PRODUCT INFORMATION

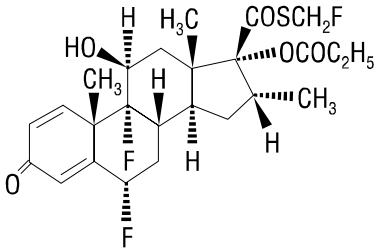
FLOVENT® ROTADISK® 50 mcg
(fluticasone propionate inhalation powder, 50 mcg)

FLOVENT® ROTADISK® 100 mcg
(fluticasone propionate inhalation powder, 100 mcg)

FLOVENT® ROTADISK® 250 mcg
(fluticasone propionate inhalation powder, 250 mcg)

For Oral Inhalation Only
For Use With the DISKHALER® Inhalation Device

DESCRIPTION: The active component of FLOVENT ROTADISK 50 mcg, FLOVENT ROTADISK 100 mcg, and FLOVENT ROTADISK 250 mcg is fluticasone propionate, a 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.

FLOVENT ROTADISK 50 mcg, FLOVENT ROTADISK 100 mcg, and FLOVENT ROTADISK 250 mcg contain a dry powder presentation of fluticasone propionate intended for oral inhalation only. Each double-foil ROTADISK contains 4 blisters. Each blister contains a mixture of 50, 100, or 250 mcg of microfine fluticasone propionate blended with lactose (which contains milk proteins) to a total weight of 25 mg. The contents of each blister are inhaled using a specially designed plastic device for inhaling powder called the DISKHALER. After a fluticasone propionate ROTADISK is loaded into the DISKHALER, a blister containing medication is pierced and the fluticasone propionate is dispersed into the air stream created when the patient inhales through the mouthpiece.

The amount of drug delivered to the lung will depend on patient factors such as inspiratory flow. Under standardized in vitro testing, FLOVENT ROTADISK delivers 44, 88, or 220 mcg of fluticasone propionate from FLOVENT ROTADISK 50 mcg, FLOVENT ROTADISK 100 mcg, or FLOVENT ROTADISK 250 mcg, respectively, when tested at a flow rate of 60 L/min for 3 seconds. In adult and adolescent patients with asthma, mean peak inspiratory flow (PIF) through the DISKHALER was 123 L/min (range, 88 to 159 L/min), and in pediatric patients 4 to 11 years of age with asthma, mean PIF was 110 L/min (range, 43 to 175 L/min).

CLINICAL PHARMACOLOGY: Fluticasone propionate is a synthetic, trifluorinated corticosteroid with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

The precise mechanisms of fluticasone propionate action in asthma are unknown. Inflammation is recognized as an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Though highly effective for the treatment of asthma, corticosteroids do not affect asthma symptoms immediately. However, improvement following inhaled administration of fluticasone propionate can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer.

Pharmacokinetics: ***Absorption:*** The activity of FLOVENT ROTADISK Inhalation Powder is due to the parent drug, fluticasone propionate. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and pre-systemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate inhalation powder in healthy volunteers averaged about 13.5% of the nominal dose.

Peak plasma concentrations after a 1000-mcg dose of fluticasone propionate inhalation powder ranged from 0.1 to 1.0 ng/mL.

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%.

Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism: The total 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 metabolite had approximately 2,000 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 fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

In a drug interaction study, coadministration of fluticasone propionate (1000 mcg) 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: Formal pharmacokinetic studies using fluticasone propionate were not carried out in any special populations. In a clinical study using fluticasone propionate inhalation powder, trough fluticasone propionate plasma concentrations were collected in 76 males and 74 females after inhaled administration of 100 and 500 mcg twice daily. Full pharmacokinetic profiles were obtained from 7 female patients and 13 male patients at these doses, and no overall differences in pharmacokinetic behavior were found.

Plasma concentrations of fluticasone propionate were measured 20 and 40 minutes after dosing from 29 children aged 4 to 11 years who were taking either 50 or 100 mcg twice daily of fluticasone propionate inhalation powder. Plasma concentration values ranged from below the limit of quantitation (25 pg/mL) to 117 pg/mL (50-mcg dose) or 154 pg/mL (100-mcg dose). In a study with adults taking the 100-mcg twice-daily dose, the plasma concentrations observed ranged from below the limit of quantitation to 73.1 pg/mL. The median fluticasone propionate plasma concentrations for the 100-mcg dose in children was 58.7 pg/mL; in adults the median plasma concentration was 39.5 pg/mL.

Pharmacodynamics: To confirm that systemic absorption does not play a role in the clinical response to inhaled fluticasone propionate, a double-blind clinical study comparing inhaled and oral fluticasone propionate was conducted. Doses of 100 and 500 mcg twice daily of fluticasone propionate inhalation powder were compared to oral fluticasone propionate, 20,000 mcg given once daily, and placebo for 6 weeks. Plasma levels of fluticasone propionate were detectable in all 3 active groups, but the mean values were highest in the oral group. Both doses of inhaled fluticasone propionate were effective in maintaining asthma stability and improving lung

function while oral fluticasone propionate and placebo were ineffective. This demonstrates that the clinical effectiveness of inhaled fluticasone propionate is due to its direct local effect and not to an indirect effect through systemic absorption.

The potential systemic effects of inhaled fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis were also studied in asthma patients. Fluticasone propionate given by inhalation aerosol at doses of 220, 440, 660, or 880 mcg twice daily was compared with placebo or oral prednisone 10 mg given once daily for 4 weeks. For most patients, the ability to increase cortisol production in response to stress, as assessed by 6-hour cosyntropin stimulation, remained intact with inhaled fluticasone propionate treatment. No patient had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing with placebo or fluticasone propionate 220 mcg twice daily. For patients treated with 440, 660, and 880 mcg twice daily, 10%, 16%, and 12%, respectively, had an abnormal response as compared to 29% of patients treated with prednisone.

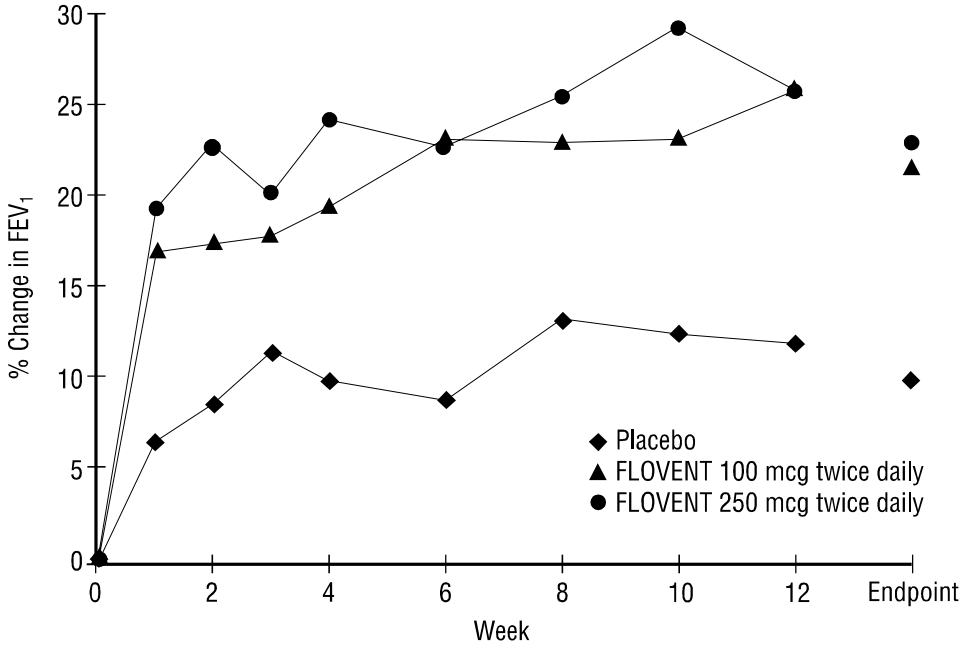
In clinical trials with fluticasone propionate inhalation powder, using doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL) were noted in patients receiving fluticasone propionate or placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out in 64 patients randomized to fluticasone propionate 500 mcg twice daily or placebo, 1 patient receiving fluticasone propionate (4%) had an abnormal response to 6-hour cosyntropin infusion at 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

Clinical Trials: Double-blind, parallel, placebo-controlled, US clinical trials were conducted in 1197 adolescent and adult asthma patients to assess the efficacy and safety of FLOVENT ROTADISK in the treatment of asthma. Fixed doses of 50, 100, 250, and 500 mcg twice daily were compared to placebo to provide information about appropriate dosing to cover a range of asthma severity. Asthmatic patients included in these studies were those not adequately controlled with beta-agonists alone, and those already maintained on daily inhaled corticosteroids. In these efficacy trials, at all doses, measures of pulmonary function (forced expiratory volume in 1 second [FEV_1] and morning peak expiratory flow rate [AM PEFR]) were statistically significantly improved as compared with placebo. All doses were delivered by inhalation of the contents of 1 or 2 blisters from the DISKHALER twice daily.

Displayed in the figure below are results of pulmonary function tests for 2 recommended dosages of fluticasone propionate inhalation powder (100 and 250 mcg twice daily) and placebo from a 12-week trial in 331 adolescent and adult asthma patients (baseline FEV_1 = 2.63 L/sec) inadequately controlled on bronchodilators alone. Because this trial used predetermined criteria for lack of efficacy, which caused more patients in the placebo group to be withdrawn, pulmonary function results at Endpoint, which is the last evaluable FEV_1 result and includes most patients' lung function data, are also provided. Pulmonary function at both fluticasone

propionate dosages improved significantly compared with placebo by the first week of treatment, and this improvement was maintained over the duration of the trial.

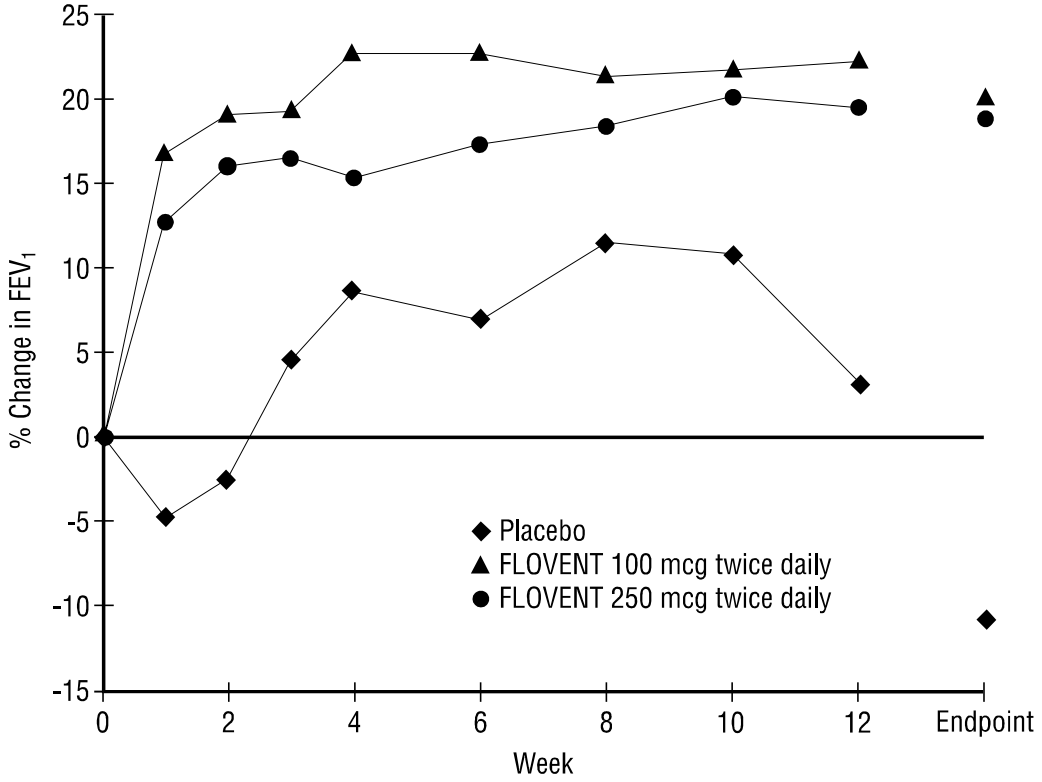
A 12-Week Clinical Trial in Patients Inadequately Controlled on Bronchodilators Alone: Mean Percent Change From Baseline in FEV_1 Prior to AM Dose



In a second clinical study of 75 patients, 500 mcg twice daily was evaluated in a similar population. In this trial fluticasone propionate significantly improved pulmonary function as compared with placebo.

Displayed in the figure below are results of pulmonary function tests for 2 recommended dosages of fluticasone propionate inhalation powder (100 and 250 mcg twice daily) and placebo from a 12-week trial in 342 adolescent and adult asthma patients (baseline FEV_1 = 2.49 L/sec) already receiving daily inhaled corticosteroid therapy (≥336 mcg/day of beclomethasone dipropionate or ≥800 mcg/day of triamcinolone acetonide) in addition to as-needed albuterol and theophylline (38% of all patients). Because this trial also used predetermined criteria for lack of efficacy, which caused more patients in the placebo group to be withdrawn, pulmonary function results at Endpoint are included. Pulmonary function at both fluticasone propionate dosages improved significantly compared with placebo by the first week of treatment and the improvement was maintained over the duration of the trial.

A 12-Week Clinical Trial in Patients Already Receiving Inhaled Corticosteroids: Mean Percent Change From Baseline in FEV_1 Prior to AM Dose



In a second clinical study of 139 patients, treatment with 500 mcg twice daily was evaluated in a similar patient population. In this trial fluticasone propionate significantly improved pulmonary function as compared with placebo.

In the 4 trials described above, all dosages of fluticasone propionate were efficacious; however, at higher dosages, patients were less likely to discontinue study participation due to asthma deterioration (as defined by predetermined criteria for lack of efficacy including lung function and patient-recorded variables such as AM PEFR, albuterol use, and nighttime awakenings due to asthma).

In a clinical trial of 96 severe asthmatic patients requiring chronic oral prednisone therapy (average baseline daily prednisone dose was 10 mg), fluticasone propionate given by inhalation aerosol at doses of 660 and 880 mcg twice daily was evaluated. Both doses enabled a statistically significantly larger percentage of patients to wean successfully from oral prednisone as compared with placebo (69% of the patients on 660 mcg twice daily and 88% of the patients on 880 mcg twice daily as compared with 3% of patients on placebo). Accompanying the reduction in oral corticosteroid use, patients treated with fluticasone propionate had significantly improved lung function and fewer asthma symptoms as compared with the placebo group. These data were obtained from a clinical study using fluticasone propionate inhalation aerosol; no direct

assessment of the clinical comparability of equal nominal doses for the FLOVENT ROTADISK and FLOVENT Inhalation Aerosol formulations in this population has been conducted.

Pediatric Experience: In a 12-week, placebo-controlled clinical trial of 263 patients aged 4 to 11 years inadequately controlled on bronchodilators alone (baseline morning peak expiratory flow = 200 L/min), fluticasone propionate inhalation powder doses of 50 and 100 mcg twice daily significantly improved morning peak expiratory flow (28% and 34% change from baseline at Endpoint, respectively) compared to placebo (11% change). In a second placebo-controlled, 52-week trial of 325 patients aged 4 to 11 years, approximately half of whom were receiving inhaled corticosteroids at baseline, doses of fluticasone propionate inhalation powder of 50 and 100 mcg twice daily improved lung function by the first week of treatment, and the improvement continued over 1 year compared to placebo. In both studies, patients on active treatment were significantly less likely to discontinue treatment due to lack of efficacy.

INDICATIONS AND USAGE: FLOVENT ROTADISK is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

FLOVENT ROTADISK is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS: FLOVENT ROTADISK is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see DESCRIPTION and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site Specific*).

WARNINGS:

Particular care is needed for patients who are transferred from systemically active corticosteroids to FLOVENT ROTADISK because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although fluticasone propionate inhalation powder may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to fluticasone propionate inhalation powder. In a clinical trial of 96 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive reduction of prednisone dose was allowed only when lung function, symptoms, and as-needed beta-agonist use were better than or comparable to that seen before initiation of prednisone dose reduction. Lung function (FEV_1 or AM PEFR), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to fluticasone propionate inhalation powder may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, and arthritis.

Persons who are on 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 on corticosteroids. In such children or adults who have not had these diseases, 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.

Fluticasone propionate inhalation powder is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with FLOVENT ROTADISK, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with inhaled fluticasone propionate should be discontinued and alternative therapy instituted.

Patients should be instructed to contact their physicians immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with fluticasone propionate inhalation powder. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS:

General: During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Fluticasone propionate will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of fluticasone propionate inhalation powder in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing fluticasone propionate inhalation powder.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when fluticasone propionate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, fluticasone propionate inhalation powder should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

A reduction of growth velocity in children or adolescents may occur as a result of poorly controlled asthma or from the therapeutic use of corticosteroids, including inhaled corticosteroids. A 52-week placebo-controlled study to assess the potential growth effects of fluticasone propionate inhalation powder at 50 and 100 mcg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) 4 to 11 years of age. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and 5.66 cm/year in the 100-mcg group (n = 89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the 100-mcg group (n = 79). The clinical significance of these growth data is not certain. In children 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: boys – 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th

percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year. The effects of long-term treatment of children with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known. 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. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

The long-term effects of fluticasone propionate in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or longer. In clinical studies with patients treated for 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including fluticasone propionate.

In clinical studies with inhaled fluticasone propionate, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on treatment with fluticasone propionate inhalation powder, but at times therapy with fluticasone propionate may need to be interrupted.

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

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see ADVERSE REACTIONS).

Information for Patients: Patients being treated with FLOVENT ROTADISK 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 use FLOVENT ROTADISK at regular intervals as directed. Results of clinical trials indicated significant improvement may occur within the first day or two of treatment;

however, the full benefit may not be achieved until treatment has been administered for 1 to 2 weeks or longer. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

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

For the proper use of FLOVENT ROTADISK Inhalation Powder and to attain maximum improvement, the patient should read and follow carefully the accompanying Patient's Instructions for Use.

Drug Interactions: In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single dose of fluticasone propionate (1000 mcg) 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. Care should be exercised when FLOVENT 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 2 times the maximum recommended daily inhalation dose in adults and approximately 10 times the maximum recommended daily inhalation dose in children on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately 1/4 the maximum recommended daily inhalation dose in adults and comparable to the maximum recommended daily inhalation 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 1/5 the maximum recommended daily inhalation 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 1/10 and 1/3, respectively, the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) 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 (approximately 1/30 the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg

(approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) of fluticasone propionate. 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 1/3 and 2 times, respectively, the maximum recommended daily inhalation 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. Subcutaneous administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (approximately 1/25 the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) resulted in measurable radioactivity in milk. Because other corticosteroids are excreted in human milk, caution should be exercised when fluticasone propionate inhalation powder is administered to a nursing woman.

Pediatric Use: Two hundred fourteen (214) patients 4 to 11 years of age and 142 patients 12 to 16 years of age were treated with fluticasone propionate inhalation powder in US clinical trials. The safety and effectiveness of FLOVENT ROTADISK Inhalation Powder in children below 4 years of age have not been established.

Inhaled corticosteroids, including fluticasone propionate, may cause a reduction in growth in children and adolescents (see PRECAUTIONS). 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. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

Geriatric Use: Safety data have been collected on 280 patients (FLOVENT® DISKUS® n = 83, FLOVENT ROTADISK n = 197) 65 years of age or older and 33 patients (FLOVENT DISKUS n = 14, FLOVENT ROTADISK n = 19) 75 years of age or older who have been treated with fluticasone propionate inhalation powder in US and non-US clinical trials. There were no differences in adverse reactions compared to those reported by younger patients. In addition, there were no apparent differences in efficacy between patients 65 years of age or older and younger patients. Fifteen patients 65 years of age or older and 1 patient 75 years of age or older were included in the efficacy evaluation of US clinical studies.

ADVERSE REACTIONS: The following incidence of common adverse experiences is based upon 6 placebo-controlled clinical trials in which 1384 patients ≥4 years of age (520 females and 864 males) previously treated with as-needed bronchodilators and/or inhaled corticosteroids were treated with fluticasone propionate inhalation powder (doses of 50 to 500 mcg twice daily for up to 12 weeks) or placebo.

Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in Controlled Clinical Trials With FLOVENT ROTADISK in Patients ≥4 Years Previously Receiving Bronchodilators and/or Inhaled Corticosteroids

Adverse Event	Placebo (n = 438) %	FLOVENT 50 mcg Twice Daily (n = 255) %	FLOVENT 100 mcg Twice Daily (n = 331) %	FLOVENT 250 mcg Twice Daily (n = 176) %	FLOVENT 500 mcg Twice Daily (n = 184) %
Ear, nose, and throat					
Pharyngitis	7	6	8	8	13
Nasal congestion	5	4	4	7	7
Sinusitis	4	5	4	6	4
Rhinitis	4	4	9	2	3
Dysphonia	0	<1	4	6	4
Oral candidiasis	1	3	3	4	11
Respiratory					
Upper respiratory infection	13	16	17	22	16
Influenza	2	3	3	3	4
Bronchitis	2	4	2	1	2
Other					
Headache	11	11	9	14	15
Diarrhea	1	2	2	0	4
Back problems	<1	<1	1	1	4
Fever	3	4	4	2	2
Average duration of exposure (days)	53	77	68	78	60

The table above includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in any of the fluticasone propionate inhalation powder groups and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account.

These adverse reactions were mostly mild to moderate in severity, with <2% of patients discontinuing the studies because of adverse events. Rare cases of immediate and delayed

hypersensitivity reactions, including rash and other rare events of angioedema and bronchospasm, have been reported.

Other adverse events that occurred in these clinical trials using fluticasone propionate inhalation powder with an incidence of 1% to 3% and which occurred at a greater incidence than with placebo were:

Ear, Nose, and Throat: Otitis media, tonsillitis, nasal discharge, earache, laryngitis, epistaxis, sneezing.

Eye: Conjunctivitis.

Gastrointestinal: Abdominal pain, viral gastroenteritis, gastroenteritis/colitis, abdominal discomfort.

Miscellaneous: Injury.

Mouth and Teeth: Mouth irritation.

Musculoskeletal: Sprain/strain, pain in joint, disorder/symptoms of neck, muscular soreness, aches and pains.

Neurological: Migraine, nervousness.

Respiratory: Chest congestion, acute nasopharyngitis, dyspnea, irritation due to inhalant.

Skin: Dermatitis, urticaria.

Urogenital: Dysmenorrhea, candidiasis of vagina, pelvic inflammatory disease, vaginitis/vulvovaginitis, irregular menstrual cycle.

There were no clinically relevant differences in the pattern or severity of adverse events in children compared with those reported in adults.

Fluticasone propionate inhalation aerosol (660 or 880 mcg twice daily) was administered for 16 weeks to asthmatics requiring oral corticosteroids. Adverse events reported more frequently in these patients compared to patients not on oral corticosteroids included sinusitis, nasal discharge, oropharyngeal candidiasis, headache, joint pain, nausea and vomiting, muscular soreness, malaise/fatigue, and insomnia.

Observed During Clinical Practice: In addition to adverse experiences reported from clinical trials, the following experiences 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 experiences 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.

Ear, Nose, and Throat: Aphonia, facial and oropharyngeal edema, hoarseness, and throat soreness and irritation.

Endocrine and Metabolic: Cushingoid features, growth velocity reduction in children/adolescents, hyperglycemia, osteoporosis, and weight gain.

Eye: Cataracts.

Non-Site Specific: Very rare anaphylactic reaction, very rare anaphylactic reaction in patients with severe milk protein allergy.

Psychiatry: Agitation, aggression, depression, and restlessness.

Respiratory: Asthma exacerbation, bronchospasm, chest tightness, cough, immediate bronchospasm, paradoxical bronchospasm, pneumonia, and wheeze.

Skin: Contusions, ecchymoses, and pruritus.

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see PRECAUTIONS: Eosinophilic Conditions).

OVERDOSAGE: Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS). Inhalation by healthy volunteers of a single dose of 4000 mcg of fluticasone propionate inhalation powder or single doses of 1760 or 3520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of 1320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. The oral and subcutaneous median lethal doses in mice and rats were >1000 mg/kg (>2000 and >4100 times, respectively, the maximum recommended daily inhalation dose in adults and >9600 and >19,000 times, respectively, the maximum recommended daily inhalation dose in children on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION: FLOVENT ROTADISK should be administered by the orally inhaled route in patients 4 years of age and older. Individual patients will experience a variable time to onset and degree of symptom relief. Generally, fluticasone propionate inhalation powder has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhaled administration of fluticasone propionate can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment.

After asthma stability has been achieved, it is always desirable to titrate to the lowest effective dose to reduce the possibility of side effects. Doses as low as 50 mcg twice daily have been shown to be effective in some patients. For patients who do not respond adequately to the starting dose after 2 weeks of therapy, higher doses may provide additional asthma control. The safety and efficacy of FLOVENT ROTADISK when administered in excess of recommended doses have not been established.

Rinsing the mouth after inhalation is advised.

The recommended starting dose and the highest recommended dose of fluticasone propionate inhalation powder, based on prior anti-asthma therapy, are listed in the following table.

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults and Adolescents		
Bronchodilators alone	100 mcg twice daily	500 mcg twice daily
Inhaled corticosteroids	100-250 mcg twice daily*	500 mcg twice daily
Oral corticosteroids†	1000 mcg twice daily‡	1000 mcg twice daily‡
Children 4 to 11 Years		
Bronchodilators alone	50 mcg twice daily	100 mcg twice daily
Inhaled corticosteroids	50 mcg twice daily	100 mcg twice daily

* Starting doses above 100 mcg twice daily for adults and adolescents and 50 mcg twice daily for children 4 to 11 years of age may be considered for patients with poorer asthma control or those who have previously required doses of inhaled corticosteroids that are in the higher range for that specific agent.

NOTE: In all patients, it is desirable to titrate to the lowest effective dose once asthma stability is achieved.

† **For Patients Currently Receiving Chronic Oral Corticosteroid Therapy:** Prednisone should be reduced no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of therapy with FLOVENT. Patients should be carefully monitored for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency (see WARNINGS). Once prednisone reduction is complete, the dosage of fluticasone propionate should be reduced to the lowest effective dosage.

‡ This dosing recommendation is based on clinical data from a study conducted using FLOVENT Inhalation Aerosol. No clinical trials have been conducted in patients on oral corticosteroids using the ROTADISK formulation; no direct assessment of the clinical comparability of equal nominal doses for the FLOVENT ROTADISK and FLOVENT Inhalation Aerosol formulations in this population has been conducted.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with fluticasone propionate inhalation powder, efficacy and safety did not differ from that in younger patients. Consequently, no dosage adjustment is recommended.

Directions for Use: Illustrated Patient's Instructions for Use accompany each package of FLOVENT ROTADISK.

HOW SUPPLIED: FLOVENT ROTADISK 50 mcg is a circular double-foil pack containing 4 blisters of the drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and the tube is packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the

foil pouch of 15 ROTADISKS and 1 dark orange- and peach-colored DISKHALER inhalation device (NDC 0173-0511-00).

FLOVENT ROTADISK 100 mcg is a circular double-foil pack containing 4 blisters of the drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and the tube is packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the foil pouch of 15 ROTADISKS and 1 dark orange- and peach-colored DISKHALER inhalation device (NDC 0173-0509-00).

FLOVENT ROTADISK 250 mcg is a circular double-foil pack containing 4 blisters of the drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and the tube is packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the foil pouch of 15 ROTADISKS and 1 dark orange- and peach-colored DISKHALER inhalation device (NDC 0173-0504-00).

Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place. Keep out of reach of children. Do not puncture any fluticasone propionate ROTADISK blister until taking a dose using the DISKHALER.

Use the ROTADISK blisters within 2 months after opening of the moisture-protective foil overwrap or before the expiration date, whichever comes first. Place the sticker provided with the product on the tube and enter the date the foil overwrap is opened and the 2-month use date.

GlaxoSmithKline
Research Triangle Park, NC 27709

March 2003 RL-1185