In addition, patients receiving fluticasone propionate report superior impact (as compared to placebo and antihistamine) on work and school attendance and performance, and home and leisure/recreation activities affected as a result of symptoms of allergic rhinitis.

5.2. Pharmacokinetic properties

Absorption: Following intranasal dosing of fluticasone propionate, (200mcg/day) steady-state maximum plasma concentrations were not quantifiable in most subjects (<0.01ng/mL). The highest Cmax observed was 0.017ng/mL. Direct absorption in the nose is negligible 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.

Distribution: Fluticasone propionate has a large volume of distribution at steady-state (approximately 318L). 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 250-1000mcg dose range and are characterised by a high plasma clearance (CL=1.1L/min). Peak plasma concentrations are reduced by approximately 98% within 3-4 hours and only low plasma concentrations were associated with the 7.8h 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

No clinically relevant findings were observed in preclinical studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose (Anhydrous)
Microcrystalline Cellulose and Carboxymethylcellulose (Carmellose) Sodium (Avicel RC591)
Phenylethyl Alcohol
Benzalkonium Chloride
Polysorbate 80
Dilute Hydrochloric Acid
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Do not refrigerate.

6.5 Nature and contents of containers

Flixonase Allergy Relief is supplied in an amber glass Type I or III (Ph. Eur.) bottle fitted with a metering, atomising pump, nasal adapter and a dust cover.

Each bottle provides approximately 60 metered sprays, when used as recommended.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Shake gently before use.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Consumer Healthcare (Ireland) Ltd
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Trading as: Allen & Hanburys

8. MARKETING AUTHORISATION NUMBER

PA 678/95/1

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Date of first authorisation: 02 May 2003

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October 2013