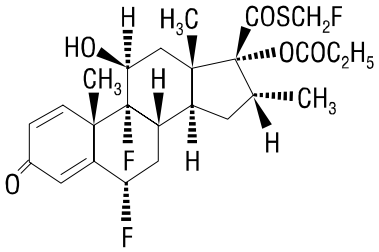
FLOVENT® DISKUS® 50 mcg
(fluticasone propionate inhalation powder, 50 mcg)

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

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

For Oral Inhalation Only

DESCRIPTION: The active component of FLOVENT DISKUS 50 mcg, FLOVENT DISKUS 100 mcg, and FLOVENT DISKUS 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 DISKUS 50 mcg, FLOVENT DISKUS 100 mcg, and FLOVENT DISKUS 250 mcg are specially designed plastic devices containing a double-foil blister strip of a powder formulation of fluticasone propionate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 50, 100, or 250 mcg of microfine fluticasone propionate in 12.5 mg of formulation containing lactose. After a blister containing medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, FLOVENT DISKUS delivers 46.(b)(4), or 235 mcg of fluticasone propionate from FLOVENT DISKUS 50 mcg, FLOVENT DISKUS 100 mcg, or FLOVENT DISKUS 250 mcg, respectively, when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in 1 second [FEV_1] 20% to 30% of predicted), mean

peak inspiratory flow (PIF) through a DISKUS® device was 82.4 L/min (range, 46.1 to 115.3 L/min). In children with asthma 4 and 8 years old, mean PIF through FLOVENT DISKUS was 70 and 104 L/min, respectively (range, 48 to 123 L/min).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

CLINICAL PHARMACOLOGY:

Mechanism of Action: 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.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects over recommended doses of FLOVENT DISKUS. This is explained by a combination of a relatively high local anti-inflammatory effect, negligible oral systemic bioavailability (<1%), and the minimal pharmacological activity of the only metabolite detected in man. Lung absorption does occur (see below).

Pharmacokinetics: ***Absorption:*** The activity of FLOVENT DISKUS 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 presystemic 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 from the DISKUS® device in healthy adult volunteers averages about 18%.

Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma (n = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone

propionate inhalation powder using the DISKUS device. The mean fluticasone propionate plasma concentration was 110 pg/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 averages 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 less affinity (approximately 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

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

Hepatic Impairment: Since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Gender: Full pharmacokinetic profiles were obtained from 9 female and 16 male patients given 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Pediatrics: In a clinical study conducted in patients 4 to 11 years of age with mild to moderate asthma, fluticasone propionate concentrations were obtained in 61 patients at 20 and 40 minutes after dosing with 50 and 100 mcg twice daily of fluticasone propionate inhalation powder using the DISKUS. Plasma concentrations were low and ranged from undetectable (about 80% of the plasma samples) to 88 pg/mL. Mean fluticasone propionate plasma concentrations at the 2 dose levels were 5 and 8 pg/mL, respectively.

Special Populations: Formal pharmacokinetic studies using fluticasone propionate were not carried out in other special populations.

Drug-Drug Interactions: 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 another drug interaction study, coadministration of fluticasone propionate (1000 mcg) and ketoconazole (200 mg once daily) resulted in increased fluticasone propionate concentrations and reduced plasma cortisol area under the plasma concentration versus time curve (AUC), but had no effect on urinary excretion of cortisol. Since fluticasone propionate is a substrate of cytochrome P450 3A4, caution should

be exercised when cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole) are coadministered with fluticasone propionate as this could result in increased plasma concentrations of fluticasone propionate.

Pharmacodynamics: 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 both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out with the DISKHALER® inhalation device in 64 patients with mild, persistent asthma (mean FEV_1 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold <35 mcg/dL, one patient receiving fluticasone propionate (4%) had an abnormal response 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.

In a placebo-controlled clinical study conducted in patients 4 to 11 years of age, a 30-minute cosyntropin stimulation test was performed in 41 patients after 12 weeks of dosing with 50 or 100 mcg twice daily of fluticasone propionate via the DISKUS device. One patient receiving fluticasone propionate via DISKUS had a prestimulation plasma cortisol concentration

<5 mcg/dL, and 2 patients had a rise in cortisol of <7 mcg/dL. However, all poststimulation values were >18 mcg/dL.

Clinical Trials: Four double-blind, parallel, placebo-controlled, US clinical trials were conducted in 1036 adolescent and adult patients (≥12 years of age) with asthma to assess the efficacy and safety of FLOVENT DISKUS. These studies included fixed doses of 100, 250, and 500 mcg twice daily compared to placebo to provide information about appropriate dosing to cover a range of asthma severity. Patients with asthma included in these studies were those not adequately controlled with bronchodilators alone, and those already maintained on daily inhaled corticosteroids. All doses were delivered by inhalation of the contents of 1 or 2 blisters from the DISKUS twice daily.

Displayed in the figures below are results of pulmonary function tests (mean percent change from baseline in FEV_1 prior to AM dose) for 3 recommended dosages of fluticasone propionate inhalation powder (100, 250, and 500 mcg twice daily) and placebo from the four 12-week trials in adolescents and adults. Because these trials 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 recommended dosages of fluticasone propionate improved significantly compared with placebo by the first week of treatment, and improvement was maintained for up to 1 year or more.

Figure 1: A 12-Week Clinical Trial Evaluating FLOVENT DISKUS 100 mcg Twice Daily in Adolescents and Adults Receiving Bronchodilators Alone

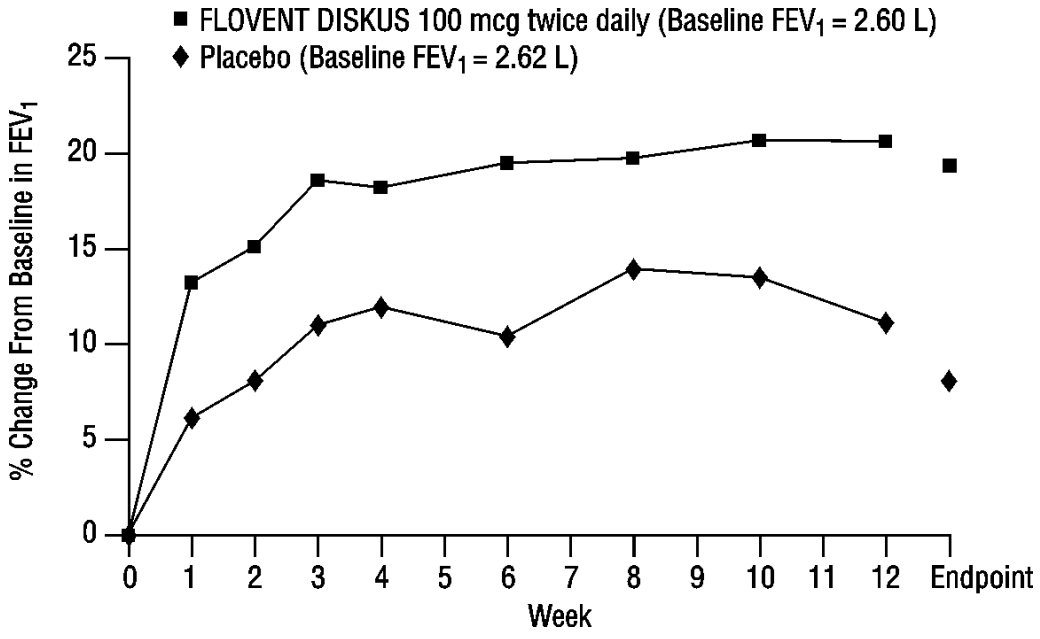


Figure 2: A 12-Week Clinical Trial Evaluating FLOVENT DISKUS 100 mcg Twice Daily in Adolescents and Adults Receiving Inhaled Corticosteroids

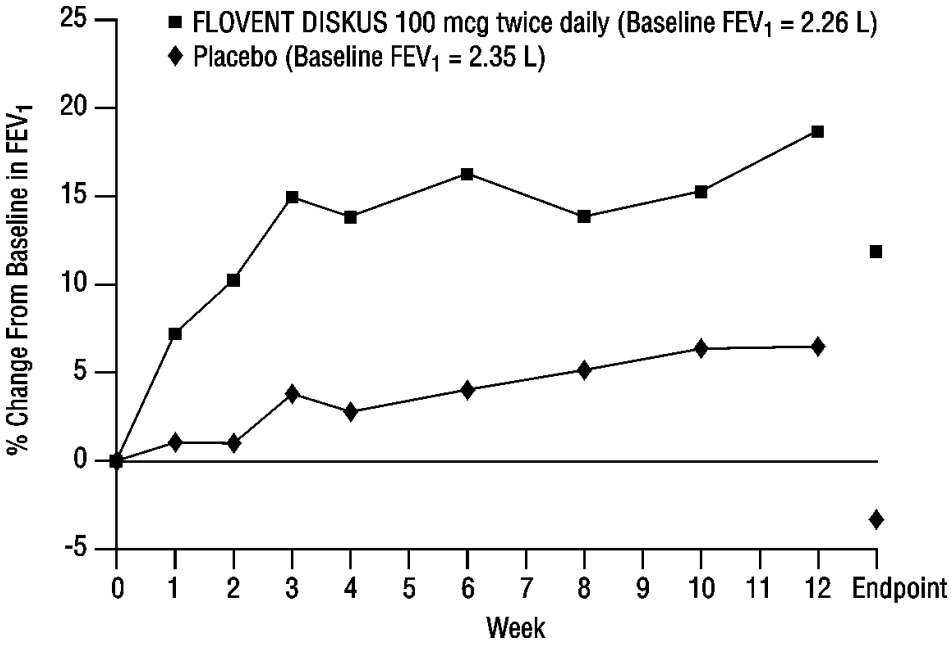


Figure 3: A 12-Week Clinical Trial Evaluating FLOVENT DISKUS 250 mcg Twice Daily in Adolescents and Adults Receiving Inhaled Corticosteroids or Bronchodilators Alone

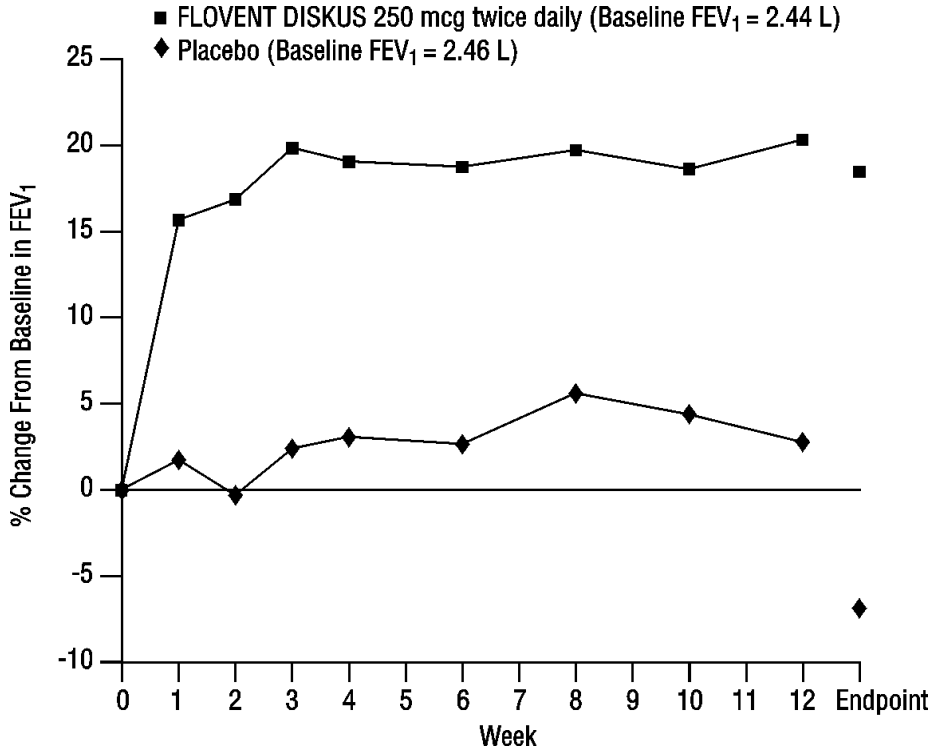
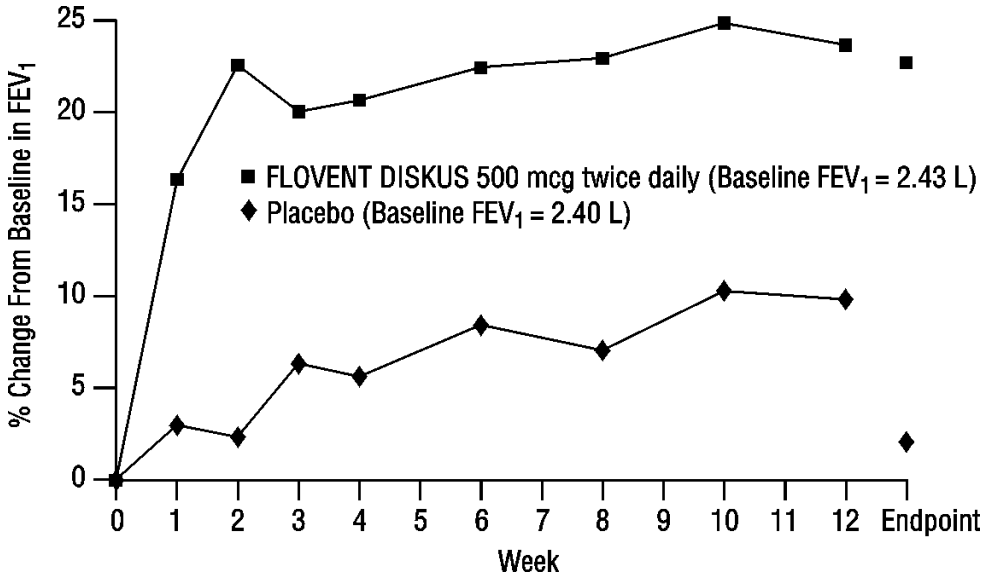


Figure 4: A 12-Week Clinical Trial Evaluating FLOVENT DISKUS 500 mcg Twice Daily in Adolescents and Adults Receiving Inhaled Corticosteroids or Bronchodilators Alone



In all efficacy trials, measures of pulmonary function (FEV_1) and morning peak expiratory flow rate (AM PEFR) were statistically significantly improved as compared with placebo at all twice-daily doses. Patients on all fluticasone propionate dosages were also significantly 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) compared with placebo.

In a clinical trial of 111 patients with severe asthma requiring chronic oral prednisone therapy (average baseline daily prednisone dose was 14 mg), fluticasone propionate given by inhalation powder at doses of 500 and 1000 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 (75% of the patients on 500 mcg twice daily and 89% of the patients on 1000 mcg twice daily as compared with 9% 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.

Pediatric Experience: A 12-week, placebo-controlled clinical trial was conducted in 437 patients (177 on fluticasone propionate via DISKUS) aged 4 to 11 years, approximately half of whom were receiving inhaled corticosteroids at baseline. In this study, doses of fluticasone propionate inhalation powder 50 and 100 mcg twice daily significantly improved FEV_1 (15% and 18% change from baseline at Endpoint, respectively) compared to placebo (7% change). Morning peak expiratory flow rate was also significantly improved with doses of fluticasone propionate 50 and 100 mcg twice daily (26% and 27% change from baseline at Endpoint, respectively)

compared to placebo (14% change). In this study, patients on active treatment were significantly less likely to discontinue treatment 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).

Two other 12-week placebo-controlled clinical trials were conducted in 504 pediatric patients with asthma, approximately half of whom were receiving inhaled corticosteroids at baseline. In these studies, fluticasone propionate inhalation powder was efficacious at doses of 50 and 100 mcg twice daily when compared to placebo on major endpoints including lung function and symptom scores. Pulmonary function improved significantly compared with placebo by the first week of treatment, and patients treated with fluticasone propionate were also less likely to discontinue study participation due to asthma deterioration. One hundred ninety-two (192) patients received fluticasone propionate for up to 1 year during an open-label extension. Data from this open-label extension suggested that lung function improvements could be maintained up to 1 year.

INDICATIONS AND USAGE: FLOVENT DISKUS is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric 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 DISKUS is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS: FLOVENT DISKUS 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.

WARNINGS: Particular care is needed for patients who are transferred from systemically active corticosteroids to FLOVENT DISKUS because deaths due to adrenal insufficiency have occurred in patients with asthma 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 glucocorticoid 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 111 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, arthritis, and eosinophilic conditions.

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

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 DISKUS, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with FLOVENT DISKUS 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: Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS: Pediatric Use.)

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 may appear in a small number of patients, particularly at higher doses. If such changes occur, fluticasone propionate inhalation powder should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

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 tuberculosis 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 DISKUS 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.

It is important that patients understand how to use the DISKUS inhalation device appropriately and how it should be used in relation to other asthma medications they are taking. Patients should be given the following information:

1. Patients should use FLOVENT DISKUS 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.
2. FLOVENT DISKUS should not be used with a spacer device.
3. If you are pregnant or nursing, contact your physician about the use of FLOVENT DISKUS.
4. Effective and safe use of FLOVENT DISKUS includes an understanding of the way that it should be used:
   - Never exhale into the DISKUS.
   - Never attempt to take the DISKUS apart.
   - Always activate and use the DISKUS in a level, horizontal position.
   - Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
   - Always keep the DISKUS in a dry place.
   - Discard **6 weeks (50-mcg strength) or 2 months (100- and 250-mcg strengths)** after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads “0”), whichever comes first.
5. Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult their physicians without delay.
6. For the proper use of FLOVENT DISKUS and to attain maximum improvement, the patient should read and follow carefully the Patient's Instructions for Use accompanying the product.

Drug Interactions: In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single dose of fluticasone propionate (1,000 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 cytochrome P450 3A4 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 (less than the maximum recommended daily inhalation dose in adults and approximately equal 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.

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 (less than 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, (less than 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 (less than 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 3 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 administration of a subcutaneous dose of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis), a subcutaneous or an oral dose of 100 mcg/kg to rats (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis), and an oral dose of 300 mcg/kg to rabbits (approximately 3 times 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. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of 10 mcg/kg of tritiated fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) resulted in measurable radioactivity in the milk. Since there are no data from controlled trials on the use of FLOVENT DISKUS by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue FLOVENT DISKUS, taking into account the importance of FLOVENT DISKUS to the mother.

Pediatric Use: Five hundred twenty (520) patients 4 to 11 years of age and 66 patients 12 to 16 years of age were treated with FLOVENT DISKUS in US pivotal clinical trials. The safety and effectiveness of FLOVENT DISKUS in children below 4 years of age have not been established.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm/year (range, 0.3 to 1.8 cm/year) and appears to depend upon the dose and duration of exposure. The specific growth effects of inhaled fluticasone propionate have also been studied in a controlled clinical trial (see data below). This effect was observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of children and adolescents receiving orally inhaled corticosteroids, including FLOVENT DISKUS, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including FLOVENT DISKUS, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

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.

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 7 placebo-controlled US clinical trials in which 1176 pediatric, adolescent, and adult patients (466 females and 710 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 US Controlled Clinical Trials With FLOVENT DISKUS in Patients Previously Receiving Bronchodilators and/or Inhaled Corticosteroids

Adverse Event	Placebo (n = 543) %	FLOVENT 50 mcg Twice Daily (n = 178) %	FLOVENT 100 mcg Twice Daily (n = 305) %	FLOVENT 250 mcg Twice Daily (n = 86) %	FLOVENT 500 mcg Twice Daily (n = 64) %
Ear, nose, and throat					
Upper respiratory tract infection	16	20	18	21	14

Throat irritation	8	13	13	3	22
Sinusitis/sinus infection	6	9	10	6	6
Upper respiratory inflammation	3	5	5	0	5
Rhinitis	2	4	3	1	2
Oral candidiasis	7	<1	9	6	5
Gastrointestinal					
Nausea and vomiting	4	8	4	1	2
Gastrointestinal discomfort and pain	3	4	3	2	2
Viral gastrointestinal infection	1	4	3	3	5
Non-site specific					
Fever	4	7	7	1	2
Viral infection	2	2	2	0	5
Lower respiratory					
Viral respiratory infection	4	4	5	1	2
Cough	4	3	5	1	5
Bronchitis	1	2	3	0	8
Neurological					
Headache	7	12	12	2	14
Musculoskeletal and trauma					
Muscle injury	1	2	0	1	5
Musculoskeletal pain	2	4	3	2	5
Injury	<1	2	<1	0	5
Average duration of exposure (days)	56	76	73	79	78

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 that occurred at a greater incidence than with placebo were:

Cardiovascular: Palpitations.

Drug Interaction, Overdose, and Trauma: Soft tissue injuries, contusions and hematomas, wounds and lacerations, postoperative complications, burns, poisoning and toxicity, pressure-induced disorders.

Ear, Nose, and Throat: Ear signs and symptoms; rhinorrhea/postnasal drip; hoarseness/dysphonia; epistaxis; tonsillitis; nasal signs and symptoms; laryngitis; unspecified oropharyngeal plaques; otitis; ear, nose, throat, and tonsil signs and symptoms; ear, nose, and throat polyps; allergic ear, nose, and throat disorders; throat constriction.

Endocrine and Metabolic: Fluid disturbances, weight gain, goiter, disorders of uric acid metabolism, appetite disturbances.

Eye: Keratitis and conjunctivitis, blepharoconjunctivitis.

Gastrointestinal: Diarrhea, gastrointestinal signs and symptoms, oral ulcerations, dental discomfort and pain, gastroenteritis, gastrointestinal infections, abdominal discomfort and pain, oral erythema and rashes, mouth and tongue disorders, oral discomfort and pain, tooth decay.

Hepatobiliary Tract and Pancreas: Cholecystitis.

Lower Respiratory: Lower respiratory infections.

Musculoskeletal: Muscle pain, arthralgia and articular rheumatism, muscle cramps and spasms, musculoskeletal inflammation.

Neurological: Dizziness, sleep disorders, migraines, paralysis of cranial nerves.

Non-Site Specific: Chest symptoms; malaise and fatigue; pain; edema and swelling; bacterial infections; fungal infections; mobility disorders; cysts, lumps, and masses.

Psychiatry: Mood disorders.

Reproduction: Bacterial reproductive infections.

Skin: Skin rashes, urticaria, photodermatitis, dermatitis and dermatosis, viral skin infections, eczema, fungal skin infections, pruritus, acne and folliculitis.

Urology: Urinary infections.

Three of the 7 placebo-controlled US clinical trials were pediatric studies. A total of 592 patients 4 to 11 years were treated with FLOVENT DISKUS (doses of 50 or 100 mcg twice daily) or placebo; an additional 174 patients 4 to 11 years received FLOVENT® ROTADISK® (fluticasone propionate inhalation powder) at the same doses. There were no clinically relevant differences in the pattern or severity of adverse events in children compared with those reported in adults.

In the first 16 weeks of a 52-week clinical trial in adult asthma patients who previously required oral corticosteroids (daily doses of 5 to 40 mg oral prednisone), the effects of FLOVENT DISKUS 500 mcg twice daily (n = 41) and 1000 mcg twice daily (n = 36) were compared with placebo (n = 34) for the frequency of reported adverse events. Adverse events, whether or not considered drug related by the investigators, reported in more than five patients in

the group taking FLOVENT DISKUS and that occurred more frequently with FLOVENT DISKUS than with placebo are shown below (percent FLOVENT DISKUS and percent placebo). In considering these data, the increased average duration of exposure for patients taking FLOVENT DISKUS (105 days for FLOVENT DISKUS versus 75 days for placebo) should be taken into account.

Ear, Nose, and Throat: Hoarseness/dysphonia (9% and 0%), nasal congestion/blockage (16% and 0%), oral candidiasis (31% and 21%), rhinitis (13% and 9%), sinusitis/sinus infection (33% and 12%), throat irritation (10% and 9%), and upper respiratory tract infection (31% and 24%).

Gastrointestinal: Nausea and vomiting (9% and 0%).

Lower Respiratory: Cough (9% and 3%) and viral respiratory infections (9% and 6%).

Musculoskeletal: Arthralgia and articular rheumatism (17% and 3%) and muscle pain (12% and 0%).

Non-Site Specific: Malaise and fatigue (16% and 9%) and pain (10% and 3%).

Skin: Pruritus (6% and 0%) and skin rashes (8% and 3%).

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

Ear, Nose, and Throat: Aphonia and throat soreness.

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

Eye: Cataracts.

Psychiatry: Agitation, aggression, depression, and restlessness.

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

Skin: Contusions and ecchymoses.

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 (>2200 and >4400 times, respectively, the maximum recommended daily inhalation dose in adults and >10,000 and >20,000 times, respectively, the maximum recommended daily inhalation dose in children on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION: FLOVENT DISKUS 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. 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 DISKUS 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 asthma therapy, are listed in the following table.

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

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†	500-1000 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.

† **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 DISKUS. 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.

‡ The choice of starting dose should be made on the basis of individual patient assessment. A controlled clinical study of 111 oral corticosteroid-dependent patients with asthma showed few significant differences between the 2 doses of FLOVENT DISKUS on safety and efficacy endpoints. However, inability to decrease the dose of oral corticosteroids further during corticosteroid reduction may be indicative of the need to increase the dose of fluticasone propionate up to the maximum of 1000 mcg twice daily.

Pediatric Use: Because individual responses may vary, children previously maintained on fluticasone propionate ROTADISK® 50 or 100 mcg twice daily may require dosage adjustments upon transfer to FLOVENT DISKUS.

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. Based on available data for FLOVENT DISKUS, no dosage adjustment is recommended.

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

HOW SUPPLIED: FLOVENT DISKUS 50 mcg is supplied as a disposable, orange-colored device containing 60 blisters. The DISKUS inhalation device is packaged within an

orange-colored, plastic-coated, moisture-protective foil pouch (NDC 0173-0600-02). FLOVENT DISKUS 50 mcg is also supplied in an institutional pack of one orange-colored, disposable DISKUS inhalation device containing 28 blisters. The DISKUS inhalation device is packaged within an orange-colored, plastic-coated foil pouch (NDC 0173-0600-00).

FLOVENT DISKUS 100 mcg is supplied as a disposable, orange-colored device containing 60 blisters. The DISKUS inhalation device is packaged within an orange-colored, plastic-coated, moisture-protective foil pouch (NDC 0173-0602-02). FLOVENT DISKUS 100 mcg is also supplied in an institutional pack of one orange-colored, disposable DISKUS inhalation device containing 28 blisters. The DISKUS inhalation device is packaged within an orange-colored, plastic-coated foil pouch (NDC 0173-0602-00).

FLOVENT DISKUS 250 mcg is supplied as a disposable, orange-colored device containing 60 blisters. The DISKUS inhalation device is packaged within an orange-colored, plastic-coated, moisture-protective foil pouch (NDC 0173-0601-02). FLOVENT DISKUS 250 mcg is also supplied in an institutional pack of one orange-colored, disposable DISKUS inhalation device containing 28 blisters. The DISKUS inhalation device is packaged within an orange-colored, plastic-coated foil pouch (NDC 0173-0601-00).

Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation device is not reusable. The device should be discarded 6 weeks (50-mcg strength) or 2 months (100- and 250-mcg strengths) after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads "0"), whichever comes first. Do not attempt to take the device apart.

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