PRESCRIBING INFORMATION

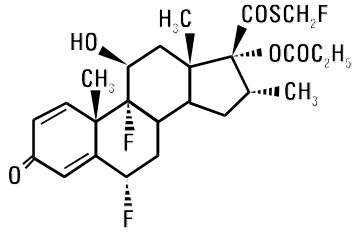
FLONASE®

(fluticasone propionate)
Nasal Spray, 50 mcg

SHAKE GENTLY
For Intranasal Use Only. **BEFORE USE.**

DESCRIPTION

Fluticasone propionate, the active component of FLONASE Nasal Spray, is a synthetic corticosteroid having the chemical name S-(fluoromethyl)6α,9-difluoro-11β-17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FLONASE Nasal Spray, 50 mcg is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. FLONASE Nasal Spray also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol, and has a pH between 5 and 7.

It is necessary to prime the pump before first use or after a period of non-use (1 week or more). After initial priming (6 actuations), each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. Each 16-g bottle of FLONASE Nasal Spray provides 120 metered sprays. After 120 metered sprays, the amount of fluticasone propionate delivered per actuation may not be consistent and the unit should be discarded.

CLINICAL PHARMACOLOGY

Mechanism of Action: Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity. In vitro dose response studies on a cloned human glucocorticoid receptor system involving binding and gene expression afforded 50% responses at 1.25 and 0.17 nM concentrations, respectively. Fluticasone propionate was 3-fold to 5-fold more potent

than dexamethasone in these assays. Data from the McKenzie vasoconstrictor assay in man also support its potent glucocorticoid activity.

In preclinical studies, fluticasone propionate revealed progesterone-like activity similar to the natural hormone. However, the clinical significance of these findings in relation to the low plasma levels (see Pharmacokinetics) is not known.

The precise mechanism through which fluticasone propionate affects allergic rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. In 7 trials in adults, FLONASE Nasal Spray has decreased nasal mucosal eosinophils in 66% (35% for placebo) of patients and basophils in 39% (28% for placebo) of patients. The direct relationship of these findings to long-term symptom relief is not known.

FLONASE Nasal Spray, like other corticosteroids, is an agent that does not have an immediate effect on allergic symptoms. A decrease in nasal symptoms has been noted in some patients 12 hours after initial treatment with FLONASE Nasal Spray. Maximum benefit may not be reached for several days. Similarly, when corticosteroids are discontinued, symptoms may not return for several days.

Pharmacokinetics: ***Absorption:*** The activity of FLONASE Nasal Spray is due to the parent drug, fluticasone propionate. Indirect calculations indicate that fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. After intranasal treatment of patients with allergic rhinitis for 3 weeks, fluticasone propionate plasma concentrations were above the level of detection (50 pg/mL) only when recommended doses were exceeded and then only in occasional samples at low plasma levels. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral dosing of radiolabeled drug have demonstrated that fluticasone propionate is highly extracted from plasma and absorption is low. Oral bioavailability is negligible, and the majority of the circulating radioactivity is due to an inactive metabolite.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 91% with no obvious concentration relationship. Fluticasone propionate is weakly and reversibly bound to erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism: The total blood clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This inactive metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid

receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations: Fluticasone propionate nasal spray was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained.

Drug-Drug Interactions: In a multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics. In another drug interaction study, coadministration of orally inhaled fluticasone propionate (1,000 mcg, 5 times the maximum daily intranasal dose) and ketoconazole (200 mg once daily) resulted in increased fluticasone propionate concentrations and reduced plasma cortisol area under the plasma concentration versus time curve (AUC), but had no effect on urinary excretion of cortisol. Due to very low plasma concentrations achieved after intranasal dosing, clinically significant drug interactions are unlikely; however, since fluticasone propionate is a substrate of cytochrome P450 3A4, caution should be exercised when known strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole) are coadministered with fluticasone propionate as this could result in increased plasma concentrations of fluticasone propionate.

Pharmacodynamics: In a trial to evaluate the potential systemic and topical effects of FLONASE Nasal Spray on allergic rhinitis symptoms, the benefits of comparable drug blood levels produced by FLONASE Nasal Spray and oral fluticasone propionate were compared. The doses used were 200 mcg of FLONASE Nasal Spray, the nasal spray vehicle (plus oral placebo), and 5 and 10 mg of oral fluticasone propionate (plus nasal spray vehicle) per day for 14 days. Plasma levels were undetectable in the majority of patients after intranasal dosing, but present at low levels in the majority after oral dosing. FLONASE Nasal Spray was significantly more effective in reducing symptoms of allergic rhinitis than either the oral fluticasone propionate or the nasal vehicle. This trial demonstrated that the therapeutic effect of FLONASE Nasal Spray can be attributed to the topical effects of fluticasone propionate.

In another trial, the potential systemic effects of FLONASE Nasal Spray on the hypothalamic-pituitary-adrenal (HPA) axis were also studied in allergic patients. FLONASE Nasal Spray given as 200 mcg once daily or 400 mcg twice daily was compared with placebo or oral prednisone 7.5 or 15 mg given in the morning. FLONASE Nasal Spray at either dose for 4 weeks did not affect the adrenal response to 6-hour cosyntropin stimulation, while both doses of oral prednisone significantly reduced the response to cosyntropin.

Clinical Trials: A total of 13 randomized, double-blind, parallel-group, multicenter, vehicle placebo-controlled clinical trials were conducted in the United States in adults and pediatric patients (4 years of age and older) to investigate regular use of FLONASE Nasal Spray in

patients with seasonal or perennial allergic rhinitis. The trials included 2,633 adults (1,439 men and 1,194 women) with a mean age of 37 (range, 18 to 79 years). A total of 440 adolescents (405 boys and 35 girls), mean age of 14 (range, 12 to 17 years), and 500 children (325 boys and 175 girls), mean age of 9 (range, 4 to 11 years) were also studied. The overall racial distribution was 89% white, 4% black, and 7% other. These trials evaluated the total nasal symptom scores (TNSS) that included rhinorrhea, nasal obstruction, sneezing, and nasal itching in known allergic patients who were treated for 2 to 24 weeks. Subjects treated with FLONASE Nasal Spray exhibited significantly greater decreases in TNSS than vehicle placebo-treated patients. Nasal mucosal basophils and eosinophils were also reduced at the end of treatment in adult studies; however, the clinical significance of this decrease is not known.

There were no significant differences between fluticasone propionate regimens whether administered as a single daily dose of 200 mcg (two 50-mcg sprays in each nostril) or as 100 mcg (one 50-mcg spray in each nostril) twice daily in 6 clinical trials. A clear dose response could not be identified in clinical trials. In 1 trial, 200 mcg/day was slightly more effective than 50 mcg/day during the first few days of treatment; thereafter, no difference was seen.

Two randomized, double-blind, parallel-group, multicenter, vehicle placebo-controlled 28-day trials were conducted in the United States in 732 patients (243 given FLONASE) 12 years of age and older to investigate "as-needed" use of FLONASE Nasal Spray (200 mcg) in patients with seasonal allergic rhinitis. Patients were instructed to take the study medication only on days when they thought they needed the medication for symptom control, not to exceed 2 sprays per nostril on any day, and not more than once daily. "As-needed" use was prospectively defined as average use of study medication no more than 75% of study days. Average use of study medications was 57% to 70% of days for all treatment arms. The studies demonstrated significantly greater reduction in TNSS (sum of nasal congestion, rhinorrhea, sneezing, and nasal itching) with FLONASE Nasal Spray 200 mcg compared to placebo. The relative difference in efficacy with as-needed use as compared to regularly administered doses was not studied.

Three randomized, double-blind, parallel-group, vehicle placebo-controlled trials were conducted in 1,191 patients to investigate regular use of FLONASE Nasal Spray in patients with perennial nonallergic rhinitis. These trials evaluated the patient-rated TNSS (nasal obstruction, postnasal drip, rhinorrhea) in patients treated for 28 days of double-blind therapy and in 1 of the 3 trials for 6 months of open-label treatment. Two of these trials demonstrated that patients treated with FLONASE Nasal Spray at a dose of 100 mcg twice daily exhibited statistically significant decreases in TNSS compared with patients treated with vehicle.

Individualization of Dosage: Patients should use FLONASE Nasal Spray at regular intervals for optimal effect.

Adult patients may be started on a 200-mcg once-daily regimen (two 50-mcg sprays in each nostril once daily). An alternative 200-mcg/day dosage regimen can be given as 100 mcg twice daily (one 50-mcg spray in each nostril twice daily).

Individual patients will experience a variable time to onset and different degree of symptom relief. In 4 randomized, double-blind, vehicle placebo-controlled, parallel-group allergic rhinitis

studies and 2 studies of patients in an outdoor "park" setting (park studies), a decrease in nasal symptoms in treated subjects compared to placebo was shown to occur as soon as 12 hours after treatment with a 200-mcg dose of FLONASE Nasal Spray. Maximum effect may take several days. Regular-use patients who have responded may be able to be maintained (after 4 to 7 days) on 100 mcg/day (1 spray in each nostril once daily).

Some patients (12 years of age and older) with seasonal allergic rhinitis may find as-needed use of FLONASE Nasal Spray (not to exceed 200 mcg daily) effective for symptom control (see Clinical Trials). Greater symptom control may be achieved with scheduled regular use. Efficacy of as-needed use of FLONASE Nasal Spray has not been studied in pediatric patients under 12 years of age with seasonal allergic rhinitis, or patients with perennial allergic or nonallergic rhinitis.

Pediatric patients (4 years of age and older) should be started with 100 mcg (1 spray in each nostril once daily). Treatment with 200 mcg (2 sprays in each nostril once daily or 1 spray in each nostril twice daily) should be reserved for pediatric patients not adequately responding to 100 mcg daily. Once adequate control is achieved, the dosage should be decreased to 100 mcg (1 spray in each nostril) daily.

Maximum total daily doses should not exceed 2 sprays in each nostril (total dose, 200 mcg/day). There is no evidence that exceeding the recommended dose is more effective.

INDICATIONS AND USAGE

FLONASE Nasal Spray is indicated for the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

Safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been adequately established.

CONTRAINDICATIONS

FLONASE Nasal Spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

WARNINGS

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

The concomitant use of intranasal corticosteroids with other inhaled corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis.

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Avoid spraying in eyes.

PRECAUTIONS

General: Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS: Pediatric Use).

Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the administration of FLONASE Nasal Spray. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of corticosteroids, including fluticasone propionate.

Use of excessive doses of corticosteroids may lead to signs or symptoms of hypercorticism and/or suppression of HPA function.

Although systemic effects have been minimal with recommended doses of FLONASE Nasal Spray, potential risk increases with larger doses. Therefore, larger than recommended doses of FLONASE Nasal Spray should be avoided.

When used at higher than recommended doses or in rare individuals at recommended doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of FLONASE Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral corticosteroid therapy.

In clinical studies with fluticasone propionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of treatment with FLONASE Nasal Spray. Patients using FLONASE Nasal Spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

Intranasal corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred.

Information for Patients: Patients being treated with FLONASE Nasal Spray should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay.

Patients should use FLONASE Nasal Spray at regular intervals for optimal effect. Some patients (12 years of age and older) with seasonal allergic rhinitis may find as-needed use of 200 mcg once daily effective for symptom control (see Clinical Trials).

A decrease in nasal symptoms may occur as soon as 12 hours after starting therapy with FLONASE Nasal Spray. Results in several clinical trials indicate statistically significant improvement within the first day or two of treatment; however, the full benefit of FLONASE Nasal Spray may not be achieved until treatment has been administered for several days. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

For the proper use of FLONASE Nasal Spray and to attain maximum improvement, the patient should read and follow carefully the patient's instructions accompanying the product.

Drug Interactions: In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg; 5 times the maximum daily intranasal dose) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased mean fluticasone propionate concentrations, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. This interaction may be due to an inhibition of cytochrome P450 3A4 by ketoconazole, which is also the route of metabolism of fluticasone propionate. No drug interaction studies have been conducted with FLONASE Nasal Spray; however, care should be exercised when fluticasone propionate is coadministered with long-term ketoconazole and other known cytochrome P450 3A4 inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 20 times the maximum recommended daily intranasal dose in adults and approximately 10 times the maximum recommended daily intranasal dose in children on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately 2 times the maximum recommended daily intranasal dose in adults and approximately equivalent to the maximum recommended daily intranasal dose in children on a mcg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 2 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively (approximately equivalent to and 4 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis, respectively) revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 25 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis) of fluticasone propionate to the rabbit. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY).

Fluticasone propionate crossed the placenta following oral administration of 100 mcg/kg to rats or 300 mcg/kg to rabbits (approximately 4 and 25 times, respectively, the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nursing Mothers: It is not known whether fluticasone propionate is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of 10 mcg/kg of tritiated fluticasone propionate (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis) resulted in measurable radioactivity in the milk. Since there are no data from controlled trials on the use of intranasal fluticasone propionate by nursing mothers, caution should be exercised when FLONASE Nasal Spray is administered to a nursing woman.

Pediatric Use: Six hundred fifty (650) patients aged 4 to 11 years and 440 patients aged 12 to 17 years were studied in US clinical trials with fluticasone propionate nasal spray. The safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been established.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory

evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including FLONASE Nasal Spray, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including FLONASE Nasal Spray, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

A 1-year placebo-controlled clinical growth study was conducted in 150 pediatric patients (ages 3 to 9 years) to assess the effect of FLONASE Nasal Spray (single daily dose of 200 mcg, the maximum approved dose) on growth velocity. From the primary population of 56 patients receiving FLONASE Nasal Spray~~subjects~~ and 52 receiving placebo ~~subjects~~, the point estimate for growth velocity with FLONASE Nasal Spray was 0.14 cm/year lower than that noted with placebo (95% confidence interval ranging from 0.54 cm/year lower than placebo to 0.27 cm/year higher than placebo). Thus, no statistically significant effect on growth was noted compared to placebo. No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.

The potential for FLONASE Nasal Spray to cause growth suppression in susceptible patients or when given at higher doses cannot be ruled out.

Geriatric Use: A limited number of patients 65 years of age and older (n = 129) or 75 years of age and older (n = 11) have been treated with FLONASE Nasal Spray in US and non-US clinical trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients.

ADVERSE REACTIONS

In controlled US studies, more than 3,300 patients with seasonal allergic, perennial allergic, or perennial nonallergic rhinitis received treatment with intranasal fluticasone propionate. In general, adverse reactions in clinical studies have been primarily associated with irritation of the nasal mucous membranes, and the adverse reactions were reported with approximately the same frequency by patients treated with the vehicle itself. The complaints did not usually interfere with treatment. Less than 2% of patients in clinical trials discontinued because of adverse events; this rate was similar for vehicle placebo and active comparators.

Systemic corticosteroid side effects were not reported during controlled clinical studies up to 6 months' duration with FLONASE Nasal Spray. If recommended doses are exceeded, however, or if individuals are particularly sensitive or taking FLONASE Nasal Spray in conjunction with administration of other corticosteroids, symptoms of hypercorticism, e.g., Cushing syndrome, could occur.

The following incidence of common adverse reactions (>3%, where incidence in fluticasone propionate-treated subjects exceeded placebo) is based upon 7 controlled clinical trials in which 536 patients (57 girls and 108 boys aged 4 to11 years, 137 female and 234 male adolescents and adults) were treated with FLONASE Nasal Spray 200 mcg once daily over 2 to 4 weeks and 2 controlled clinical trials in which 246 patients (119 female and 127 male adolescents and adults) were treated with FLONASE Nasal Spray 200 mcg once daily over 6 months. Also included in the table are adverse events from 2 studies in which 167 children (45 girls and 122 boys aged 4 to11 years) were treated with FLONASE Nasal Spray 100 mcg once daily for 2 to 4 weeks.

Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in Controlled Clinical Trials With FLONASE Nasal Spray in Patients ≥4 Years With Seasonal or Perennial Allergic Rhinitis

Adverse Experience	Vehicle Placebo (n = 758) %	FLONASE 100 mcg Once Daily (n = 167) %	FLONASE 200 mcg Once Daily (n = 782) %
Headache	14.6	6.6	16.1
Pharyngitis	7.2	6.0	7.8
Epistaxis	5.4	6.0	6.9
Nasal burning/nasal irritation	2.6	2.4	3.2
Nausea/vomiting	2.0	4.8	2.6
Asthma symptoms	2.9	7.2	3.3
Cough	2.8	3.6	3.8

Other adverse events that occurred in ≤3% but ≥1% of patients and that were more common with fluticasone propionate (with uncertain relationship to treatment) included: blood in nasal mucus, runny nose, abdominal pain, diarrhea, fever, flu-like symptoms, aches and pains, dizziness, bronchitis.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of fluticasone propionate in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate or a combination of these factors.

General: Hypersensitivity reactions, including angioedema, skin rash, edema of the face and tongue, pruritus, urticaria, bronchospasm, wheezing, dyspnea, and anaphylaxis/anaphylactoid reactions, which in rare instances were severe.

Ear, Nose, and Throat: Alteration or loss of sense of taste and/or smell and, rarely, nasal septal perforation, nasal ulcer, sore throat, throat irritation and dryness, cough, hoarseness, and voice changes.

Eye: Dryness and irritation, conjunctivitis, blurred vision, glaucoma, increased intraocular pressure, and cataracts.

Cases of growth suppression have been reported for intranasal corticosteroids, including FLONASE (see PRECAUTIONS: Pediatric Use).

OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS). Intranasal administration of 2 mg (10 times the recommended dose) of fluticasone propionate twice daily for 7 days to healthy human volunteers was well tolerated. Single oral doses up to 16 mg have been studied in human volunteers with no acute toxic effects reported. Repeat oral doses up to 80 mg daily for 10 days in volunteers and repeat oral doses up to 10 mg daily for 14 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. Acute overdosage with this dosage form is unlikely since 1 bottle of FLONASE Nasal Spray contains approximately 8 mg of fluticasone propionate.

The oral and subcutaneous median lethal doses in mice and rats were >1,000 mg/kg (>20,000 and >41,000 times, respectively, the maximum recommended daily intranasal dose in adults and >10,000 and >20,000 times, respectively, the maximum recommended daily intranasal dose in children on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION

Patients should use FLONASE Nasal Spray at regular intervals for optimal effect.

Adults: The recommended starting dosage in **adults** is 2 sprays (50 mcg of fluticasone propionate each) in each nostril once daily (total daily dose, 200 mcg). The same dosage divided into 100 mcg given twice daily (e.g., 8 a.m. and 8 p.m.) is also effective. After the first few days, patients may be able to reduce their dosage to 100 mcg (1 spray in each nostril) once daily for maintenance therapy. Some patients (12 years of age and older) with seasonal allergic rhinitis may find as-needed use of 200 mcg once daily effective for symptom control (see Clinical Trials). Greater symptom control may be achieved with scheduled regular use.

Adolescents and Children (4 Years of Age and Older): Patients should be started with 100 mcg (1 spray in each nostril once daily). Patients not adequately responding to 100 mcg may use 200 mcg (2 sprays in each nostril). Once adequate control is achieved, the dosage should be decreased to 100 mcg (1 spray in each nostril) daily.

The maximum total daily dosage should not exceed 2 sprays in each nostril (200 mcg/day). (See Individualization of Dosage and Clinical Trials sections.)

FLONASE Nasal Spray is not recommended for children under 4 years of age.

Directions for Use: Illustrated patient's instructions for proper use accompany each package of FLONASE Nasal Spray.

HOW SUPPLIED

FLONASE Nasal Spray 50 mcg is supplied in an amber glass bottle fitted with a white metering atomizing pump, white nasal adapter, and green dust cover in a box of 1 (NDC 0173-0453-01) with patient's instructions for use. Each bottle contains a net fill weight of 16 g and will provide 120 actuations. Each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. The correct amount of medication in each spray cannot be assured after 120 sprays even though the bottle is not completely empty. The bottle should be discarded when the labeled number of actuations has been used.

Store between 4° and 30°C (39° and 86°F).

GlaxoSmithKline
Research Triangle Park, NC 27709

April 29, 2003 RL-

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/s/

Badrul Chowdhury
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