PRESCRIBING INFORMATION

FLOVENT® HFA 44 mcg
(fluticasone propionate 44 mcg)
Inhalation Aerosol

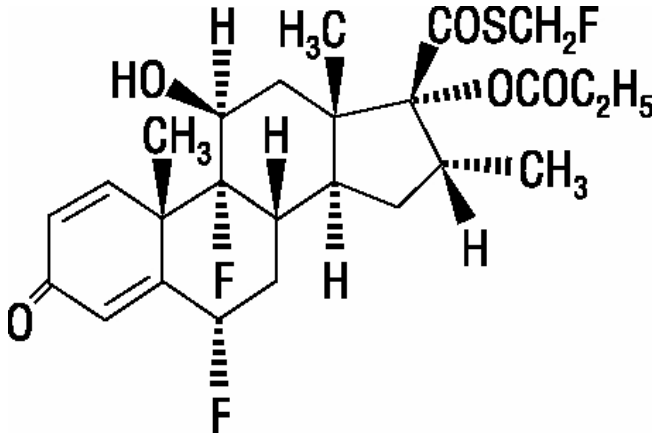
FLOVENT® HFA 110 mcg
(fluticasone propionate 110 mcg)
Inhalation Aerosol

FLOVENT® HFA 220 mcg
(fluticasone propionate 220 mcg)
Inhalation Aerosol

For Oral Inhalation Only

DESCRIPTION

The active component of FLOVENT HFA 44 mcg Inhalation Aerosol, FLOVENT HFA 110 mcg Inhalation Aerosol, and FLOVENT HFA 220 mcg Inhalation Aerosol 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 HFA 44 mcg Inhalation Aerosol, FLOVENT HFA 110 mcg Inhalation Aerosol, and FLOVENT HFA 220 mcg Inhalation Aerosol are pressurized metered-dose aerosol units fitted with a counter. FLOVENT HFA is intended for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

After priming, each actuation of the inhaler delivers 50, 125, or 250 mcg of fluticasone propionate in 60 mg of suspension (for the 44-mcg product) or in 75 mg of suspension (for the 110- and 220-mcg products) from the valve. Each actuation delivers 44, 110, or 220 mcg of fluticasone propionate from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the device and inspiration through the delivery system.

Each 10.6-g canister (44 mcg) and each 12-g canister (110 and 220 mcg) provides 120 inhalations.

FLOVENT HFA should be primed before using for the first time by releasing 4 test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well for 5 seconds and releasing 1 test spray into the air away from the face.

This product does not contain any chlorofluorocarbon (CFC) as the propellant.

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 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, 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 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.

Preclinical: In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to 7 minutes in humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both

extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (i.e., 380 to 1,300 times the maximum human exposure based on comparisons of area under the plasma concentration versus time curve [AUC] values), primarily producing ataxia, tremors, dyspnea, or salivation. These events are similar to effects produced by the structurally related CFCs, which have been used extensively in metered-dose inhalers.

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. Systemic exposure as measured by AUC in healthy subjects (N = 24) who received 8 inhalations, as a single dose, of fluticasone propionate HFA using the 44-, 110-, and 220-mcg strengths increased proportionally with dose. The geometric means (95% CI) of $AUC_{0\text{-}24\ hr}$ for the 44-, 110-, and 220-mcg strengths were 488 (362, 657); 1,284 (904; 1,822); and 2,495 (1,945; 3,200) pg•hr/mL, respectively, and the geometric means of C_{max} were 126 (108, 148), 254 (202, 319), and 421 (338, 524) pg/mL, respectively. Systemic exposure from fluticasone propionate HFA 220 mcg was 30% lower than that from the fluticasone propionate CFC inhaler. Systemic exposure was measured in patients with asthma who received 2 inhalations of fluticasone propionate HFA 44 mcg (n = 20), 110 mcg (n = 15), or 220 mcg (n = 17) twice daily for at least 4 weeks. The geometric means (95% CI) of $AUC_{0\text{-}12\ hr}$ for the 44-, 110-, and 220-mcg strengths were 76 (33, 175), 298 (191, 464), and 601 (431, 838) pg•hr/mL, respectively. C_{max} occurred in about 1 hour, and the geometric means were 25 (18, 36), 61 (46, 81), and 103 (73, 145) pg/mL, respectively.

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 cytochrome P450 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.

Special Populations: 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.

Pediatric: Two pharmacokinetic studies evaluated the systemic exposure to fluticasone propionate at steady state in children with asthma aged 4 to 11 years following inhalation of fluticasone propionate HFA. In an open-label, multiple-dose, 2-period crossover study, 13 children aged 4 to 11 years received 88 mcg of fluticasone propionate HFA twice daily for 7.5 days in one period and 88 mcg of fluticasone propionate CFC twice daily for 7.5 days in the other period. The geometric means (95% CI) of $AUC_{(last)}$ were 28 pg•hr/mL (10, 80) following fluticasone propionate HFA and 65 pg•hr/mL (27, 153) following fluticasone propionate CFC, indicating that systemic exposure was 55% lower using fluticasone propionate HFA. The geometric means (95% CI) of C_{max} were 15.1 pg/mL (8.5, 27) following fluticasone propionate HFA and 20.4 pg/mL (13, 32) following fluticasone propionate CFC, indicating that C_{max} was 26% lower using fluticasone propionate HFA. T_{max} was similar for both treatments. AUC_{last} and C_{max} in this pediatric population were 37% and 60%, respectively, of those in adult patients receiving the same dose.

In a second open-label, single-dose, 2-period crossover study, 21 children with asthma aged 5 to 11 years received 264 mcg of fluticasone propionate HFA administered with and without an AeroChamber Plus® Valved Holding Chamber (VHC). The geometric means (95% CI) of AUC_{last} were 261 pg•hr/mL (252, 444) with the use of the VHC and 40 pg•hr/mL (16, 208) without the VHC. The geometric means (95% CI) of C_{max} were 52 pg/mL (46, 70) with the VHC and 19 pg/mL (17, 41) without the VHC. The median T_{max} was 1 hour with or without the VHC. Therefore, systemic exposure was higher with the VHC in these pediatric patients with asthma. (See PRECAUTIONS: Pediatric Use for population pharmacokinetics information on children aged 6 months to <4 years.)

Gender: In 19 male and 33 female patients with asthma, systemic exposure was similar from 2 inhalations of fluticasone propionate CFC 44, 110, and 220 mcg twice daily. (See PRECAUTIONS: Pediatric Use for population pharmacokinetics information on children aged 1 to <4 years.)

Drug Interactions: Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the highly potent cytochrome P450 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 exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased systemic fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another 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.

Similar definitive studies with fluticasone propionate HFA were not performed, but results should be independent of the formulation and drug delivery device.

Pharmacodynamics: Serum cortisol concentrations, urinary excretion of cortisol, and urine 6-β-hydroxycortisol excretion collected over 24 hours in 24 healthy subjects following 8 inhalations of fluticasone propionate HFA 44, 110, and 220 mcg decreased with increasing dose. However, in patients with asthma treated with 2 inhalations of fluticasone propionate HFA 44, 110, and 220 mcg twice daily for at least 4 weeks, differences in serum cortisol $AUC_{(0\text{-}12\ hr)}$ concentrations (n = 65) and 24-hour urinary excretion of cortisol (n = 47) compared with placebo were not related to dose and generally not significant. In the study with healthy volunteers, the effect of propellant was also evaluated by comparing results following the 220-mcg strength inhaler containing HFA-134a propellant with the same strength of inhaler containing CFC 11/12 propellant. A lesser effect on the hypothalamic-pituitary-adrenal (HPA) axis with the HFA formulation was observed for serum cortisol, but not urine cortisol and 6-betahydroxy cortisol excretion. In addition, in a crossover study of children with asthma aged 4 to 11 years (N = 40), 24-hour urinary excretion of cortisol was not affected after a 4-week treatment period with 88 mcg of fluticasone propionate HFA twice daily compared with urinary excretion after the 2-week placebo period. The ratio (95% CI) of urinary excretion of cortisol over 24 hours following fluticasone propionate HFA versus placebo was 0.987 (0.796, 1.223). (See PRECAUTIONS: Pediatric Use for pharmacodynamic information on children aged 6 months to <4 years.)

The potential systemic effects of fluticasone propionate HFA on the HPA axis were also studied in patients with asthma. Fluticasone propionate given by inhalation aerosol at dosages of 440 or 880 mcg twice daily was compared with placebo in oral corticosteroid-dependent patients with asthma (range of mean dose of prednisone at baseline, 13 to 14 mg/day) in a 16-week study. Consistent with maintenance treatment with oral corticosteroids, abnormal plasma cortisol responses to short cosyntropin stimulation (peak plasma cortisol <18 mcg/dL) were present at baseline in the majority of patients participating in this study (69% of patients later randomized

to placebo and 72% to 78% of patients later randomized to fluticasone propionate HFA). At week 16, 8 patients (73%) on placebo compared to 14 (54%) and 13 (68%) patients receiving fluticasone propionate HFA (440 and 880 mcg b.i.d., respectively) had post-stimulation cortisol levels of <18 mcg/dL.

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 fluticasone propionate powder and oral fluticasone propionate was conducted. Fluticasone propionate inhalation powder in dosages of 100 and 500 mcg twice daily was compared to oral fluticasone propionate 20,000 mcg 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 dosages 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.

CLINICAL TRIALS

Adolescent and Adult Patients: Three randomized, double-blind, parallel-group, placebo-controlled clinical trials were conducted in the US in 980 adolescent and adult patients (≥12 years of age) with asthma to assess the efficacy and safety of FLOVENT HFA in the treatment of asthma. Fixed dosages of 88, 220, and 440 mcg twice daily (each dose administered as 2 inhalations of the 44-, 110-, and 220-mcg strengths, respectively) and 880 mcg twice daily (administered as 4 inhalations of the 220-mcg strength) 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 (Study 1), those already receiving inhaled corticosteroids (Study 2), and those requiring oral corticosteroid therapy (Study 3). In all 3 studies, patients (including placebo-treated patients) were allowed to use VENTOLIN® (albuterol, USP) Inhalation Aerosol as needed for relief of acute asthma symptoms. In Studies 1 and 2, other maintenance asthma therapies were discontinued.

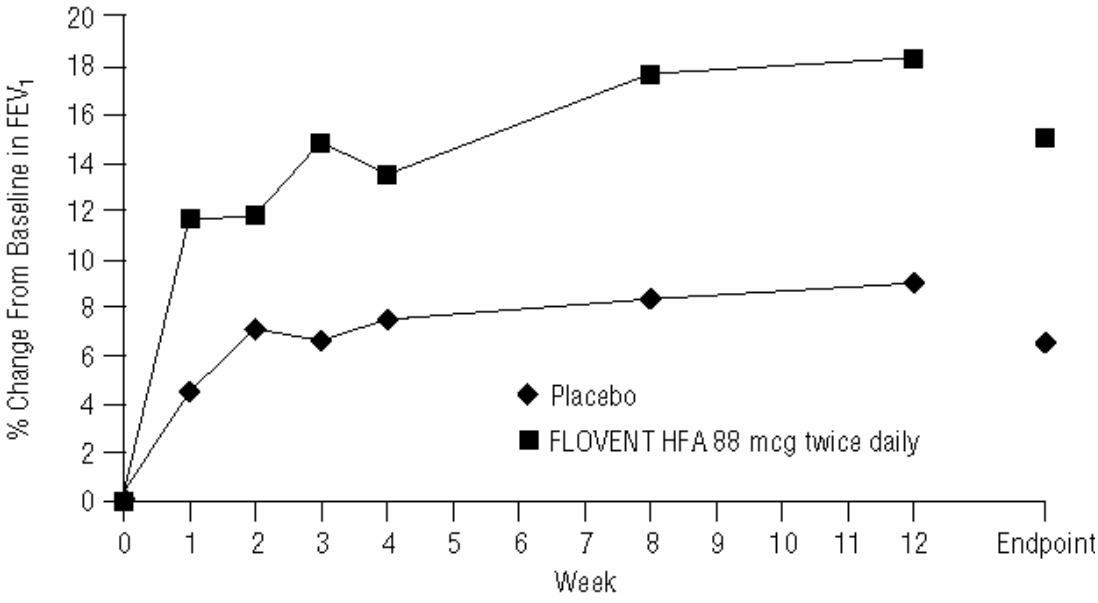
Study 1 enrolled 397 patients with asthma inadequately controlled on bronchodilators alone. FLOVENT HFA was evaluated at dosages of 88, 220, and 440 mcg twice daily for 12 weeks. Baseline FEV_1 values were similar across groups (mean 67% of predicted normal). All 3 dosages of FLOVENT HFA significantly improved asthma control as measured by improvement in AM pre-dose FEV_1 compared with placebo. Pulmonary function (AM pre-dose FEV_1) improved significantly with FLOVENT HFA compared with placebo after the first week of treatment, and this improvement was maintained over the 12-week treatment period.

At Endpoint (last observation), mean change from baseline in AM pre-dose percent predicted FEV_1 was greater in all 3 groups treated with FLOVENT HFA (9.0% to 11.2%) compared with the placebo group (3.4%). The mean differences between the groups treated with FLOVENT HFA 88, 220, and 440 mcg and the placebo group were significant, and the

corresponding 95% confidence intervals were (2.2%, 9.2%), (2.8%, 9.9%), and (4.3%, 11.3%), respectively.

Figure 1 displays results of pulmonary function tests (mean percent change from baseline in FEV_1 prior to AM dose) for the recommended starting dosage of FLOVENT HFA (88 mcg twice daily) and placebo from Study 1. This trial 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.

Figure 1. A 12-Week Clinical Trial in Patients ≥12 Years of Age Inadequately Controlled on Bronchodilators Alone: Mean Percent Change From Baseline in FEV_1 Prior to AM Dose (Study 1)

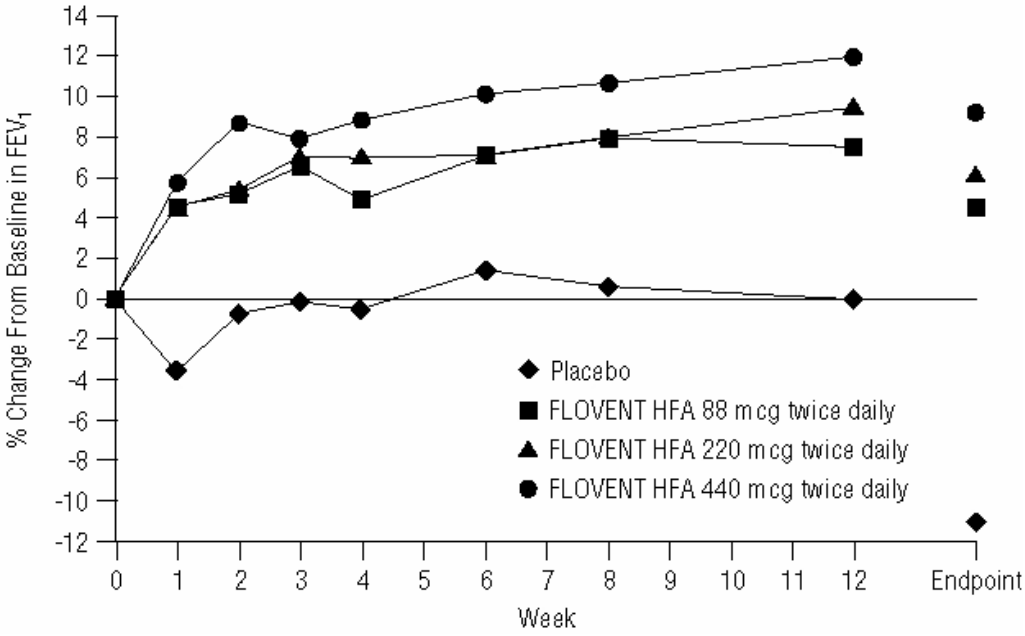


In Study 2, FLOVENT HFA at dosages of 88, 220, and 440 mcg twice daily was evaluated over 12 weeks of treatment in 415 patients with asthma who were already receiving an inhaled corticosteroid at a daily dose within its recommended dose range in addition to as-needed albuterol. Baseline FEV_1 values were similar across groups (mean 65% to 66% of predicted normal). All 3 dosages of FLOVENT HFA significantly improved asthma control (as measured by improvement in FEV_1), compared with placebo. Discontinuations from the study for lack of efficacy (defined by a pre-specified decrease in FEV_1 or peak expiratory flow [PEF], or an increase in use of VENTOLIN or nighttime awakenings requiring treatment with VENTOLIN) were lower in the groups treated with FLOVENT HFA (6% to 11%) compared to placebo (50%). Pulmonary function (AM pre-dose FEV_1) improved significantly with FLOVENT HFA compared with placebo after the first week of treatment, and the improvement was maintained over the 12-week treatment period.

At Endpoint (last observation), mean change from baseline in AM pre-dose percent predicted FEV_1 was greater in all 3 groups treated with FLOVENT HFA (2.2% to 4.6%) compared with the placebo group (-8.3%). The mean differences between the groups treated with FLOVENT HFA 88, 220, and 440 mcg and the placebo group were significant, and the corresponding 95% confidence intervals were (7.1%, 13.8%), (8.2%, 14.9%), and (9.6%, 16.4%), respectively.

Figure 2 displays the mean percent change from baseline in FEV_1 from Week 1 through Week 12. This study also used predetermined criteria for lack of efficacy, resulting in withdrawal of more patients in the placebo group; therefore, pulmonary function results at Endpoint are displayed.

Figure 2. A 12-Week Clinical Trial in Patients ≥12 Years of Age Already Receiving Daily Inhaled Corticosteroids: Mean Percent Change From Baseline in FEV_1 Prior to AM Dose (Study 2)

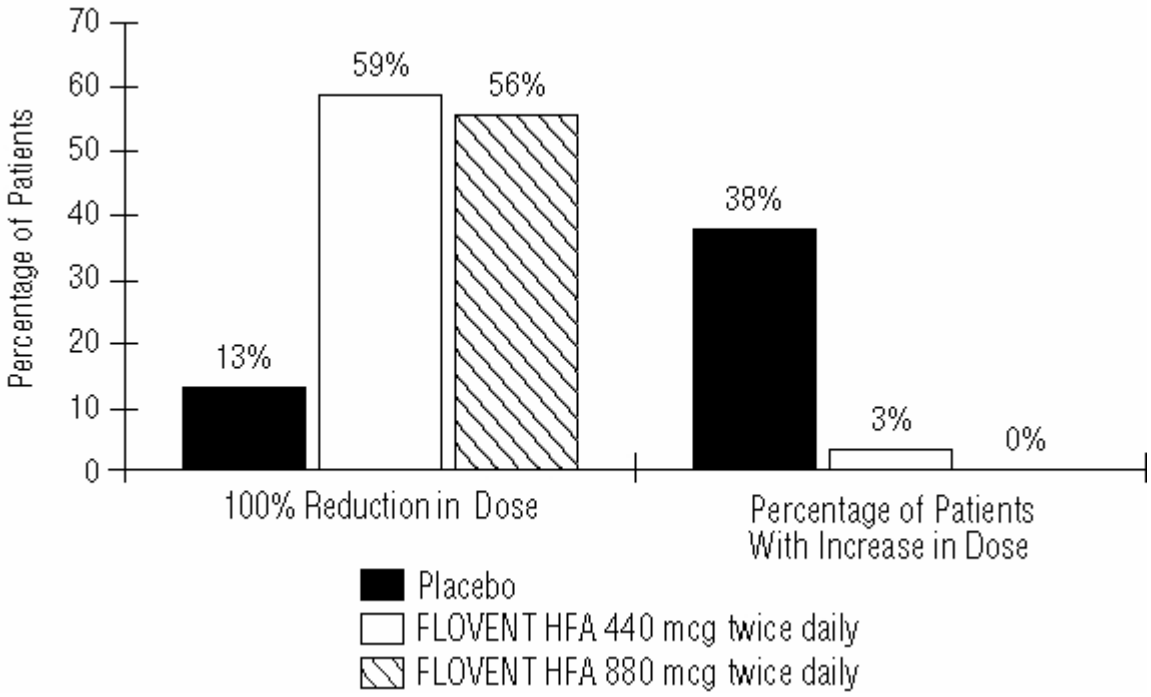


In both studies, use of VENTOLIN, AM and PM PEF, and asthma symptom scores showed numerical improvement with FLOVENT HFA compared to placebo.

Study 3 enrolled 168 patients with asthma requiring oral prednisone therapy (average baseline daily prednisone dose ranged from 13 to 14 mg). FLOVENT HFA at dosages of 440 and 880 mcg twice daily was evaluated over a 16-week treatment period. Baseline FEV_1 values were similar across groups (mean 59% to 62% of predicted normal). Over the course of the study, patients treated with either dosage of FLOVENT HFA required a significantly lower mean daily oral prednisone dose (6 mg) compared with placebo-treated patients (15 mg). Both dosages of FLOVENT HFA enabled a larger percentage of patients (59% and 56% in the groups treated

with FLOVENT HFA 440 and 880 mcg, respectively, twice daily) to eliminate oral prednisone as compared with placebo (13%) (see Figure 3). There was no efficacy advantage of FLOVENT HFA 880 mcg twice daily compared to 440 mcg twice daily. Accompanying the reduction in oral corticosteroid use, patients treated with either dosage of FLOVENT HFA had significantly improved lung function, fewer asthma symptoms, and less use of VENTOLIN Inhalation Aerosol compared with the placebo-treated patients.

Figure 3. A 16-Week Clinical Trial in Patients ≥12 Years of Age Requiring Chronic Oral Prednisone Therapy: Change in Maintenance Prednisone Dose



Two long-term safety studies (Study 4 and Study 5) of ≥6 months' duration were conducted in 507 adolescent and adult patients with asthma. Study 4 was designed to monitor the safety of 2 doses of FLOVENT HFA, while Study 5 compared fluticasone propionate HFA and fluticasone propionate CFC. Study 4 enrolled 182 patients who were treated daily with low to high doses of inhaled corticosteroids, beta-agonists (short-acting [as needed or regularly scheduled] or long-acting), theophylline, inhaled cromolyn or nedocromil sodium, leukotriene receptor antagonists, or 5-lipoxygenase inhibitors at baseline. FLOVENT HFA at dosages of 220 and 440 mcg twice daily was evaluated over a 26-week treatment period in 89 and 93 patients, respectively. Study 5 enrolled 325 patients who were treated daily with moderate to high doses of inhaled corticosteroids, with or without concurrent use of salmeterol or albuterol, at baseline. Fluticasone propionate HFA at a dosage of 440 mcg twice daily and fluticasone propionate CFC at a dosage of 440 mcg twice daily were evaluated over a 52-week treatment period in 163 and 162 patients, respectively. Baseline FEV_1 values were similar across groups (mean 81% to 84%

of predicted normal). Throughout the 52-week treatment period, asthma control was maintained with both formulations of fluticasone propionate compared to baseline. In both studies, none of the patients were withdrawn due to lack of efficacy.

Pediatric Patients: A 12-week clinical trial conducted in 241 patients aged 4 to 11 years with asthma was supportive of efficacy but inconclusive due to measurable levels of fluticasone propionate in 6/48 (13%) of the plasma samples from patients randomized to placebo. Efficacy in patients 4 to 11 years of age is extrapolated from adult data with FLOVENT HFA and other supporting data (see PRECAUTIONS: Pediatric Use).

INDICATIONS AND USAGE

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

FLOVENT HFA Inhalation Aerosol is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

FLOVENT HFA Inhalation Aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see DESCRIPTION).

WARNINGS

1. 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 HPA function.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to FLOVENT HFA. In a clinical trial of 168 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone dose on a weekly basis following initiation of treatment with FLOVENT HFA. 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 (FEV_1 or 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 (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.

Transfer of patients from systemic corticosteroid therapy to FLOVENT HFA 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.

2. Bronchospasm. As with other inhaled medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with FLOVENT HFA, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with FLOVENT HFA 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 FLOVENT HFA. During such episodes, patients may require therapy with oral corticosteroids.

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.

4. Drug interaction with ritonavir. A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase systemic fluticasone propionate exposure (AUC), resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Drug Interactions* and PRECAUTIONS: Drug Interactions: *Inhibitors of Cytochrome P450*). 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.

5. FLOVENT HFA should not be used to treat acute symptoms. FLOVENT HFA is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

PRECAUTIONS

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

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 HFA 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 FLOVENT HFA.

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

The long-term effects of FLOVENT HFA 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 in a clinical study for up to 4 years. 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.

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients following the long-term administration of inhaled 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 FLOVENT HFA, but at times therapy with FLOVENT HFA may need to be interrupted.

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.

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: Observed During Clinical Practice: *Eosinophilic Conditions*).

Information for Patients: Patients being treated with FLOVENT HFA 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 FLOVENT HFA in relation to other asthma medications they are taking.

1. Patients should use FLOVENT HFA 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. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.
2. Patients who are pregnant or nursing should contact their physicians about the use of FLOVENT HFA.
3. Patients should be warned to avoid exposure to chickenpox or measles and if they are exposed to consult their physicians without delay.
4. In general, the technique for administering FLOVENT HFA to children is similar to that for adults. Children should use FLOVENT HFA under adult supervision, as instructed by the patient's physician. (See the Information for the Patient leaflet accompanying the product.)
5. Prime the inhaler before using for the first time by releasing 4 test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well for 5 seconds and releasing 1 test spray into the air away from the face.

6. After inhalation, rinse the mouth with water and spit out. Do not swallow.
7. Clean the inhaler at least once a week after the evening dose. Keeping the canister and plastic actuator clean is important to prevent medicine buildup. (See the cleaning instructions in the Information for the Patient leaflet accompanying the product.)
8. Use FLOVENT HFA only with the actuator supplied with the product. When the counter reads 020, contact the pharmacist for a refill of medication or consult the physician to determine whether a prescription refill is needed. Discard the inhaler when the counter reads 000. Never try to alter the numbers or remove the counter from the metal canister.
9. For important summary information and instructions for the proper use of FLOVENT HFA, the patient should carefully read and follow the Information for the Patient leaflet accompanying the product.

Drug Interactions: ***Inhibitors of Cytochrome P450:*** Fluticasone propionate is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Drug Interactions). 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.

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 systemic fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when FLOVENT HFA is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 2 and 10 times the maximum recommended human daily inhalation dose in adults and children, respectively, on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and equivalent to the maximum recommended human daily inhalation dose in adults and children, respectively, 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 human daily inhalation dose 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 human daily inhalation dose 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. No teratogenicity was seen in the rat at inhalation doses up to 68.7 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the maximum recommended human daily inhalation dose 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 human daily inhalation dose 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: Pharmacokinetics: *Absorption*).

Fluticasone propionate crossed the placenta following administration of a subcutaneous dose of 100 mcg/kg to mice (less than the maximum recommended human daily inhalation dose 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 on a mcg/m^2 basis), and an oral dose of 300 mcg/kg to rabbits (approximately 3 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. FLOVENT HFA 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 tritiated fluticasone propionate (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis) resulted in measurable radioactivity in milk.

Since there are no data from controlled trials on the use of FLOVENT HFA by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue FLOVENT HFA, taking into account the importance of FLOVENT HFA to the mother.

Caution should be exercised when FLOVENT HFA is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of FLOVENT HFA in children 12 years of age and older have been established (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Special Populations: Pediatric*, CLINICAL TRIALS: Pediatric Patients, ADVERSE REACTIONS:

Pediatric Patients). Use of FLOVENT HFA in patients 4 to 11 years of age is supported by evidence from adequate and well-controlled studies in adults and adolescents 12 years of age and older, pharmacokinetic studies in patients 4 to 11 years of age, established efficacy of fluticasone propionate formulated as FLOVENT® DISKUS® (fluticasone propionate inhalation powder) and FLOVENT® ROTADISK® (fluticasone propionate inhalation powder) in patients 4 to 11 years of age, and supportive findings with FLOVENT HFA in a study conducted in patients 4 to 11 years of age. Types of adverse events in pediatric patients 4 to 11 years of age were generally similar to those observed in adults and adolescents.

Children Less Than 4 Years of Age: Pharmacokinetics: A 12-week, double-blind, placebo-controlled, parallel-group study was conducted in children with asthma aged 1 to <4 years. Population pharmacokinetics analyses were conducted in 164 children treated with 88 mcg of FLOVENT HFA administered twice daily with the AeroChamber Plus VHC with facemask. The predicted $AUC_{0-\tau}$ and C_{max} ranged from 58.30 to 923.90 pg•hr/mL with a median of 129.05 pg•hr/mL and from 15.71 to 85.13 pg/mL with a median of 20.30 pg/mL, respectively. Predicted geometric means for $AUC_{0-\tau}$ and C_{max} were 141 pg•hr/mL (95% CI: 127, 156) and 22 pg/mL (95% CI: 21, 23), respectively, indicating higher levels of exposure in children aged 1 to <4 years compared to those in children aged 4 to 11 years (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Special Populations: Pediatric*). Non-compartmental pharmacokinetic analyses in children aged 4 to 11 years showed $AUC_{0-\tau}$ and C_{max} ranged from not calculable to 322 pg•hr/mL with a median of 30.20 pg•hr/mL and from below the limit of quantitation (BLQ) to 87.4 pg/mL with median of 18.8 pg/mL, respectively when the same dosage of FLOVENT HFA was administered without the VHC and facemask.

In a study in children 6 to <12 months of age with reactive airways disease, plasma fluticasone propionate was measured over a 12-hour dosing period after 4 weeks of treatment with 88 mcg of FLOVENT HFA twice daily with an AeroChamber Plus VHC with facemask. The $AUC_{0-\tau}$ and C_{max} ranged from not calculable to 671.74 pg•hr/mL with a median of 104.2 pg•hr/mL and from BLQ to 106 pg/mL with a median of 32.0 pg/mL, respectively. The geometric means for $AUC_{0-\tau}$ and C_{max} were 75 pg•hr/mL (95% CI: 34, 166; N = 16) and 25 pg/mL (95% CI: 13, 45; N = 17), respectively. The geometric mean $AUC_{0-\tau}$ and C_{max} values in children 6 to <12 months of age were higher than those in children aged 4 to 11 years taking the same dosage of FLOVENT HFA without the VHC and facemask (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Special Populations: Pediatric*).

Population pharmacokinetic analysis of 102 male and 62 female subjects with asthma aged 1 to <4 years indicated that systemic exposure was not influenced by patient demographics, including gender. No overall differences in fluticasone propionate pharmacokinetics were observed between male and female patients with asthma.

Pharmacodynamics: A 12-week, double-blind, placebo-controlled, parallel-group study was conducted in children with asthma aged 1 to <4 years. Twelve-hour overnight urinary cortisol excretion after a 12-week treatment period with 88 mcg of FLOVENT HFA twice daily (n = 73) and with placebo (n = 42) were calculated. The mean and median change from baseline

in urine cortisol over 12 hours were -0.7 and 0.0 mcg for FLOVENT HFA and 0.3 and -0.2 mcg for placebo treatments, respectively.

In a 1-way crossover study in children 6 to <12 months of age with reactive airways disease (N = 21), serum cortisol was measured over a 12-hour dosing period. Patients received placebo treatment for a 2-week period followed by a 4-week treatment period with 88 mcg of FLOVENT HFA twice daily with an AeroChamber Plus VHC with facemask. The geometric mean ratio of serum cortisol over 12 hours ($AUC_{0\text{-}12\ hr}$) following FLOVENT HFA (n = 16) versus placebo (n = 18) was 0.95 (95% CI: 0.72, 1.27).

Safety: FLOVENT HFA administered as 88 mcg twice daily has been evaluated for safety in 239 pediatric patients 1 to <4 years of age in a 12-week, double-blind, placebo-controlled study. Treatments were administered with an AeroChamber Plus VHC with facemask. In pediatric patients 1 to <4 years of age receiving FLOVENT HFA, the following events occurred with a frequency >3% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: pyrexia, nasopharyngitis, upper respiratory tract infection, vomiting, otitis media, diarrhea, bronchitis, pharyngitis, and viral infection.

FLOVENT HFA administered as 88 mcg twice daily has also been evaluated for safety in 23 pediatric patients 6 to 12 months of age in an open-label placebo-controlled study. Treatments were administered with an AeroChamber Plus VHC with facemask for 2 weeks with placebo followed by 4 weeks with active drug. Adverse events after placebo and active drug were similar in kind and frequency.

In Vitro Testing of Dose Delivery With Holding Chambers: In vitro dose characterization studies were performed to evaluate the delivery of FLOVENT HFA via holding chambers with attached facemasks. The studies were conducted with 2 different holding chambers (AeroChamber Plus VHC and AeroChamber Z-STAT Plus™ VHC) and facemasks (small and medium size) at inspiratory flow rates of 4.9, 8.0, and 12.0 L/min in combination with holding times of 0, 2, 5, and 10 seconds. The flow rates were selected to be representative of inspiratory flow rates of children aged 6 to 12 months, 2 to 5 years, and over 5 years, respectively. The mean delivered dose of fluticasone propionate through the holding chambers with facemasks was lower than the 44 mcg of fluticasone propionate delivered directly from the actuator mouthpiece. The results were similar through both holding chambers (see Table 1 for data for the AeroChamber Plus VHC). The fine particle fraction (approximately 1 to 5 μm) across the flow rates used in these studies was 70% to 84% of the delivered dose, consistent with the removal of the coarser fraction by the holding chamber. In contrast, the fine particle fraction for FLOVENT HFA delivered without a holding chamber typically represents 42% to 55% of the delivered dose measured at the standard flow rate of 28.3 L/min. These data suggest that even at low flow rates and extended holding times potentially experienced in realistic situations with young children, an adequate amount of fluticasone propionate can be delivered to pediatric patients via a holding chamber and facemask at the recommended doses.

Table 1: In Vitro Medication Delivery Through AeroChamber Plus® Valved Holding Chamber With a Facemask

Age	Facemask	Flow Rate (L/min)	Holding Time (seconds)	Mean Medication Delivery Through AeroChamber Plus VHC (mcg/actuation)	Body Weight 50th Percentile (kg)*	Medication Delivered per Actuation (mcg/kg)†
6 to 12 Months	Small	4.9	0	8.3	7.5-9.9	0.8-1.1
			2	6.7		0.7-0.9
			5	7.5		0.8-1.0
			10	7.5		0.8-1.0
2 to 5 Years	Small	8.0	0	7.3	12.3-18.0	0.4-0.6
			2	6.8		0.4-0.6
			5	6.7		0.4-0.5
			10	7.7		0.4-0.6
2 to 5 Years	Medium	8.0	0	7.8	12.3-18.0	0.4-0.6
			2	7.7		0.4-0.6
			5	8.1		0.5-0.7
			10	9.0		0.5-0.7
>5 Years	Medium	12.0	0	12.3	18.0	0.7
			2	11.8		0.7
			5	12.0		0.7
			10	10.1		0.6

* Centers for Disease Control growth charts, developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). Ranges correspond to the average of the 50th percentile weight for boys and girls at the ages indicated.

† A single inhalation of FLOVENT HFA in a 70-kg adult without use of a valved holding chamber and facemask delivers approximately 44 mcg, or 0.6 mcg/kg.

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 HFA, 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 HFA, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

Since a cross study comparison in adolescent and adult patients (≥12 years of age) indicated that systemic exposure of inhaled fluticasone propionate from FLOVENT HFA would be higher than exposure from FLOVENT ROTADISK, results from a study to assess the potential growth effects of FLOVENT ROTADISK in pediatric patients (4 to 11 years of age) are provided.

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 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: boys – 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year.

The clinical significance of these growth data is not certain. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

Geriatric Use: Of the total number of patients treated with FLOVENT HFA in US and non-US clinical trials, 173 were 65 years of age or older, 19 of which were 75 years of age or older. No apparent differences in safety or efficacy were observed between these patients and younger patients. No overall differences in safety 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. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adolescent and Adult Patients: The incidence of common adverse events in Table 2 is based upon 2 placebo-controlled US clinical trials in which 812 adolescent and adult patients (457 females and 355 males) previously treated with as-needed bronchodilators and/or inhaled corticosteroids were treated twice daily for up to 12 weeks with 2 inhalations of FLOVENT HFA 44 mcg Inhalation Aerosol, FLOVENT HFA 110 mcg Inhalation Aerosol, FLOVENT HFA 220 mcg Inhalation Aerosol (dosages of 88, 220, or 440 mcg twice daily) or placebo.

Table 2. Overall Adverse Events With >3% Incidence in US Controlled Clinical Trials With FLOVENT HFA in Patients ≥12 Years of Age With Asthma Previously Receiving Bronchodilators and/or Inhaled Corticosteroids

Adverse Event	FLOVENT HFA 88 mcg Twice Daily (n = 203) %	FLOVENT HFA 220 mcg Twice Daily (n = 204) %	FLOVENT HFA 440 mcg Twice Daily (n = 202) %	Placebo (n = 203) %
Ear, nose, and throat				
Upper respiratory tract infection	18	16	16	14
Throat irritation	8	8	10	5
Upper respiratory inflammation	2	5	5	1
Sinusitis/sinus infection	6	7	4	3
Hoarseness/dysphonia	2	3	6	<1
Gastrointestinal				
Candidiasis mouth/throat & non-site specific	4	2	5	<1
Lower respiratory				
Cough	4	6	4	5
Bronchitis	2	2	6	5
Neurological				
Headache	11	7	5	6
Average duration of exposure (days)	73	74	76	60

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 HFA

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 events were mostly mild to moderate in severity. Rare cases of immediate and delayed hypersensitivity reactions, including urticaria and rash, have been reported.

Other adverse events that occurred in the groups receiving FLOVENT HFA in these studies with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

Ear, Nose, and Throat: Sinusitis/sinus infection, rhinitis, pharyngitis/throat infection, rhinorrhea/post-nasal drip, nasal sinus disorders, laryngitis.

Gastrointestinal: Diarrhea, viral gastrointestinal infections, gastrointestinal signs and symptoms, dyspeptic symptoms, gastrointestinal discomfort and pain, hyposalivation.

Musculoskeletal: Musculoskeletal pain, muscle pain, muscle stiffness/tightness/rigidity.

Neurological: Dizziness, migraines.

Non-Site Specific: Fever, viral infections, pain, chest symptoms.

Skin: Viral skin infections.

Trauma: Muscle injuries, soft tissue injuries, injuries.

Urogenital: Urinary infections.

Fluticasone propionate inhalation aerosol (440 or 880 mcg twice daily) was administered for 16 weeks to patients with asthma requiring oral corticosteroids (Study 3). Adverse events not included in Table 2, but reported by >3 patients in either group treated with FLOVENT HFA and more commonly than in the placebo group included rhinitis, nausea and vomiting, arthralgia and articular rheumatism, musculoskeletal pain, muscle pain, malaise and fatigue, and sleep disorders.

In 2 long-term studies (26 and 52 weeks), treatment with FLOVENT HFA at dosages up to 440 mcg twice daily was well tolerated. The pattern of adverse events was similar to that observed in the 12-week studies. There were no new and/or unexpected adverse events with long-term treatment.

Pediatric Patients: FLOVENT HFA has been evaluated for safety in 56 pediatric patients aged 4 to 11 years who received 88 mcg twice daily for 4 weeks. Types of adverse events in these pediatric patients were generally similar to those observed in adults and adolescents.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during postmarketing use of fluticasone propionate. 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 a combination of their seriousness, frequency of reporting, or potential causal connection to fluticasone propionate.

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

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

Eye: Cataracts.

Non-Site Specific: Very rare anaphylactic reaction.

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, chest tightness, cough, dyspnea, immediate and delayed bronchospasm, paradoxical bronchospasm, pneumonia, and wheeze.

Skin: Contusions, cutaneous hypersensitivity reactions, ecchymoses, and pruritus.

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate (see PRECAUTIONS: Eosinophilic Conditions).

OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS: General). Inhalation by healthy volunteers of a single dose 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. The oral median lethal dose in mice was >1,000 mg/kg (approximately ≥2,300 and >11,000 times the maximum human daily inhalation dose in adults and children on a mg/m^2 basis, respectively), and the subcutaneous median lethal dose in rats was >1,000 mg/kg (approximately >4,600 and >22,000 times the maximum human daily inhalation dose in adults and children on a mg/m^2 basis, respectively).

DOSAGE AND ADMINISTRATION

FLOVENT HFA should be administered by the orally inhaled route only in patients 4 years of age 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 HFA when administered in excess of recommended dosages have not been established.

The recommended starting dosage and the highest recommended dosage of FLOVENT HFA, based on prior asthma therapy, are listed in Table 3.

Table 3. Recommended Dosages of FLOVENT HFA

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
Adolescent and adult patients (≥12 years)		
Bronchodilators alone	88 mcg twice daily	440 mcg twice daily
Inhaled corticosteroids	88-220 mcg twice daily*	440 mcg twice daily
Oral corticosteroids†	440 mcg twice daily	880 mcg twice daily
Pediatric patients (4 to 11 years)‡	88 mcg twice daily	88 mcg twice daily

* **For Patients Currently Receiving Inhaled Corticosteroid Therapy:** Starting dosages above 88 mcg twice daily 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 to 5 mg/day on a weekly basis, beginning after at least 1 week of therapy with FLOVENT HFA. 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 HFA should be reduced to the lowest effective dosage.

‡ Recommended pediatric dosage is 88 mcg twice daily regardless of prior therapy.

FLOVENT HFA should be primed before using for the first time by releasing 4 test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well for 5 seconds and releasing 1 test spray into the air away from the face.

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

Directions for Use: An Information for the Patient leaflet containing illustrated instructions for use accompany each package of FLOVENT HFA.

HOW SUPPLIED

FLOVENT HFA 44 mcg Inhalation Aerosol is supplied in 10.6-g pressurized aluminum canisters containing 120 metered actuations in boxes of 1 (NDC 0173-0718-20).

FLOVENT HFA 110 mcg Inhalation Aerosol is supplied in 12-g pressurized aluminum canisters containing 120 metered actuations in boxes of 1 (NDC 0173-0719-20).

FLOVENT HFA 220 mcg Inhalation Aerosol is supplied in 12-g pressurized aluminum canisters containing 120 metered actuations in boxes of 1 (NDC 0173-0720-20).

Each canister is fitted with a dose counter, supplied with a dark orange oral actuator with a peach strapcap, and sealed in a plastic-coated, moisture-protective foil pouch with a desiccant that should be discarded when the pouch is opened. Each canister is packaged with an Information for the Patient leaflet.

The dark orange actuator supplied with FLOVENT HFA should not be used with any other product canisters, and actuators from other products should not be used with a FLOVENT HFA canister.

The correct amount of medication in each actuation cannot be assured after the counter reads 000, even though the canister is not completely empty and will continue to operate. The inhaler should be discarded when the counter reads 000.

Keep out of reach of children. Avoid spraying in eyes.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw into fire or incinerator.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. SHAKE WELL FOR 5 SECONDS BEFORE USING.

FLOVENT HFA does not contain chlorofluorocarbons (CFCs) as the propellant.

GlaxoSmithKline
Research Triangle Park, NC 27709

June 2008 FLH:1PI

PHARMACIST—DETACH HERE AND GIVE LEAFLET TO PATIENT

Information for the Patient

FLOVENT® *[flō′vent]* HFA 44 mcg
(fluticasone propionate 44 mcg)
Inhalation Aerosol

FLOVENT® HFA 110 mcg
(fluticasone propionate 110 mcg)
Inhalation Aerosol

FLOVENT® HFA 220 mcg
(fluticasone propionate 220 mcg)
Inhalation Aerosol

FOR ORAL INHALATION ONLY

Read this leaflet carefully before you start to use FLOVENT HFA Inhalation Aerosol.

Keep this leaflet because it has important summary information about FLOVENT HFA. This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about something, you should ask your doctor or pharmacist.

Read the new leaflet that comes with each refill of your prescription because there may be new information.

What is FLOVENT HFA?

FLOVENT HFA contains a medicine called fluticasone propionate, which is a synthetic corticosteroid. Corticosteroids are natural substances found in the body that help fight inflammation. Corticosteroids are used to treat asthma because they reduce airway inflammation.

FLOVENT HFA is used to treat asthma in patients 4 years of age and older. When inhaled regularly, FLOVENT HFA also helps to prevent symptoms of asthma.

FLOVENT HFA comes in 3 strengths. Your doctor has prescribed the one that is best for your condition.

Who should not use FLOVENT HFA?

Do not use FLOVENT HFA if you:

- are allergic to any of the ingredients in FLOVENT HFA or other inhaled corticosteroids. See "What are the ingredients in FLOVENT HFA?" below.
- have an acute asthma attack or status asthmaticus. **FLOVENT HFA is not a bronchodilator and should not be used to give you fast relief from your breathing problems during an asthma attack.** Always use a short-acting bronchodilator (rescue medicine), such as

albuterol inhaler, during a sudden asthma attack. You must take FLOVENT HFA at regular times as recommended by your doctor, and not as an emergency medicine.

What should I tell my doctor before taking FLOVENT HFA?

Tell your doctor if you are:

- pregnant or planning to become pregnant. It is not known if FLOVENT HFA will harm your unborn baby.
- breastfeeding a baby. It is not known if FLOVENT HFA passes into your breast milk.
- exposed to chickenpox or measles.

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

- a medicine containing ritonavir (commonly used to treat HIV infection or AIDS). The anti-HIV medicines NORVIR® (ritonavir capsules) Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA® (lopinavir/ritonavir) Tablets contain ritonavir.
- any other corticosteroids.

How should I use FLOVENT HFA?

1. It is important that you inhale each dose as your doctor has prescribed. The prescription label provided by your pharmacist will usually tell you what dose to take and how often. If it doesn't, or if you are not sure, ask your doctor or pharmacist. DO NOT inhale more doses or use your FLOVENT HFA more often than your doctor has prescribed.
2. It may take 1 to 2 weeks or longer for this medicine to work, and it is very important that you use it regularly. **Do not stop taking FLOVENT HFA, even if you are feeling better, unless your doctor tells you to.**
3. If you miss a dose, just take your next scheduled dose when it is due. **Do not double the dose.**
4. Your doctor may prescribe additional medicine (such as fast-acting bronchodilators) for emergency relief if a sudden asthma attack occurs. Contact your doctor if:
   - an asthma attack does not respond to the additional medicine or
   - you need more of the additional medicine than usual.
5. 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 HFA.

What are the possible side effects of FLOVENT HFA?

Common side effects in adults and children using FLOVENT HFA include:

- a cold or upper respiratory tract infection
- throat irritation

- headache
- thrush (fungal infection) in the mouth and throat

Other common side effects in children include:

- fever
- diarrhea
- ear infection
- vomiting
- bronchitis
- inflammation of the nose and throat
- viral infection

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of FLOVENT HFA. 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.

What are the ingredients in FLOVENT HFA?

Active ingredient: fluticasone propionate (micronized)
Inactive ingredient: propellant HFA-134a

Instructions for Using FLOVENT HFA

The parts of your FLOVENT HFA

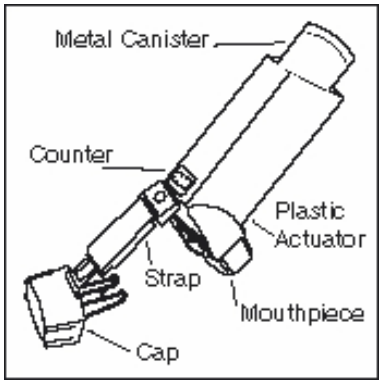


Figure 1

There are 2 main parts to your FLOVENT HFA inhaler—the metal canister that holds the medicine and the dark orange plastic actuator that sprays the medicine from the canister (see Figure 1).

The canister has a counter to show how many sprays of medicine you have left. The number shows through a window in the back of the actuator. The counter starts at 124. The number will count down by 1 each time you spray the inhaler. The counter will stop counting at 000.

Never try to change the numbers or take the counter off the metal canister. The counter cannot be reset, and it is permanently attached to the canister.

The mouthpiece of the actuator is covered by a cap. A strap on this cap keeps it attached to the actuator.

Do not use the actuator with a canister of medicine from any other inhaler. And do not use a FLOVENT HFA canister with an actuator from any other inhaler.

Using your FLOVENT HFA

- The inhaler should be at room temperature before you use it.
- Take your FLOVENT HFA inhaler out of the moisture-protective foil pouch just before you use it for the first time. Safely throw away the foil pouch and the drying packet that comes inside the pouch.
- **Priming the inhaler:**

  Before you use FLOVENT HFA for the first time, you must prime the inhaler so that you will get the right amount of medicine when you use it. To prime the inhaler, take the cap off the mouthpiece and shake the inhaler well for 5 seconds. Then spray the inhaler into the air away from your face. **Avoid spraying in eyes.** Shake and spray the inhaler like this 3 more times to finish priming it. The counter should now read 120.

  You must prime the inhaler again if you have not used it in more than 7 days or if you drop it. Take the cap off the mouthpiece and shake the inhaler well for 5 seconds. Then spray it 1 time into the air away from your face.
- An adult should watch a child use the inhaler to be sure it is used correctly. If a child needs help using the inhaler, an adult should help the child use the inhaler with or without a holding chamber attached to a facemask. The adult should follow the instructions that came with the holding chamber.

Read the following 7 steps before using FLOVENT HFA and follow them at each use. If you have any questions, ask your doctor or pharmacist.

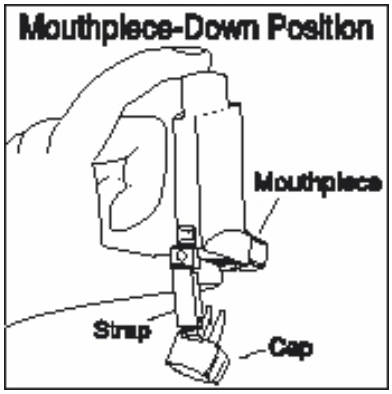


Figure 2

1. **Take the cap off the mouthpiece of the actuator** (see Figure 2).
   Look inside the mouthpiece for foreign objects, and take out any you see.
   Make sure the canister fits firmly in the actuator.
   Shake the inhaler well for 5 seconds.
2. Hold the inhaler with the mouthpiece down (see Figure 2). **Breathe out through your mouth** and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it.

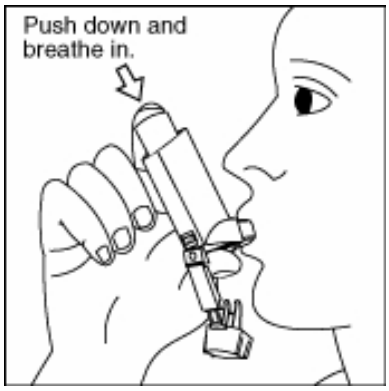


Figure 3

3. Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth (see Figure 3)
   Right after the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.
4. **Hold your breath as long as you can,** up to 10 seconds. Then breathe normally.
5. **Wait about 30 seconds and shake the inhaler well** for 5 seconds. Repeat steps 2 through 4.
6. After you finish taking this medicine, rinse your mouth with water. Spit out the water. Do not swallow it.
7. Put the cap back on the mouthpiece after each time you use the inhaler. Make sure it snaps firmly into place.

Cleaning your FLOVENT HFA

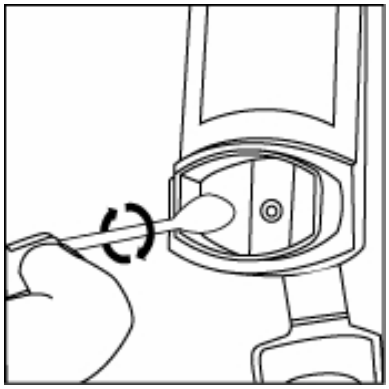


Figure 4

Clean the inhaler at least once a week after your evening dose. It is important to keep the canister and plastic actuator clean so the medicine will not build-up and block the spray.

1. Take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator. Do not take the canister out of the plastic actuator.
2. Use a clean cotton swab dampened with water to clean the small circular opening where the medicine sprays out of the canister. Gently twist the swab in a circular motion to take off any medicine (see Figure 4). Repeat with a new swab dampened with water to take off any medicine still at the opening.
3. Wipe the inside of the mouthpiece with a clean tissue dampened with water. Let the actuator air-dry overnight.
4. Put the cap back on the mouthpiece after the actuator has dried.

Storing your FLOVENT HFA

Store at room temperature with the mouthpiece down.

Keep out of reach of children.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw into fire or incinerator.

Replacing your FLOVENT HFA

- **When the counter reads 020**, you should refill your prescription or ask your doctor if you need a refill of your prescription.
- **When the counter reads 000**, throw the inhaler away. You should not keep using the inhaler because you will not receive the right amount of medicine.
- **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.

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

FLOVENT is a registered trademark of GlaxoSmithKline.

NORVIR and KALETRA are registered trademarks of Abbott Laboratories.

GlaxoSmithKline
Research Triangle Park, NC 27709

June 2008 FLH:1PIL