HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLOVENT DISKUS safely and effectively. See full prescribing information for FLOVENT DISKUS.

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

Initial U.S. Approval: 1994

----------RECENT MAJOR CHANGES ----------

Warnings and Precautions, Hypersensitivity Reactions, ~~February 2010~~March 2010
Including Anaphylaxis (5.6), Reduction in Bone Mineral Density (5.7), Drug Interaction With Strong Cytochrome P450 3A4 Inhibitors (5.11)

---------- INDICATIONS AND USAGE----------

FLOVENT DISKUS is an inhaled corticosteroid indicated for:

- Maintenance treatment of asthma as prophylactic therapy in patients 4 years and older. (1)
- Treatment of asthma for patients requiring oral corticosteroid therapy. (1)

FLOVENT DISKUS is NOT indicated for the relief of acute bronchospasm. (1)

----------DOSAGE AND ADMINISTRATION----------

For oral inhalation only. Dosing is based on prior asthma therapy. (2)

Previous Therapy	Recommended Starting Dosage	Highest Recommended Dosage
Patients aged ≥12 years		
Bronchodilators alone	100 mcg twice daily	500 mcg twice daily
Inhaled corticosteroids	100-250 mcg twice daily	500 mcg twice daily
Oral corticosteroids	500-1,000 mcg twice daily	1,000 mcg twice daily
Patients aged 4-11 years	50 mcg twice daily	100 mcg twice daily

---------- DOSAGE FORMS AND STRENGTHS----------

Inhalation powder with 50, 100, or 250 mcg per actuation. (3)

---------- CONTRAINDICATIONS ----------

- Primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Localized infections: *Candida albicans* infection of the mouth and pharynx. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse mouth following inhalation. (5.1)
- Immunosuppression: Potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex. More serious or even fatal course of chickenpox or measles in susceptible patients. Use caution in patients with above because of the potential for worsening of these infections. (5.3)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to FLOVENT DISKUS. (5.4)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue FLOVENT DISKUS slowly. (5.5)
- Hypersensitivity reactions, including anaphylaxis, may occur after administration of FLOVENT DISKUS. Discontinue FLOVENT DISKUS if such reactions occur. (4, 5.6)
- Effect on growth: Monitor growth of pediatric patients. (5.8)
- Glaucoma and cataracts: Close monitoring is warranted. (5.9)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence >3%) include upper respiratory tract infection or inflammation, throat irritation, sinusitis, rhinitis, oral candidiasis, nausea and vomiting, gastrointestinal discomfort, fever, cough, bronchitis, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

Use with strong cytochrome P450 3A4 inhibitors such as ritonavir and ketoconazole is not recommended. Systemic corticosteroid effects may occur. (7.1, 7.2)

---------- USE IN SPECIFIC POPULATIONS ----------

Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: ~~February 2010~~ March 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLOVENT® DISKUS® is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 4 years 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.

2 DOSAGE AND ADMINISTRATION

FLOVENT DISKUS should be administered by the orally inhaled route only in patients 4 years and older. Individual patients will experience a variable time to onset and degree of symptom relief. 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 dosage to reduce the possibility of side effects. For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, higher dosages may provide additional asthma control. The safety and efficacy of FLOVENT DISKUS when administered in excess of recommended dosages have not been established.

The recommended starting dosage and the highest recommended dosage of FLOVENT DISKUS, based on prior asthma therapy, are listed in Table 1.

Table 1. Recommended Dosages of FLOVENT DISKUS

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

Previous Therapy	Recommended Starting Dosage	Highest Recommended Dosage
Adult and adolescent patients (aged ≥12 years)		
Bronchodilators alone	100 mcg twice daily	500 mcg twice daily
Inhaled corticosteroids	100-250 mcg twice daily[a]	500 mcg twice daily
Oral corticosteroids[b]	500-1,000 mcg twice daily[c]	1,000 mcg twice daily
Pediatric patients (aged 4-11 years)[d]	50 mcg twice daily[a]	100 mcg twice daily

[a] Starting dosages above 100 mcg twice daily for adult and adolescent patients and 50 mcg twice daily for pediatric patients aged 4 to 11 years 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 the specific agent.

[b] For patients currently receiving chronic oral corticosteroid therapy, prednisone should be reduced no faster than 2.5 to 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 and Precautions (5.4)]*. Once prednisone reduction is complete, the dosage of FLOVENT DISKUS should be reduced to the lowest effective dosage.

[c] The choice of starting dosage 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 1,000 mcg twice daily.

[d] Because individual responses may vary, pediatric patients previously maintained on other inhaled corticosteroids may require dosage adjustments upon transfer to FLOVENT DISKUS.

3 DOSAGE FORMS AND STRENGTHS

FLOVENT DISKUS is an inhalation powder. Each actuation delivers 46, 94, or 229 mcg of fluticasone propionate from the DISKUS® inhalation unit. FLOVENT DISKUS is supplied as a disposable orange inhalation unit containing 60 blisters of powder formulation packaged in a plastic-coated, moisture-protective foil pouch.

4 CONTRAINDICATIONS

The use of FLOVENT DISKUS is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required *[see Warnings and Precautions (5.2)]*.
- Severe hypersensitivity to milk proteins *[see Warnings and Precautions (5.6), Adverse Reactions (6.2), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with FLOVENT DISKUS. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with FLOVENT DISKUS continues, but at times therapy with FLOVENT DISKUS may need to be interrupted. Patients should rinse the mouth after inhalation of FLOVENT DISKUS *[see Adverse Reactions (6.1)]*.

5.2 Acute Asthma Episodes

FLOVENT DISKUS is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm. 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 FLOVENT DISKUS. During such episodes, patients may require therapy with oral corticosteroids.

5.3 Immunosuppression

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.

Because of the potential for worsening infections, inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, viral or parasitic infections; or ocular herpes simplex.

5.4 Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids 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 hypothalamic-pituitary-adrenal (HPA) function.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to FLOVENT DISKUS. In a clinical trial of 111 patients, prednisone reduction was accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during transfer to FLOVENT DISKUS. Successive reduction of prednisone dose was allowed only when lung function; symptoms; and as-needed, short-acting beta-agonist use were better than or comparable to that seen before initiation of prednisone dose reduction. Lung function (forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [AM PEF]), 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.

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 inhaled corticosteroids may provide control of asthma symptoms during these episodes, in recommended doses they supply less than normal physiological amounts of glucocorticoid (cortisol) systemically and do 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 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.

Transfer of patients from systemic corticosteroid therapy to FLOVENT DISKUS may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions. 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.

5.5 Hypercorticism and Adrenal Suppression

Fluticasone propionate will often help control 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 FLOVENT DISKUS 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. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing FLOVENT DISKUS.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with FLOVENT DISKUS 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 FLOVENT DISKUS is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of FLOVENT DISKUS should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma.

5.6 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, and bronchospasm, may occur after administration of FLOVENT DISKUS. There have been reports of anaphylactic reactions in patients with severe milk protein allergy; therefore, patients with severe milk protein allergy should not take FLOVENT DISKUS *[see Contraindications (4)]*.

5.7 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term outcomes is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of

osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

5.8 Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients *[see Use in Specific Populations (8.4)]*. Monitor the growth of pediatric patients receiving FLOVENT DISKUS routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including FLOVENT DISKUS, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms.

5.9 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients following the long-term administration of inhaled corticosteroids, including fluticasone propionate. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

5.10 Paradoxical Bronchospasm

As with other inhaled 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 immediately and alternative therapy instituted.

5.11 Drug Interaction With Strong Cytochrome P450 3A4 Inhibitors

The use of strong cytochrome P450 [CYP] 3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with FLOVENT DISKUS is not recommended because increased systemic corticosteroid adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

5.12 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions. Some of these patients have 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.

6 ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.1)]*

- Immunosuppression *[see Warnings and Precautions (5.3)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.5)]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.7)]*
- Growth effects *[see Warnings and Precautions (5.8)]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The incidence of common adverse reactions in Table 2 is based upon 7 placebo-controlled US clinical trials in which 1,176 pediatric, adolescent, and adult patients (466 females and 710 males) previously treated with as-needed bronchodilators and/or inhaled corticosteroids were treated twice daily for up to 12 weeks with FLOVENT DISKUS (doses of 50 to 500 mcg) or placebo.

Table 2. Adverse Reactions With >3% Incidence in US Controlled Clinical Trials With FLOVENT DISKUS in Patients With Asthma Previously Receiving Bronchodilators and/or Inhaled Corticosteroids

Adverse Event	FLOVENT DISKUS 50 mcg Twice Daily (n = 178) %	FLOVENT DISKUS 100 mcg Twice Daily (n = 305) %	FLOVENT DISKUS 250 mcg Twice Daily (n = 86) %	FLOVENT DISKUS 500 mcg Twice Daily (n = 64) %	Placebo (n = 543) %
Ear, nose, and throat					
Upper respiratory tract infection	20	18	21	14	16
Throat irritation	13	13	3	22	8
Sinusitis/sinus infection	9	10	6	6	6
Upper respiratory inflammation	5	5	0	5	3
Rhinitis	4	3	1	2	2
Oral candidiasis	<1	9	6	5	7
Gastrointestinal					
Nausea and vomiting	8	4	1	2	4

Gastrointestinal discomfort and pain	4	3	2	2	3
Viral gastrointestinal infection	4	3	3	5	1
Non-site specific					
Fever	7	7	1	2	4
Viral infection	2	2	0	5	2
Lower respiratory					
Viral respiratory infection	4	5	1	2	4
Cough	3	5	1	5	4
Bronchitis	2	3	0	8	1
Neurological					
Headache	12	12	2	14	7
Musculoskeletal and trauma					
Muscle injury	2	0	1	5	1
Musculoskeletal pain	4	3	2	5	2
Injury	2	<1	0	5	<1

Table 2 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 groups treated with FLOVENT DISKUS and were more common than in the placebo group. Less than 2% of patients discontinued from the studies because of adverse reactions. The average duration of exposure was 73 to 79 days in the active treatment groups compared with 56 days in the placebo group.

Additional Adverse Reactions: Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were reported more frequently by patients with asthma treated with FLOVENT DISKUS compared with patients treated with placebo include the following: palpitations; soft tissue injuries; contusions and hematomas; wounds and lacerations; burns; poisoning and toxicity; pressure-induced disorders; hoarseness/dysphonia; epistaxis; ear, nose, throat, and tonsil signs and symptoms; ear, nose, and throat polyps; allergic ear, nose, and throat disorders; throat constriction; fluid disturbances; weight gain; appetite disturbances; keratitis and conjunctivitis; blepharoconjunctivitis; gastrointestinal signs and symptoms; oral ulcerations; dental discomfort and pain; oral erythema and rashes; mouth and tongue disorders; oral discomfort and pain; tooth decay; cholecystitis; arthralgia and articular rheumatism; muscle cramps and spasms; musculoskeletal inflammation; dizziness; sleep disorders; migraines; paralysis of cranial nerves; edema and swelling; bacterial infections; fungal infections; mobility disorders; mood disorders; bacterial reproductive infections; photodermatitis; dermatitis and dermatosis; viral skin infections; eczema; pruritus; acne and folliculitis; urinary infections.

Three (3) 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 (dosages 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 patients with asthma 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 1,000 mcg twice daily (n = 36) were compared with placebo (n = 34) for the frequency of reported adverse events. The average duration of exposure for patients taking FLOVENT DISKUS was 105 days compared with 75 days for placebo. Adverse events, whether or not considered drug related by the investigators, reported in more than 5 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).

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%).

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use of fluticasone propionate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. 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, facial and oropharyngeal edema, and throat soreness.

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

Eye: Cataracts.

Immune System Disorders: Immediate and delayed hypersensitivity reactions, including anaphylaxis, rash, angioedema, and bronchospasm, have been reported. Anaphylactic reactions in patients with severe milk protein allergy have been reported.

Psychiatry: Agitation, aggression, anxiety, depression, and restlessness. Behavioral changes, including hyperactivity and irritability, have been reported very rarely and primarily in children.

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

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 *[see Warnings and Precautions (5.12)]*.

7 DRUG INTERACTIONS

7.1 Strong Cytochrome P450 3A4 Inhibitors

Fluticasone propionate is a substrate of CYP 3A4. The use of strong CYP 3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with FLOVENT DISKUS is not recommended because increased systemic corticosteroid adverse effects may occur.

A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP 3A4 inhibitor) can significantly increase plasma fluticasone propionate concentration, resulting in significantly reduced serum cortisol concentrations *[see Clinical Pharmacology (12.3)]*. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the curve (AUC), but had no effect on urinary excretion of cortisol. Coadministration of fluticasone propionate and ketoconazole is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies with FLOVENT DISKUS in pregnant women. FLOVENT DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects: Subcutaneous studies in the mouse and rat at doses approximately 0.1 and 0.4, respectively, times the maximum recommended human daily inhalation dose (MRHD) in adults on a mg/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 approximately 0.03 times the MRHD in adults on a mg/m^2 basis. However, no teratogenic effects were reported at oral doses up to approximately 2 times the MRHD in adults on a mg/m^2 basis. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration *[see Clinical Pharmacology (12.3)]*.

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.

8.3 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 tritiated fluticasone propionate at a dose approximately 0.04 times the MRHD in adults on a mg/m^2 basis resulted in measurable radioactivity in milk.

Since there are no data from controlled trials on the use of FLOVENT DISKUS by nursing mothers, caution should be exercised when FLOVENT DISKUS is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of FLOVENT DISKUS in children 4 years and older have been established *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*. The safety and effectiveness of FLOVENT DISKUS in children younger than 4 years have not been established.

Effects on Growth: Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. A reduction of growth velocity in children or teenagers may occur as a result of poorly controlled asthma or from use of corticosteroids including inhaled corticosteroids. The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known.

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 dose and duration of exposure. 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 effects on growth velocity of treatment with orally inhaled corticosteroids for over 1 year, including the impact on final adult height, are unknown. 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 (FLOVENT ROTADISK) at 50 and 100 mcg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to 11 years. 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). In children aged 8.5 years, 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 clinical significance of these growth data is not certain.

8.5 Geriatric Use

Safety data have been collected on 280 patients (FLOVENT DISKUS n = 83, FLOVENT ROTADISK n = 197) 65 years or older and 33 patients (FLOVENT DISKUS n = 14, FLOVENT ROTADISK n = 19) 75 years or older who have been treated with fluticasone propionate inhalation powder in US and non-US clinical trials. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using FLOVENT DISKUS have not been conducted in patients with 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.

8.7 Renal Impairment

Formal pharmacokinetic studies using FLOVENT DISKUS have not been conducted in patients with renal impairment.

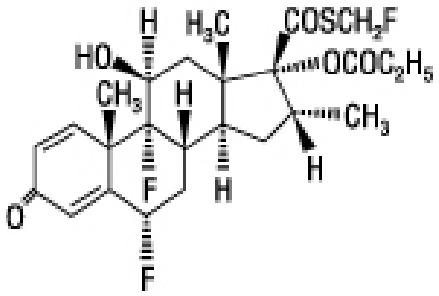
10 OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.5)]*. Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate CFC inhalation aerosol was well tolerated. Doses of 1,320 mcg administered to healthy human volunteers twice daily for 7 to 15 days were 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.

No deaths were seen in mice given an oral dose of 1,000 mg/kg (approximately 2,000 and 9,600 times the MRHD in adults and children aged 4 to 11 years, respectively, on a mg/m^2 basis). No deaths were seen in rats given an oral dose of 1,000 mg/kg (approximately 4,100 and 19,000 times the MRHD in adults and children aged 4 to 11 years, respectively, on a mg/m^2 basis).

11 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 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 inhalation delivery systems containing a double-foil blister strip of a powder formulation of fluticasone propionate intended for oral inhalation only. The DISKUS inhalation unit, which is the delivery component, is an integral part of the drug product. Each blister on the double-foil strip within the unit contains 50, 100, or 250 mcg of microfine fluticasone propionate in 12.5 mg of formulation containing lactose (which contains milk proteins). After a blister containing medication is opened by activating the DISKUS, 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, 94, or 229 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 (FEV_1 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS 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 may depend on patient factors, such as inspiratory flow profile.

12 CLINICAL PHARMACOLOGY

12.1 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 clinical significance of these findings is unknown.

Inflammation is 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, neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Though effective for the treatment of asthma, corticosteroids do not affect asthma symptoms immediately. Individual patients will experience a variable time to onset and degree of symptom relief. 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 patients with asthma have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects with recommended doses of orally inhaled fluticasone propionate. 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.

12.2 Pharmacodynamics

In clinical trials with fluticasone propionate inhalation powder using dosages up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) 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, 1 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 aged 4 to 11 years, 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.

The potential systemic effects of inhaled fluticasone propionate on the HPA axis were also studied in patients with asthma. Fluticasone propionate given by inhalation aerosol at dosages 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 with 29% of patients treated with prednisone.

12.3 Pharmacokinetics

Absorption: Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. 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 absolute bioavailability of fluticasone propionate from the DISKUS device in healthy volunteers averages 7.8%.

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 dosage 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 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

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

Specific Populations: *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 aged 4 to 11 years 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 peak fluticasone propionate plasma concentrations at the 50- and 100-mcg dose levels were 5 and 8 pg/mL, respectively.

Hepatic and Renal Impairment: Formal pharmacokinetic studies using FLOVENT DISKUS have not been conducted in patients with hepatic or renal impairment. However, 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.

Drug Interactions: *Ritonavir:* Fluticasone propionate is a substrate of CYP 3A4. Coadministration of fluticasone propionate and the strong CYP 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable, peak levels (C_{max}) averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and $AUC_{(0-\tau)}$ averaged 8.43 pg•hr/mL (range, 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range, 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma

fluticasone propionate concentration resulted in a significant decrease (86%) in serum cortisol AUC.

Ketoconazole: In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Following orally inhaled fluticasone propionate alone, $AUC_{(2\text{-last})}$ averaged 1.559 ng•hr/mL (range, 0.555 to 2.906 ng•hr/mL) and $AUC_{(2\text{-}\infty)}$ averaged 2.269 ng•hr/mL (range, 0.836 to 3.707 ng•hr/mL). Fluticasone propionate $AUC_{(2\text{-last})}$ and $AUC_{(2\text{-}\infty)}$ increased to 2.781 ng•hr/mL (range, 2.489 to 8.486 ng•hr/mL) and 4.317 ng•hr/mL (range, 3.256 to 9.408 ng•hr/mL), respectively, after coadministration of ketoconazole with orally inhaled fluticasone propionate. This increase in plasma fluticasone propionate concentration resulted in a decrease (45%) in serum cortisol AUC.

Erythromycin: In a multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 2 and 10 times the MRHD in adults and children aged 4 to 11 years, respectively, on a mg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately 0.2 times and approximately equivalent to the MRHD in adults and children aged 4 to 11 years, respectively, on a mg/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 in vivo mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 0.2 times the MRHD in adults on a mg/m^2 basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology: Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg (approximately 0.1 and 0.4 times the MRHD in adults on a mg/m^2 basis, respectively) revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (approximately 0.03 times the MRHD in adults on a mg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 2 times the

MRHD in adults on a mg/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 (12.3)]*.

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

14 CLINICAL STUDIES

14.1 Adult and Adolescent Patients 12 Years and Older

Four randomized, double-blind, parallel-group, placebo-controlled, US clinical trials were conducted in 1,036 adult and adolescent patients (aged ≥12 years) with asthma to assess the efficacy and safety of FLOVENT DISKUS in the treatment of asthma. Fixed dosages of 100, 250, and 500 mcg twice daily were compared with placebo to provide information about appropriate dosing to cover a range of asthma severity. Patients in these studies included those inadequately 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 FLOVENT DISKUS twice daily.

Figures 1 through 4 display results of pulmonary function tests (mean percent change from baseline in FEV_1 prior to AM dose) for 3 recommended dosages of FLOVENT DISKUS (100, 250, and 500 mcg twice daily) and placebo from the four 12-week trials in adolescents and adults. These trials used predetermined criteria for lack of efficacy (indicators of worsening asthma), resulting in withdrawal of more patients in the placebo group. Therefore, pulmonary function results at Endpoint (the last evaluable FEV_1 result, including most patients' lung function data) are also displayed. Pulmonary function, as determined by percent change from baseline in FEV_1 at recommended dosages of FLOVENT DISKUS 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

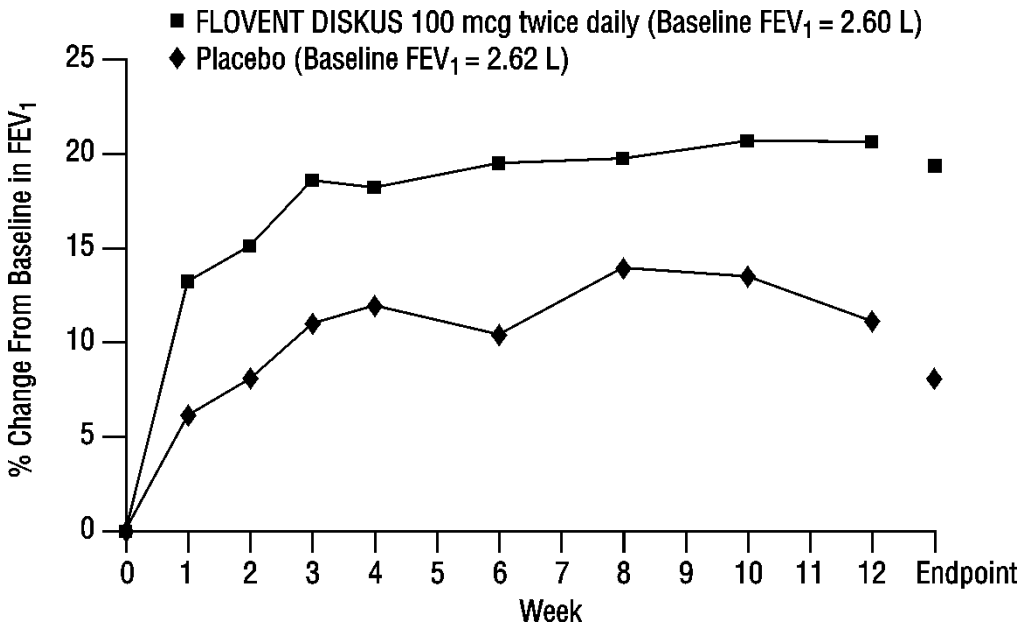


Figure 2. A 12-Week Clinical Trial Evaluating FLOVENT DISKUS 100 mcg Twice Daily in Adolescents and Adults Receiving Inhaled Corticosteroids

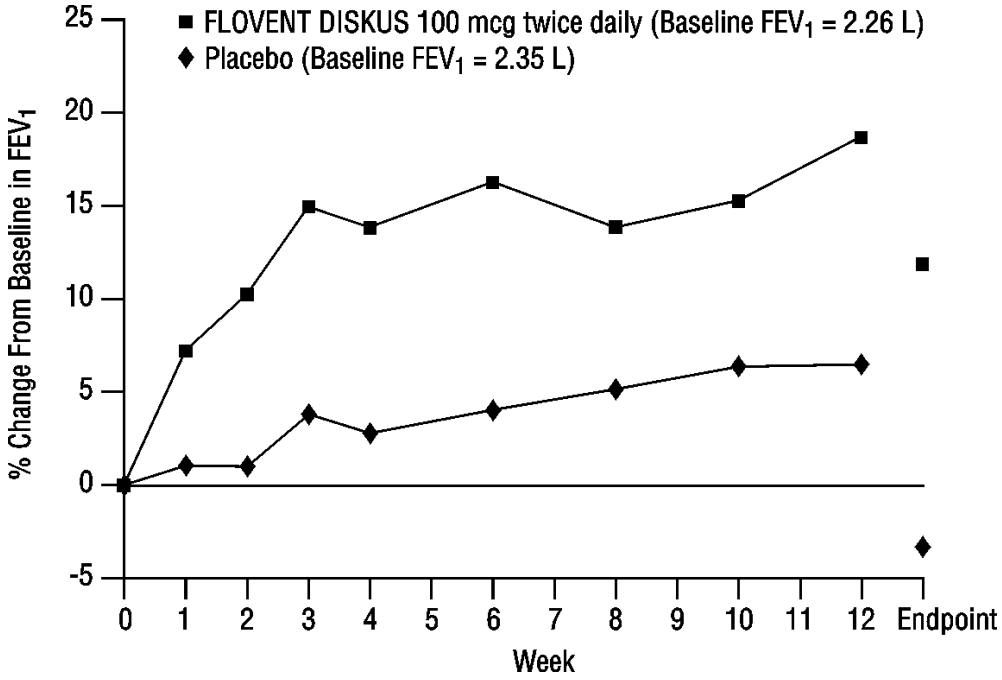


Figure 3. A 12-Week Clinical Trial Evaluating FLOVENT DISKUS 250 mcg Twice Daily in Adolescents and Adults Receiving Inhaled Corticosteroids or Bronchodilators Alone

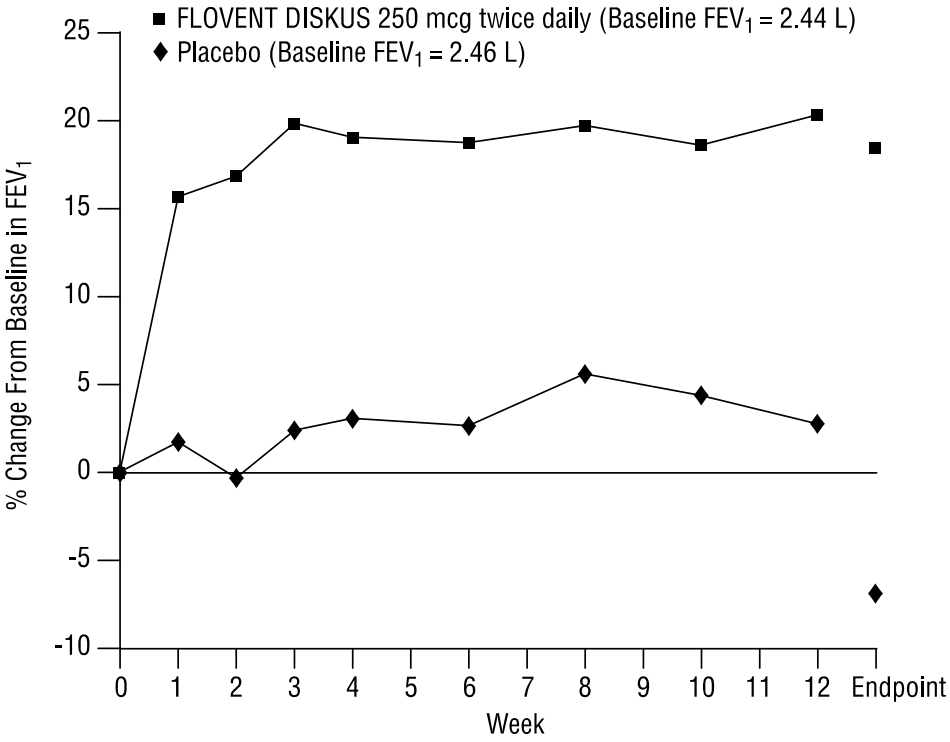
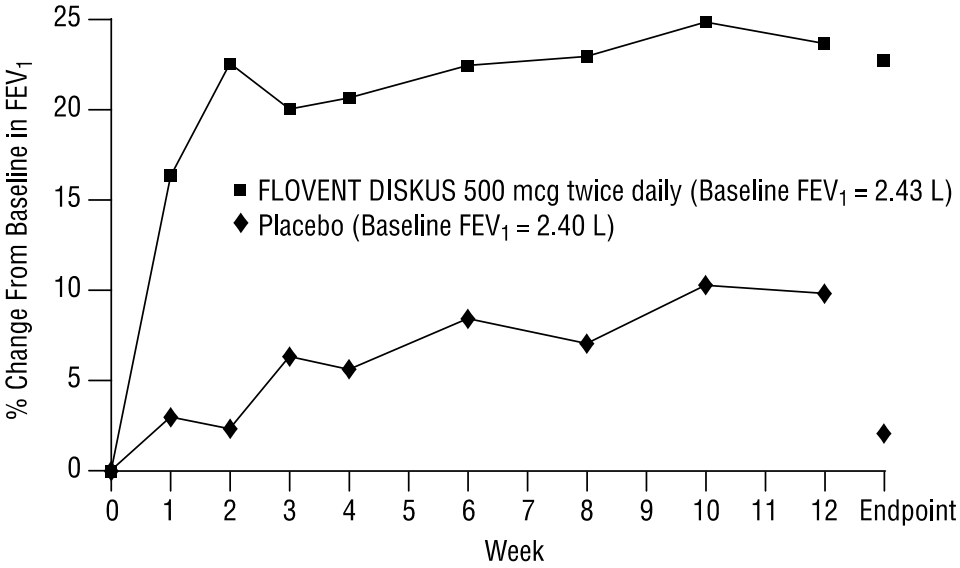


Figure 4. A 12-Week Clinical Trial Evaluating FLOVENT DISKUS 500 mcg Twice Daily in Adolescents and Adults Receiving Inhaled Corticosteroids or Bronchodilators Alone



In all 4 efficacy trials, measures of pulmonary function (FEV_1) were statistically significantly improved as compared with placebo at all twice-daily doses. Patients on all dosages of FLOVENT DISKUS were also 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 PEF, 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 1,000 mcg twice daily was evaluated. Both doses enabled a statistically significantly larger percentage of patients to wean from oral prednisone as compared with placebo (75% of the patients on 500 mcg twice daily and 89% of the patients on 1,000 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.

14.2 Pediatric Patients Aged 4 to 11 Years

A 12-week, placebo-controlled clinical trial was conducted in 437 pediatric patients (177 received FLOVENT DISKUS), 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 with placebo (7% change). AM PEF 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 with 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 PEF, 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, FLOVENT DISKUS was efficacious at doses of 50 and 100 mcg twice daily when compared with 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 FLOVENT DISKUS were also less likely to discontinue study participation due to asthma deterioration. One hundred ninety-two (192) patients received FLOVENT DISKUS 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

FLOVENT DISKUS 50 mcg (NDC 0173-0600-02), FLOVENT DISKUS 100 mcg (NDC 0173-0602-02), and FLOVENT DISKUS 250 mcg (NDC 0173-0601-02) are each supplied as a

disposable orange inhalation unit containing 60 blisters of powder formulation packaged in a plastic-coated, moisture-protective foil pouch in a carton of 1.

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. FLOVENT DISKUS should be discarded 6 weeks (50-mcg strength) or 2 months (100- and 250-mcg strengths) after removal from the moisture-protective foil 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.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling accompanying the product.

17.1 Oral Candidiasis

Patients should be advised that localized infections with *Candida albicans* have occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while still continuing therapy with FLOVENT DISKUS, but at times therapy with FLOVENT DISKUS may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised.

17.2 Status Asthmaticus and Acute Asthma Symptoms

Patients should be advised that FLOVENT DISKUS is not a bronchodilator and is not intended for use as rescue medication for acute asthma exacerbations. Acute asthma symptoms should be treated with an inhaled, short-acting beta-$_2$ agonist such as albuterol. Patients should be instructed to contact their physicians immediately if there is deterioration of their asthma.

17.3 Immunosuppression

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and if they are exposed to consult their physicians without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.

17.4 Hypercorticism and Adrenal Suppression

Patients should be advised that FLOVENT DISKUS may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to FLOVENT DISKUS.

17.5 Hypersensitivity Reactions, Including Anaphylaxis

Patients should be advised that hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, and bronchospasm, may occur after administration of FLOVENT DISKUS. Patients should discontinue FLOVENT DISKUS if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy; therefore, patients with severe milk protein allergy should not take FLOVENT DISKUS.

17.6 Reduction in Bone Mineral Density

Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk.

17.7 Reduced Growth Velocity

Patients should be informed that orally inhaled corticosteroids, including FLOVENT DISKUS, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route.

17.8 Ocular Effects

Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); regular eye examinations should be considered.

17.9 Use Daily for Best Effect

Patients should use FLOVENT DISKUS at regular intervals as directed. Individual patients will experience a variable time to onset and degree of symptom relief and the full benefit may not be achieved until treatment has been administered for 1 to 2 weeks or longer. Patients should not increase the prescribed dosage but should contact their physicians if symptoms do not improve or if the condition worsens. Patients should be instructed not to stop use of FLOVENT DISKUS abruptly. Patients should contact their physicians immediately if they discontinue use of FLOVENT DISKUS.

GlaxoSmithKline
Research Triangle Park, NC 27709

~~February~~ March 2010
FLD:4PI

Patient Information

FLOVENT® *[flō´vent]* 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

Read this Patient Information before you start to use FLOVENT DISKUS and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is FLOVENT DISKUS?

FLOVENT DISKUS is an inhaled prescription corticosteroid medicine for the long-term treatment of asthma in people aged 4 and older.

- FLOVENT DISKUS helps to prevent symptoms of asthma
- FLOVENT DISKUS does not treat the sudden symptoms of an asthma attack, such as wheezing, cough, shortness of breath, and chest pain or tightness. **Always have a fast-acting bronchodilator medicine (rescue inhaler) with you to treat sudden symptoms.**

It is not known if FLOVENT DISKUS is safe and effective in children younger than 4 years of age.

Who should not use FLOVENT DISKUS?

Do not use FLOVENT DISKUS

- to treat sudden symptoms of asthma. **FLOVENT DISKUS is not a rescue inhaler and should not be used to give you fast relief from your asthma attack.** Always use a rescue inhaler such as albuterol, during a sudden asthma attack.
- if you have severe allergy to milk proteins or fluticasone propionate. Ask your doctor if you are not sure.

What should I tell my doctor before taking FLOVENT DISKUS?

Before you use FLOVENT DISKUS, tell your doctor if you:

- have liver problems.

- have been exposed to chickenpox or measles.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if FLOVENT DISKUS will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known if FLOVENT DISKUS passes into your breast milk. You and your doctor should decide if you should use FLOVENT DISKUS while you breast-feed.

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. FLOVENT DISKUS may affect the way other medicines work, and other medicines may affect how FLOVENT DISKUS works. Especially, tell your doctor if you take:

- anti-viral medicines, including medicines that contain ritonavir (commonly used to treat HIV infection or AIDS).
- any other corticosteroid medicines.
- ketoconazole (NIZORAL®), an antifungal medicine.

This is not a complete list of medicines that can affect FLOVENT DISKUS. Ask your doctor if you are not sure if any of your medicines are the kinds listed above.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I use FLOVENT DISKUS?

- Read the detailed Instructions for Use at the end of this leaflet.
- An adult should always watch a child use FLOVENT DISKUS to make sure that it is used correctly, as instructed by your doctor.
- FLOVENT DISKUS comes in 3 strengths. Your doctor has prescribed the one that is best for your condition.
- Use FLOVENT DISKUS exactly as your doctor tells you to use it. Do not change the dose yourself. Your doctor will tell you how many times to inhale your FLOVENT DISKUS and when to use your FLOVENT DISKUS. **Do not** inhale more doses or use your FLOVENT DISKUS more often than your doctor has prescribed.
- FLOVENT DISKUS delivers your dose of medicine as a very fine powder **that most people, but not all, can taste or feel**. Whether or not you can taste or feel your dose of medicine, you should not take more than the prescribed dose. If you are not sure you are getting your dose of FLOVENT DISKUS, contact your doctor or pharmacist.
- It may take 1 to 2 weeks or longer after you start FLOVENT DISKUS for your asthma symptoms to get better. You must use FLOVENT DISKUS regularly. **Do not stop using FLOVENT DISKUS, even if you are feeling better, unless your doctor tells you to.**

- If you miss a dose, just take your next dose at your regular time. **Do not take 2 doses at the same time unless your doctor tells you to. If you are not sure about your dosing, call your doctor.**
- Your doctor may prescribe a rescue inhaler for emergency relief of sudden asthma attacks. Contact your doctor right away if:
  - an asthma attack does not respond to your rescue inhaler or
  - you need more of your rescue inhaler than usual.
- If you also use another medicine by inhalation, you should ask your doctor for instructions on when to use it while you are also using FLOVENT DISKUS.
- Do not use FLOVENT DISKUS with a spacer device.

What should I avoid while taking FLOVENT DISKUS?

If you have not had or have not been vaccinated against chickenpox, measles, or active tuberculosis, you should stay away from people who are infected.

What are the possible side effects of FLOVENT DISKUS?

FLOVENT DISKUS can cause serious side effects, including:

- **fungal infection (thrush) in your mouth and throat.** Tell your doctor if you have any redness or white-colored coating in your mouth.
- **decreased ability to fight infections.** Symptoms of infection may include: fever, pain, aches, chills, feeling tired, nausea and vomiting. Tell your doctor about any signs of infection while you use FLOVENT DISKUS.
- **decreased adrenal function (adrenal insufficiency).** Symptoms of decreased adrenal function include tiredness, weakness, nausea and vomiting, and low blood pressure. Decreased adrenal function can lead to death.
- **allergic reaction (anaphylaxis).** Call your doctor and stop FLOVENT DISKUS right away if you have any symptoms of an allergic reaction:
  - swelling of the face, throat, and tongue
  - rash
  - hives
  - breathing problems
- **lower bone mineral density.** This may be a problem for people who already have a higher chance of low bone density (osteoporosis).
- **slow growth in children.** The growth of children using FLOVENT DISKUS should be checked regularly.
- **eye problems including glaucoma and cataracts.** Tell your doctor about any vision changes while using FLOVENT DISKUS. Your doctor may tell you to have your eyes checked.

- **increased wheezing (bronchospasm).** Increased wheezing can happen right away after using FLOVENT DISKUS. Always have a rescue inhaler with you to treat sudden wheezing.

Call your doctor right away if you have any of the serious side effects listed above or if you have worsening lung symptoms.

The most common side effects of FLOVENT DISKUS include:

- a cold or upper respiratory tract infection
- throat irritation
- nausea and vomiting
- fever
- headache

Tell your doctor if you have any side effects that bother you or that do not go away. These are not all the possible side effects of FLOVENT DISKUS. For more information ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or 1-800-332-1088.

How should I store FLOVENT DISKUS?

Store FLOVENT DISKUS at room temperature between 68°F to 77°F (20°C to 25°C). Store FLOVENT DISKUS in a dry place away from heat and sunlight.

FLOVENT DISKUS is not reusable. Safely throw away medicine that is out of date or no longer needed.

Do not try to take FLOVENT DISKUS apart.

Keep FLOVENT DISKUS and all medicines out of the reach of children.

General information about the safe and effective use of FLOVENT DISKUS.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use FLOVENT DISKUS for a condition for which it was not prescribed. Do not give FLOVENT DISKUS to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about FLOVENT DISKUS. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or doctor for information about FLOVENT DISKUS that is written for health professionals.

For more information go to www.floventdiskus.com or call 1-888-825-5249.

What are the ingredients in FLOVENT DISKUS?

Active ingredient: fluticasone propionate (microfine)
Inactive ingredient: lactose (which contains milk proteins)

Instructions for Using FLOVENT DISKUS

The parts of your FLOVENT DISKUS

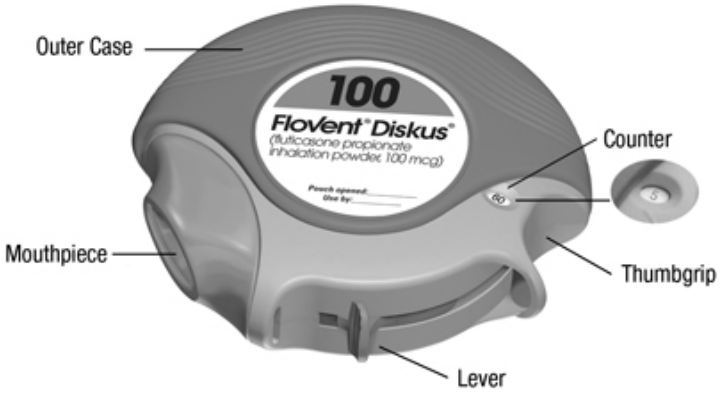


Figure 1

The counter shows you how many doses are left. The counter number will count down each time you use FLOVENT DISKUS. After you have used 55 doses (23 doses from the sample pack), the numbers 5 to 0 will show in **red** to warn you that there are only a few doses left (see Figure 1).

Using your FLOVENT DISKUS

- Take FLOVENT DISKUS out of the moisture-protective foil pouch just before you use it for the first time. Safely throw away the foil pouch.
- FLOVENT DISKUS will be in the closed position. Write the “Pouch opened” and “Use by” dates in the blank lines on the label (see Figure 1). The “Use by” date for FLOVENT DISKUS 50 mcg is 6 weeks from the date you opened the pouch. The “Use by” date for FLOVENT DISKUS 100 mcg and FLOVENT DISKUS 250 mcg is 2 months from the date you opened the pouch.

Read the following steps before using FLOVENT DISKUS and follow them at each use. If you have any questions, ask your doctor or pharmacist.

Figure 2

Figure 3

1. Open

Hold FLOVENT DISKUS in one hand and put the thumb of your other hand on the thumbgrip. Push your thumb away from you as far as it will go until the mouthpiece shows and snaps into place (see Figure 2).

2. Click

Hold FLOVENT DISKUS in a level, flat position with the mouthpiece towards you. Slide the lever away from you as far as it will go until it clicks (see Figure 3). The number on the dose counter will count down by 1. FLOVENT DISKUS is now ready to use.

To avoid releasing a dose by mistake before you are ready to inhale:

- **Do not close FLOVENT DISKUS.**
- **Do not tilt FLOVENT DISKUS.**
- **Do not play with the lever.**
- **Do not slide the lever more than once.**

Figure 4

Figure 5

3. Inhale

Before you inhale your dose of FLOVENT DISKUS, breathe out as far as you can while you hold FLOVENT DISKUS level and away from your mouth (see Figure 4). **Never breathe out into the FLOVENT DISKUS mouthpiece.**

Put the mouthpiece to your lips (see Figure 5). Breathe in quickly and deeply through FLOVENT DISKUS. Do not breathe in through your nose.

Remove FLOVENT DISKUS from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly.

Rinse your mouth with water after inhaling the medicine. Spit out the water. Do not swallow it.

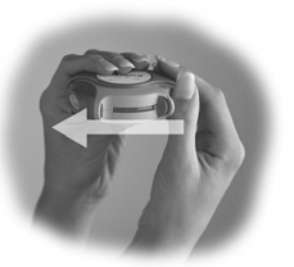


Figure 6

4. **Close FLOVENT DISKUS when you are finished taking a dose.** Put your thumb on the thumbgrip and slide it back towards you as far as it will go (see Figure 6). FLOVENT DISKUS will click shut. The lever will automatically return to its original position.

   FLOVENT DISKUS is now ready for you to take your next scheduled dose in about 12 hours. When you are ready for your next dose, you will repeat steps 1 through 4.

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NIZORAL is a registered trademark of Janssen Pharmaceutica.

GlaxoSmithKline
Research Triangle Park, NC 27709

~~February~~ March 2010 FLD:4PIL

Patient Information

FLOVENT® *[flō´vent]* 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

Read this Patient Information before you start to use FLOVENT DISKUS and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is FLOVENT DISKUS?

FLOVENT DISKUS is an inhaled prescription corticosteroid medicine for the long-term treatment of asthma in people aged 4 and older.

- FLOVENT DISKUS helps to prevent symptoms of asthma
- FLOVENT DISKUS does not treat the sudden symptoms of an asthma attack, such as wheezing, cough, shortness of breath, and chest pain or tightness. **Always have a fast-acting bronchodilator medicine (rescue inhaler) with you to treat sudden symptoms.**

It is not known if FLOVENT DISKUS is safe and effective in children younger than 4 years of age.

Who should not use FLOVENT DISKUS?

Do not use FLOVENT DISKUS

- to treat sudden symptoms of asthma. **FLOVENT DISKUS is not a rescue inhaler and should not be used to give you fast relief from your asthma attack.** Always use a rescue inhaler such as albuterol, during a sudden asthma attack.
- if you have severe allergy to milk proteins or fluticasone propionate. Ask your doctor if you are not sure.

What should I tell my doctor before taking FLOVENT DISKUS?

Before you use FLOVENT DISKUS, tell your doctor if you:

- have liver problems.

- have been exposed to chickenpox or measles.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if FLOVENT DISKUS will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known if FLOVENT DISKUS passes into your breast milk. You and your doctor should decide if you should use FLOVENT DISKUS while you breast-feed.

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. FLOVENT DISKUS may affect the way other medicines work, and other medicines may affect how FLOVENT DISKUS works. Especially, tell your doctor if you take:

- anti-viral medicines, including medicines that contain ritonavir (commonly used to treat HIV infection or AIDS).
- any other corticosteroid medicines.
- ketoconazole (NIZORAL®), an antifungal medicine.

This is not a complete list of medicines that can affect FLOVENT DISKUS. Ask your doctor if you are not sure if any of your medicines are the kinds listed above.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I use FLOVENT DISKUS?

- Read the detailed Instructions for Use at the end of this leaflet.
- An adult should always watch a child use FLOVENT DISKUS to make sure that it is used correctly, as instructed by your doctor.
- FLOVENT DISKUS comes in 3 strengths. Your doctor has prescribed the one that is best for your condition.
- Use FLOVENT DISKUS exactly as your doctor tells you to use it. Do not change the dose yourself. Your doctor will tell you how many times to inhale your FLOVENT DISKUS and when to use your FLOVENT DISKUS. **Do not** inhale more doses or use your FLOVENT DISKUS more often than your doctor has prescribed.
- FLOVENT DISKUS delivers your dose of medicine as a very fine powder **that most people, but not all, can taste or feel**. Whether or not you can taste or feel your dose of medicine, you should not take more than the prescribed dose. If you are not sure you are getting your dose of FLOVENT DISKUS, contact your doctor or pharmacist.
- It may take 1 to 2 weeks or longer after you start FLOVENT DISKUS for your asthma symptoms to get better. You must use FLOVENT DISKUS regularly. **Do not stop using FLOVENT DISKUS, even if you are feeling better, unless your doctor tells you to.**

- If you miss a dose, just take your next dose at your regular time. **Do not take 2 doses at the same time unless your doctor tells you to. If you are not sure about your dosing, call your doctor.**
- Your doctor may prescribe a rescue inhaler for emergency relief of sudden asthma attacks. Contact your doctor right away if:
  - an asthma attack does not respond to your rescue inhaler or
  - you need more of the rescue inhaler than usual.
- If you also use another medicine by inhalation, you should ask your doctor for instructions on when to use it while you are also using FLOVENT DISKUS.
- Do not use FLOVENT DISKUS with a spacer device.

What should I avoid while taking FLOVENT DISKUS?

If you have not had or have not been vaccinated against chicken pox, measles, or active tuberculosis, you should stay away from people who are infected.

What are the possible side effects of FLOVENT DISKUS?

FLOVENT DISKUS can cause serious side effects, including:

- **fungal infection (thrush) in your mouth and throat.** Tell your doctor if you have any redness or white-colored coating in your mouth.
- **decreased ability to fight infections.** Symptoms of infection may include: fever, pain, aches, chills, feeling tired, nausea and vomiting. Tell your doctor about any signs of infection while you use FLOVENT DISKUS.
- **decreased adrenal function (adrenal insufficiency).** Symptoms of decreased adrenal function include tiredness, weakness, nausea and vomiting, and low blood pressure. Decreased adrenal function can lead to death.
- **allergic reaction (anaphylaxis).** Call your doctor and stop FLOVENT DISKUS right away if you have any symptoms of an allergic reaction:
  - swelling of the face, throat, and tongue
  - hives
  - rash
  - breathing problems
- **lower bone mineral density.** This may be a problem for people who already have a higher chance of low bone density (osteoporosis).
- **slow growth in children.** The growth of children using FLOVENT DISKUS should be checked regularly.
- **eye problems including glaucoma and cataracts.** Tell your doctor about any vision changes while using FLOVENT DISKUS. Your doctor may tell you to have your eyes checked.

- **increased wheezing (bronchospasm).** Increased wheezing can happen right away after using FLOVENT DISKUS. Always have a rescue inhaler with you to treat sudden wheezing.

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The parts of your FLOVENT DISKUS

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