CENTER FOR DRUG EVALUATION AND RESEARCH

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FINAL PRINTED LABELING

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TRIAL EXHIBIT
PTX0059
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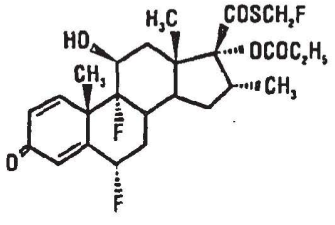
FLONASE®

(fluticasone propionate)
Nasal Spray, 50 mcg

SHAKE GENTLY BEFORE USE.

For Intranasal Use Only.

DESCRIPTION: Fluticasone propionate, the active ingredient of FLONASE Nasal Spray, is a synthetic corticosteroid with the chemical name of S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6. 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 (six actuations), each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. Each 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: 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 threefold to fivefold 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 seven 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, 1093 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 approximately 2000 times less affinity 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.

In a multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg three times daily) did not affect fluticasone propionate pharmacokinetics.

In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1000 mcg, 5 times the maximum daily intranasal dose) and ketoconazole (200 mg once daily) resulted in

increased fluticasone propionate concentrations, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Excretion: 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 was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained.

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, multicenter, vehicle-controlled clinical trials were conducted in the United States in adults and pediatric patients (4 years of age and older) with seasonal or perennial allergic rhinitis. The trials included 2633 adults (1439 men and 1194 women) with a mean age of 37 years (range, 18 to 79). A total of 440 adolescents (405 boys and 35 girls), mean age of 14 (range, 12 to 17), and 500 children (325 boys and 175 girls), mean age of 9 (range, 4 to 11) 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 six clinical trials. A clear dose response could not be identified in clinical trials. In one trial, 200 mcg/day was slightly more effective than 50 mcg/day during the first few days of treatment; thereafter, no difference was seen.

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Three randomized, double-blind, parallel, vehicle-controlled trials were conducted in 1191 patients with perennial nonallergic rhinitis. These trials evaluated the patient-rated total nasal symptom scores (nasal obstruction, postnasal drip, rhinorrhea) in patients treated for 28 days of double-blind therapy and in one 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 total nasal symptom scores compared with patients treated with vehicle.

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

Individual patients will experience a variable time to onset and different degree of symptom relief. In 4 randomized, double-blind, 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. Patients who have responded may be able to be maintained (after 4 to 7 days) on 100 mcg/day (one spray in each nostril once daily).

Pediatric patients (4 years of age and older) should be started with 100 mcg (one spray in each nostril once-a-day). Treatment with 200 mcg (two sprays in each nostril once daily or one 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 (one spray in each nostril) daily.

Maximum total daily doses should not exceed two 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.

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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.

Patients who are on immunosuppressant drugs are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in patients on immunosuppressant doses of corticosteroids. In such patients who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects 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.

PRECAUTIONS:

General: 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, suppression of HPA function, and/or reduction of growth velocity in children or teenagers. Physicians should closely follow the growth of children and adolescents taking corticosteroids, by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed.

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.

FLONASE Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infection; untreated local or systemic fungal or bacterial, or systemic viral infections or parasitic infection; 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 as directed since its effectiveness depends on its regular use. 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 the nasal spray and to attain maximum improvement, the patient should read and follow carefully the accompanying patient's instructions.

Drug Interactions: In a placebo-controlled, crossover study in eight healthy volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1000 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 the cytochrome P450 3A4 isoenzyme system 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 1000 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 when administered at high doses by the oral or subcutaneous routes. Furthermore, the compound did not delay erythroblast division in bone marrow.

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.

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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. When tritiated fluticasone propionate was administered to rats at a subcutaneous dose of 10 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis), radioactivity was excreted in the milk. Because other corticosteroids are excreted in human milk, caution should be exercised when FLONASE Nasal Spray is administered to a nursing woman.

Pediatric Use: Five hundred (500) patients aged 4 to 11 years of age 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.

Oral and, to a less clear extent, inhaled and intranasal corticosteroids have been shown to have the potential to cause a reduction in growth velocity in children and adolescents with extended use. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered (see PRECAUTIONS).

Geriatric Use: A limited number of patients above 60 years of age (n = 275) 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 3300 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's syndrome, could occur.

The following incidence of common adverse reactions (>3%, where incidence in fluticasone propionate-treated subjects exceeded placebo) is based upon seven controlled clinical trials in which 536 patients (57 girls and 108 boys aged 4 to 11 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 two 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 two studies in which 167 children (45 girls and 122 boys aged 4 to 11 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

	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.

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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, causal connection to fluticasone propionate, occurrence during clinical trials, 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.

OVERDOSAGE: Chronic overdosage with FLONASE Nasal Spray 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 one bottle of FLONASE Nasal Spray contains approximately 8 mg of fluticasone propionate.

The oral and subcutaneous median lethal doses in mice and rats were >1000 mg/kg (>20000 and >41000 times, respectively, the maximum recommended daily intranasal dose in adults and >10000 and >20000 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 as directed since its effectiveness depends on its regular use.

Adults: The recommended starting dosage in **adults** is two sprays (50 mcg of fluticasone propionate each) in each nostril once-a-day (total daily dose, 200 mcg). The same dosage divided into 100 mcg given twice-a-day (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 (one spray in each nostril) once daily for maintenance therapy.

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

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The maximum total daily dosage should not exceed two 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 providing 120 actuations, net fill weight 16 g (NDC 0173-0453-01). Each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. The bottle should be discarded when the labeled number of actuations has been reached even though the bottle is not completely empty. Each bottle is fitted with a white metering atomizing pump, white nasal adapter, and green dust cover in a box of one with patient's instructions for use.

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

GlaxoWellcome
Glaxo Wellcome Inc.
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U.S. Patent 4,335,121

INSEAL™ is covered by the following Inprint Systems patent applications:
European 94916311.7, Canada 2140025, USA 08/373,213.

November 1998 RL-645

(product illustration)

FLONASE®

(fluticasone propionate)
Nasal Spray, 50 mcg

Please read this leaflet carefully before you start to take your medicine. It provides a summary of information on your medicine. ***For further information ask your doctor or pharmacist.***

WHAT YOU SHOULD KNOW ABOUT RHINITIS

Rhinitis is a word that means inflammation of the lining of the nose. If you suffer from rhinitis, your nose becomes stuffy and runny. Rhinitis can also make your nose itchy, and you may sneeze a lot. Rhinitis can be caused by allergies to pollen, animals, molds, or other materials—or it may have a nonallergic cause.

WHAT YOU SHOULD KNOW ABOUT FLONASE NASAL SPRAY

Your doctor has prescribed FLONASE Nasal Spray, a medicine that can help treat your rhinitis. FLONASE Nasal Spray contains fluticasone propionate, which is a synthetic corticosteroid. Corticosteroids are natural substances found in the body that help fight inflammation. When you spray FLONASE into your nose, it helps to reduce the symptoms of allergic reactions and the stuffiness, runniness, itching, and sneezing that can bother you.

THINGS TO REMEMBER ABOUT FLONASE NASAL SPRAY

1. Shake gently before using.
2. Use your nasal spray as directed by your doctor. The directions are on the pharmacy label.
3. Keep your nasal spray **out of the reach of children.**

BEFORE USING YOUR NASAL SPRAY

- If you are pregnant (or intending to become pregnant),
- If you are breast-feeding a baby,
- If you are allergic to FLONASE Nasal Spray or any other nasal corticosteroid,

TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE. In some circumstances, this medicine may not be suitable and your doctor may wish to give you a different medicine. Make sure that your doctor knows what other medicines you are taking.

USING YOUR NASAL SPRAY

- Follow the instructions shown on the next few pages. If you have any problems, tell your doctor or pharmacist.
- It is important that you use it as directed by your doctor. The pharmacist's label will usually tell you what dose to take and how often. If it doesn't, or you are not sure, ask your doctor or pharmacist.

DOSAGE

- For **ADULTS**, the usual starting dosage is ***two sprays in each nostril once daily.*** Sometimes your doctor may recommend using one spray in each nostril twice a day (morning and evening). You should not use more than a total of two sprays in each nostril daily. After you have begun to feel better, one spray in each nostril daily may be adequate for you.

  For **ADOLESCENTS and CHILDREN** (4 years of age and older), the usual starting dosage is ***one spray in each nostril once daily.*** Sometimes your doctor may recommend using two sprays in each nostril daily. Then, after you have begun to feel better, one spray in each nostril daily may be adequate for you.

- DO NOT use more of your medicine or take it more often than your doctor advises.

- FLONASE may begin to work within 12 hours of the first dose, but it takes several days of regular use to reach its greatest effect. It is important that you use FLONASE Nasal Spray as prescribed by your doctor. Best results will be obtained by using the spray on a regular

basis. If symptoms disappear, contact your doctor for further instructions.

- If you also have itchy, watery eyes, you should tell your doctor. You may be given an additional medication to treat your eyes. Be careful not to confuse them, particularly if the second medication is an eye drop.
- If you miss a dose, just take your regularly scheduled next dose when it is due. DO NOT DOUBLE the dose.

HOW TO USE YOUR NASAL SPRAY

Read the complete instructions carefully and use only as directed.

BEFORE USING

1. Shake the bottle gently and then remove the dust cover (Figure 1).

2. It is necessary to prime the pump into the air the first time it is used, or when you have not used it for a week or more. To prime the pump, hold the bottle as shown with the nasal applicator pointing away from you and with your forefinger and middle finger on either side of the nasal applicator and your thumb underneath the bottle. When you prime the pump for the first time, press down and release the pump six times (Figure 2). The pump is now ready for use. If the pump is not used for 7 days, prime until a fine spray appears.

Figure 1

Figure 2

USING THE SPRAY

3. Blow your nose to clear your nostrils.

4. Close one nostril. Tilt your head forward slightly and, keeping the bottle upright, carefully insert the nasal applicator into the other nostril (Figure 3).

5. Start to breathe in through your nose, and WHILE BREATHING IN press firmly and quickly down

Figure 3

once on the applicator to release the spray. To get a full actuation, use your forefinger and middle finger to spray while supporting the base of the bottle with your thumb. Avoid spraying in eyes. Breathe gently inwards through the nostril (Figure 4).

Figure 4

6. Breathe out through your mouth.
7. If a second spray is required in that nostril, repeat steps 4 through 6.
8. Repeat steps 4 through 7 in the other nostril.
9. Wipe the nasal applicator with a clean tissue and replace the dust cover (Figure 5).

Figure 5

10. Do not use this bottle for more than the labeled number of sprays even though the bottle is not completely empty. Before you throw the bottle away, you should consult your doctor to see if a refill is needed. Do not take extra doses or stop taking FLONASE Nasal Spray without consulting your doctor.

CLEANING

Your nasal spray should be cleaned at least once a week. To do this:

1. Remove the dust cover and then gently pull upwards to free the nasal applicator.
2. Wash the applicator and dust cap under warm tap water. Allow to dry at room temperature, then place the applicator and dust cover back on the bottle.
3. If the nasal applicator becomes blocked, it can be removed as above and left to soak in warm water. Rinse with cold tap water, dry, and refit. **Do not try to unblock the nasal applicator by inserting a pin or other sharp object.**

STORING YOUR NASAL SPRAY

- Keep your FLONASE Nasal Spray **out of the reach of children**.
- Avoid spraying in eyes.

- Store between 4° and 30°C (39° and 86°F).
- Do not use your FLONASE Nasal Spray after the date shown as "EXP" on the label or box.

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

FURTHER INFORMATION

This leaflet does not contain the complete information about your medication. *If you have any questions, or are not sure about something, then you should ask your doctor or pharmacist.*

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

GlaxoWellcome

Glaxo Wellcome Inc.

Research Triangle Park, NC 27709

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U.S. Patent No. 4,335,121

November 1998 RL-645

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DEC - 8 1998

LABELING REVIEW

Application # 20-121/S-009
Products Flonase (fluticasone propionate) Nasal Spray, 50 mcg
Applicant GlaxoWellcome, Inc.

Submissions Reviewed:

Glaxo submitted proposed labeling for the package insert only in the original application. Following review of the supplement, FDA provided a revised package insert via facsimile on November 5, 1998, and requested that Glaxo include a revised patient package insert as well as a package insert in a labeling amendment to the application. Glaxo provided amended labeling to the application on November 12, 1998, including additional changes. These additional changes were verified or revised, and Glaxo submitted amended labeling on December 1, 1998.

The December 1, 1998, package insert and patient package insert were reviewed against the October 1, 1998, approved labeling for S-010.

Review:

1. The product name was revised to "Flonase (fluticasone propionate) Nasal Spray, 50 mcg,"

2. The following changes were proposed for the CLINICAL PHARMACOLOGY, Pharmacokinetics subsection of the package insert to be consistent with Flovent Rotadisk labeling.

   a. Under "***Distribution***," the 1st sentence was revised to read, "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.**"

   b. Under "***Metabolism***," the 1st paragraph was revised to read, "The total blood clearance of fluticasone propionate **is high (average, 1093 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 approximately 2000 times less affinity 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."

c. Under "***Excretion***," the first sentence was revised to read, "Following intravenous dosing, fluticasone propionate **showed polyexponential kinetics and had a terminal** elimination half-life of approximately **7.8** hours."

These revisions were approved per Ramana Uppoor, Clinical Pharmacology & Biopharmaceutics Team Leader.

3. Under CLINICAL PHARMACOLOGY, Clinical Trials subsection, the following revisions have been made.

a. The word [redacted] has been deleted from the first sentence in accordance with an October 13, 1998, FDA letter regarding final printed labeling submitted for S-005.

b. The term "total nasal symptoms scores" has been revised to "total nasal **symptom** score," in agreement with the November 5, 1998, recommended FDA labeling.

c. [redacted] has been deleted, in accordance with the October 1, 1998, approved labeling for S-010.

d. The third paragraph has been added and reads, "Three randomized, double-blind, parallel, vehicle-controlled trials were conducted in 1191 patients with perennial nonallergic rhinitis. These trials evaluated the patient-rated total nasal symptom scores (nasal obstruction, postnasal drip, rhinorrhea) in patients treated for 28 days of double-blind therapy and **in one 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 total nasal symptom scores compared with patients treated with vehicle." This language was approved (October 21, 1998, medical officer review) with revisions [boldface] which were proposed in accordance with the November 5, 1998, recommended FDA labeling.

4. Under CLINICAL PHARMACOLOGY, Individualization of Dosage subsection, the 2nd sentence has been replaced. The previous sentence read, [redacted] The proposed sentence reads, "In 4 randomized, double-blind, 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." This change is in accordance with the November 5, 1998, proposed FDA labeling.

5. Under INDICATIONS AND USAGE, the following revisions were proposed in the December 17, 1997, draft labeling.

   a. The 1st paragraph was revised to read, "FLONASE Nasal Spray is indicated for the management of nasal symptoms of seasonal and perennial allergic **and nonallergic** rhinitis in adults and pediatric patients 4 years of age and older."

   b. The 1st sentence of the 2nd paragraph, indicating that [redacted] has been deleted.

   Both of these revisions were acceptable per the October 21, 1998, medical review.

6. Under PRECAUTIONS, Pregnancy: *Teratogenic Effects* subsection, the dose correlation to human exposure has been changed from [redacted] to "less than," inaccordance with November 5, 1998, recommended FDA labeling.

7. Under PRECAUTIONS, Nursing Mothers subsection, the 2nd sentence was revised to read, "When tritiated fluticasone propionate was administered to rats at a subcutaneous dose of 10 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis), radioactivity was excreted in the milk." The revised sentence differs from recommended FDA language contained in the November 5, 1998, correspondence, but was acceptable to Lawrence Sancilio, Preclinical Reviewer, and Joseph Sun, Preclinical Team Leader, as of November 20, 1998.

8. Under PRECAUTIONS, Geriatric Use subsection, the number of treated patients was changed to n=275. The revision was acceptable per the October 21, 1998, medical officer review.

9. Under ADVERSE REACTIONS, the 1st sentence has been revised to read, "In controlled US studies, **more than 3300 patients with seasonal allergic, perennial allergic, and perennial nonallergic rhinitis** received treatment with intranasal fluticasone propionate." This proposed revision was acceptable to Alexandra Worobec, Medical Officer, in verbal communications on November 30, 1998, and per the October 21, 1998, medical officer review.

10. Under ADVERSE REACTIONS, [redacted] has been removed from the 4th paragraph and combined in the table with "nasal burning." This change was acceptable per the October 21, 1998, medical officer review.

11. Under DOSAGE AND ADMINISTRATION, Adolescents and Children subsection, the [redacted] was deleted. This revision is acceptable upon approval of this supplement for the indication for nonallergic rhinitis.

12. In the Patient's Instructions for Use, under "HOW TO USE YOUR NASAL SPRAY," item #2, third sentence, the phrase [redacted] has been deleted. Additionally, the fifth sentence has been revised to read, "If the pump is not used for 7 days, **prime** until a fine spray appears." Both of these revisions are in accordance with the October 1, 1998, approval letter for S-010.

CONCLUSIONS: All of the proposed revisions are acceptable and labeling for this supplemental application should be approved based on the December 1, 1998, submitted draft labeling.

David Hilfiker
Project Manager
Division of Pulmonary Drug Products

/S/ 12-8-98

Concurrences:
HFD-570/Worobec /S/ 12/08/98
HFD-570/Himmel
HFD-570/Sancilio
HFD-570/Sun /S/ 12/9/98
HFD-570/Uppoor /S/ 120998

Cc: Original NDA 20-121/S-009
HFD-570/division file
HFD-570/Hilfiker, Schumaker /S/ 12-8-98

APPEARS THIS WAY
ON ORIGINAL

ADDENDUM TO LABELING REVIEW

Date: October 29, 1998

By: David Hilfiker, Project Manager

For: 20-121/S-009 Flonase (fluticasone propionate) Nasal Spray
Efficacy supplement which provides for addition of perennial nonallergic rhinitis (PNAR) as an indication

Due: December 18, 1998

Reference to labeling comments on page 267 of the October 21, 1998, clinical review, and revisions to those labeling recommendations on page 4 of the October 20, 1998, clinical team leader memo.

Under CLINICAL PHARMACOLOGY, Individualization of Dosage subsection, the clinical review recommended language referring to 2 "park studies" that were conducted in support of this supplement. The term "park study" was questioned as a recognizable term for practicing physicians.

Alternate recommended language was proposed which has been used in other recent package insert in reference to this type of study. The second sentence of the Individualization of Dosage subsection was modified to read: "In 4 randomized, double-blind, 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."

David Hilfiker /S/ 10-29-98
Project Manager

/S/ 10-30-98

Cc: Original NDA 20-121/S-009
HFD-570/div file, Hilfiker, Schumaker, Worobec, Himmel

APPEARS THIS WAY
ON ORIGINAL

2. LABELING

This section presents a draft package insert incorporating the labeling changes proposed via this supplement. In section 2.I, proposed changes are indicated by underline (additions) and strikethrough (deletions). In section 2.II, these same proposed changes are annotated to the appropriate supporting data. Revisions to accommodate the new indication have been made to the following sections of the package insert:

- final paragraph of the Clinical Trials subsection of Clinical Pharmacology
- Indications and Usage
- Geriatric Use subsection of Precautions
- Adverse Reactions
- Dosage and Administration

This labeling incorporates the most recent changes made to the package insert for Flonase Nasal Spray:

- Special Supplement: Changes Being Effected of October 15, 1997
- Attachment to Approval letter for Supplement S-005 (Pediatric Use) of October 31, 1997.

As noted in the Phase IV commitments for [redacted] will be implemented gradually; the draft labeling provided with this supplement includes the change.

The changes proposed via this supplement have no impact on the patient's instructions for use, carton or bottle label for Flonase Nasal Spray.

APPEARS THIS WAY
ON ORIGINAL

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CIPLA LTD. EXHIBIT 2020 PAGE 22

11 Page(s) Redacted

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Labeling