HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FLOVENT® HFA safely and effectively. See full prescribing information for FLOVENT HFA.

FLOVENT HFA 44 mcg (fluticasone propionate 44 mcg) Inhalation Aerosol, for oral inhalation
FLOVENT HFA 110 mcg (fluticasone propionate 110 mcg) Inhalation Aerosol, for oral inhalation
FLOVENT HFA 220 mcg (fluticasone propionate 220 mcg) Inhalation Aerosol, for oral inhalation
Initial U.S. Approval: 1994

---------- INDICATIONS AND USAGE----------
FLOVENT HFA is an inhaled corticosteroid indicated for:
- Maintenance treatment of asthma as prophylactic therapy in patients aged 4 years and older. (1)
- Treatment of asthma in patients requiring oral corticosteroid therapy. (1)

Important limitation:
- Not indicated for 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 and older		
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
Patients aged 4-11 years	88 mcg twice daily	88 mcg twice daily

---------- DOSAGE FORMS AND STRENGTHS----------
Inhalation Aerosol. Inhaler containing fluticasone propionate (44, 110, or 220 mcg) as an aerosol formulation for oral inhalation. (3)

---------- CONTRAINDICATIONS ----------
- Primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures. (4)
- Hypersensitivity to any ingredient. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- *Candida albicans* infection of the mouth and pharynx may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk. (5.1)
- Potential worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infection; ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.3)
- Risk of impaired adrenal function when transferring from systemic corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to FLOVENT HFA. (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 HFA slowly. (5.5)
- Assess for decrease in bone mineral density initially and periodically thereafter. (5.7)
- Monitor growth of pediatric patients. (5.8)
- Close monitoring for glaucoma and cataracts is warranted. (5.9)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence greater than 3%) are upper respiratory tract infection or inflammation, throat irritation, sinusitis, dysphonia, candidiasis, 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----------
Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): Use not recommended. May increase risk of systemic corticosteroid effects. (7.1)

---------- 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: 10/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLOVENT® HFA Inhalation Aerosol is indicated for the maintenance treatment of asthma as prophylactic therapy in patients aged 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.

Important Limitation of Use

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

2 DOSAGE AND ADMINISTRATION

FLOVENT HFA should be administered by the orally inhaled route only in patients aged 4 years and older. After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

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 1.

Table 1. Recommended Dosages of FLOVENT HFA Inhalation Aerosol
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 and older)		
Bronchodilators alone	88 mcg twice daily	440 mcg twice daily
Inhaled corticosteroids	88-220 mcg twice daily[a]	440 mcg twice daily
Oral corticosteroids[b]	440 mcg twice daily	880 mcg twice daily
Pediatric patients (aged 4-11 years)[c]	88 mcg twice daily	88 mcg twice daily

[a] 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

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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 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 and Precautions (5.4)]*. Once prednisone reduction is complete, the dosage of FLOVENT HFA should be reduced to the lowest effective dosage.

[c] Recommended pediatric dosage is 88 mcg twice daily regardless of prior therapy. A valved holding chamber and mask may be used to deliver FLOVENT HFA to young patients.

Prime FLOVENT HFA before using for the first time by releasing 4 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 spray into the air away from the face.

3 DOSAGE FORMS AND STRENGTHS

Inhalation Aerosol. Dark orange plastic inhaler with a peach strapcap containing a pressurized metered-dose aerosol canister containing 120 metered inhalations and fitted with a counter. Each actuation delivers 44, 110, or 220 mcg of fluticasone propionate from the mouthpiece.

4 CONTRAINDICATIONS

The use of FLOVENT HFA 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)]*.
- Hypersensitivity to any of the ingredients *[see Warnings and Precautions (5.6), Adverse Reactions (6.2), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Local Effects of Inhaled Corticosteroids

In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with FLOVENT HFA. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with FLOVENT HFA continues, but at times therapy with FLOVENT HFA may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.2 Acute Asthma Episodes

FLOVENT HFA 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

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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.

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 a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is 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.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; 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 who have been previously maintained on 20 mg or more 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 FLOVENT HFA may control asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

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

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Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to FLOVENT HFA. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with FLOVENT HFA. Lung function (mean 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, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

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

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, 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 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 significant systemic absorption of inhaled corticosteroids in sensitive patients, 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 who are sensitive to these effects. If such effects occur, FLOVENT HFA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of asthma symptoms should be considered.

5.6 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of FLOVENT HFA *[see Contraindications (4)]*.

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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 consequences such as fracture 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.

A 2-year trial in 160 subjects (females aged 18 to 40 years, males 18 to 50) with asthma receiving chlorofluorocarbon (CFC)-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar regions L1 through L4.

5.8 Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving FLOVENT HFA routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including FLOVENT HFA, titrate each patient's dosage to the lowest dosage that effectively controls his/her symptoms *[see Dosage and Administration (2), Use in Specific Populations (8.4)]*.

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 medicines, 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 an inhaled, short-acting bronchodilator; FLOVENT HFA should be discontinued immediately; and alternative therapy should be instituted.

5.11 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with FLOVENT HFA is not recommended because increased systemic corticosteroid adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

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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 2 placebo-controlled U.S. clinical trials in which 812 adult and adolescent subjects (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.

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Table 2. Adverse Reactions with FLOVENT HFA with >3% Incidence and More Common than Placebo in Subjects Aged 12 Years and Older with Asthma

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 and 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

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. Less than 2% of subjects discontinued from the trials because of adverse reactions. The average duration of exposure was 73 to 76 days in the active treatment groups compared with 60 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 subjects with asthma treated with FLOVENT HFA compared with subjects treated with placebo include the following: rhinitis, rhinorrhea/post-nasal drip, nasal sinus disorders, laryngitis, diarrhea, viral gastrointestinal infections, dyspeptic symptoms, gastrointestinal discomfort and pain, hyposalivation, musculoskeletal pain, muscle pain, muscle stiffness/tightness/rigidity, dizziness, migraines, fever, viral infections, pain, chest symptoms, viral skin infections, muscle injuries, soft tissue injuries, urinary infections.

Fluticasone propionate inhalation aerosol (440 or 880 mcg twice daily) was administered for 16 weeks to 168 subjects with asthma requiring oral corticosteroids (Trial 3). Adverse reactions not

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included above, but reported by more than 3 subjects in either group treated with FLOVENT HFA and more commonly than in the placebo group included nausea and vomiting, arthralgia and articular rheumatism, and malaise and fatigue.

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

Pediatric Subjects Aged 4 to 11 Years

FLOVENT HFA has been evaluated for safety in 56 pediatric subjects who received 88 mcg twice daily for 4 weeks. Types of adverse reactions in these pediatric subjects were generally similar to those observed in adults and adolescents.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval 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 and irritation.

Endocrine and Metabolic

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

Eye

Cataracts.

Gastrointestinal Disorders

Dental caries and tooth discoloration.

Immune System Disorders

Immediate and delayed hypersensitivity reactions, including urticaria, anaphylaxis, rash, and angioedema and bronchospasm, have been reported.

Infections and Infestations

Esophageal candidiasis.

Psychiatry

Agitation, aggression, anxiety, depression, and restlessness. Behavioral changes, including

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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.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate is a substrate of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with FLOVENT HFA is not recommended because increased systemic corticosteroid adverse effects may occur.

Ritonavir

A drug interaction trial with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, 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's syndrome and adrenal suppression.

Ketoconazole

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of FLOVENT HFA in pregnant women. There are clinical considerations with the use of FLOVENT HFA in pregnant women *[see Clinical Considerations]*. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight, and/or skeletal variations in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mg/m^2 basis *[see Animal Data]*. However, fluticasone propionate administered via inhalation to rats decreased fetal body weight,

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but did not induce teratogenicity at a maternal toxic dose less than the MRHDID on a mg/m^2 basis *[see Animal Data]*. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

The estimated risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryofetal Risk: In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as pre-eclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control.

Data

Animal Data: In embryofetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate was teratogenic in both species. Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, at a dose approximately 0.5 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat no observed adverse effect level (NOAEL) was observed at approximately 0.17 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 30 mcg/kg/day). Cleft palate and fetal skeletal variations were observed in mouse fetuses at a dose approximately 0.1 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.04 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryofetal development study with pregnant rats dosed by the inhalation route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.14 times the MRHDID (on a mg/m^2 basis with a maternal inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0.03 times the MRHDID (on a mg/m^2 basis with a maternal inhalation dose of 5.5 mcg/kg/day).

In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reductions of fetal body weights, in the presence of maternal toxicity, at doses approximately 0.006 times the MRHDID and higher (on a mg/m^2 basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate for 1 fetus at dose approximately 0.04 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 4 mcg/kg/day).

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The NOAEL was observed in rabbit fetuses with a dose approximately 0.001 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

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

In a pre- and post-natal development study in pregnant rats dosed from late gestation through delivery and lactation (Gestation Day 17 to Postpartum Day 22), fluticasone propionate was not associated with decreases in pup body weight, and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to 0.3 times the MRHDID (on a mg/m^2 basis with maternal subcutaneous doses up to 50 mcg/kg/day).

8.2 Lactation

Risk Summary

There are no available data on the presence of fluticasone propionate in human milk, the effects on the breastfed child, or the effects on milk production. Other corticosteroids have been detected in human milk. However, fluticasone propionate concentrations in plasma after inhaled therapeutic doses are low and therefore concentrations in human breast milk are likely to be correspondingly low *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FLOVENT HFA and any potential adverse effects on the breastfed child from FLOVENT HFA or from the underlying maternal condition.

Data

Animal Data: Subcutaneous administration of tritiated fluticasone propionate at a dose in lactating rats approximately 0.05 times the MRHDID for adults (on a mg/m^2 basis) resulted in measurable levels in milk.

8.4 Pediatric Use

The safety and effectiveness of FLOVENT HFA in children aged 4 years and older have been established *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*. The safety and effectiveness of FLOVENT HFA in children younger than 4 years have not been established. Use of FLOVENT HFA in patients aged 4 to 11 years is supported by evidence from adequate and well-controlled trials in adults and adolescents aged 12 years and older, pharmacokinetic trials in patients aged 4 to 11 years, established efficacy of fluticasone propionate formulated as FLOVENT® DISKUS® (fluticasone propionate inhalation powder) and FLOVENT® ROTADISK® (fluticasone propionate inhalation powder) in patients aged 4 to 11 years, and supportive findings with FLOVENT HFA in a trial conducted in subjects aged 4 to 11 years.

Effects on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to

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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 trials have shown that inhaled corticosteroids may cause a reduction in growth in pediatric patients. In these trials, the mean reduction in growth velocity was approximately 1 cm/year (range: 0.3 to 1.8 cm/year) and appeared 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 trial comparison in adult and adolescent subjects (aged 12 years and older) indicated that systemic exposure of inhaled fluticasone propionate from FLOVENT HFA would be higher than exposure from FLOVENT ROTADISK, results from a trial to assess the potential growth effects of FLOVENT ROTADISK in pediatric subjects (aged 4 to 11 years) are provided.

A 52-week placebo-controlled trial to assess the potential growth effects of fluticasone propionate inhalation powder (FLOVENT ROTADISK) at 50 and 100 mcg twice daily was conducted in the U.S. 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 trial 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 trial, 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 relevance of these

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growth data is not certain.

Children Younger than 4 Years

Pharmacokinetics: [see Clinical Pharmacology (12.3)].

Pharmacodynamics: A 12-week, double-blind, placebo-controlled, parallel-group trial was conducted in children with asthma aged 1 to younger than 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, respectively.

In a 1-way crossover trial in children aged 6 to younger than 12 months with reactive airways disease (N = 21), serum cortisol was measured over a 12-hour dosing period. Subjects 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® Valved Holding Chamber (VHC) with mask. The geometric mean ratio of serum cortisol over 12 hours ($AUC_{0\text{-}12\ h}$) 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 was evaluated for safety in 239 pediatric subjects aged 1 to younger than 4 years in a 12-week, double-blind, placebo-controlled trial. Treatments were administered with an AeroChamber Plus VHC with mask. The following events occurred with a frequency greater than 3% and more frequently in subjects receiving FLOVENT HFA than in subjects receiving 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 was evaluated for safety in 23 pediatric subjects aged 6 to 12 months in an open-label placebo-controlled trial. Treatments were administered with an AeroChamber Plus VHC with mask for 2 weeks with placebo followed by 4 weeks with active drug. There was no discernable difference in the types of adverse events reported between subjects receiving placebo compared with the active drug.

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 masks. The studies were conducted with 2 different holding chambers (AeroChamber Plus VHC and AeroChamber Z-STAT Plus™ VHC) with masks (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 masks 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 3 for data for the AeroChamber Plus VHC). The fine

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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, on a per kilogram basis, young children receive a comparable dose of fluticasone propionate when delivered via a holding chamber and mask as adults do without their use.

Table 3. In Vitro Medication Delivery through AeroChamber Plus® Valved Holding Chamber with a Mask

Age	Mask	Flow Rate (L/min)	Holding Time (seconds)	Mean Medication Delivery through AeroChamber Plus VHC (mcg/actuation)	Body Weight 50th Percentile (kg)[a]	Medication Delivered per Actuation (mcg/kg)[b]
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

[a] 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.

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

8.5 Geriatric Use

Of the total number of subjects treated with FLOVENT HFA in U.S. and non-U.S. clinical trials,

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173 were aged 65 years or older, 19 of which were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using FLOVENT HFA 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

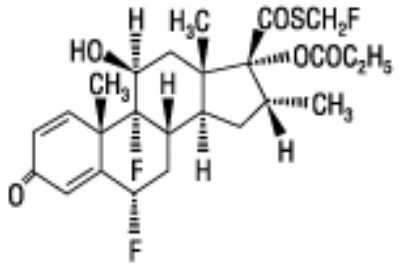
Formal pharmacokinetic studies using FLOVENT HFA have not been conducted in patients with renal impairment.

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 1,760 or 3,520 mcg of fluticasone propionate CFC inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at dosages of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in subjects were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups.

11 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

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and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FLOVENT HFA is a dark orange plastic inhaler with a peach strapcap containing a pressurized metered-dose aerosol canister fitted with a counter. Each canister contains a microcrystalline suspension of micronized fluticasone propionate 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 will depend on patient factors, such as the coordination between the actuation of the inhaler and inspiration through the delivery system.

Prime FLOVENT HFA before using for the first time by releasing 4 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 spray into the air away from the face.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is 18 times that of 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 have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. 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.

Trials in subjects 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

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anti-inflammatory effect, negligible oral systemic bioavailability (less than 1%), and the minimal pharmacological activity of the only metabolite detected in man.

12.2 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 $AUC_{(0\text{-}12\ h)}$ (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 trial 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 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 trial in 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).

The potential systemic effects of fluticasone propionate HFA on the HPA axis were also studied in subjects 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 subjects with asthma (range of mean dose of prednisone at baseline: 13 to 14 mg/day) in a 16-week trial. Consistent with maintenance treatment with oral corticosteroids, abnormal plasma cortisol responses to short cosyntropin stimulation (peak plasma cortisol less than 18 mcg/dL) were present at baseline in the majority of subjects participating in this trial (69% of subjects later randomized to placebo and 72% to 78% of subjects later randomized to fluticasone propionate HFA). At week 16, 8 subjects (73%) on placebo compared with 14 (54%) and 13 (68%) subjects receiving fluticasone propionate HFA (440 and 880 mcg twice daily, respectively) had post-stimulation cortisol levels of less than 18 mcg/dL.

12.3 Pharmacokinetics

<u>Absorption</u>

Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Trials using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (less than 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.

<u>Distribution</u>

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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 CYP3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination

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

Special Populations

Gender: No significant difference in clearance (CL/F) of fluticasone propionate was observed.

Pediatrics: A population pharmacokinetic analysis was performed for FLOVENT HFA using steady-state data from 4 controlled clinical trials and single-dose data from 1 controlled clinical trial. The combined cohort for analysis included 269 subjects (161 males and 108 females) with asthma aged 6 months to 66 years who received treatment with FLOVENT HFA. Most of these subjects (n = 215) were treated with FLOVENT HFA 44 mcg given as 88 mcg twice daily. FLOVENT HFA was delivered using an AeroChamber Plus VHC with a mask to subjects aged younger than 4 years. Data from adult subjects with asthma following FLOVENT HFA 110 mcg given as 220 mcg twice daily (n = 15) and following FLOVENT HFA 220 mcg given as 440 mcg twice daily (n = 17) at steady state were also included. Data for 22 subjects came from a single-dose crossover study of 264 mcg (6 doses of FLOVENT HFA 44 mcg) with and without AeroChamber Plus VHC in children with asthma aged 4 to 11 years.

Stratification of exposure data following FLOVENT HFA 88 mcg by age and study indicated that systemic exposure to fluticasone propionate at steady state was similar in children aged 6 to younger than 12 months, children aged 1 to younger than 4 years, and adults and adolescents aged 12 years and older. Exposure was lower in children aged 4 to 11 years, who did not use a VHC, as shown in Table 4.

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Table 4. Systemic Exposure to Fluticasone Propionate following FLOVENT HFA 88 mcg Twice Daily

Age	Valved Holding Chamber	N	$AUC_{0-\tau}$, pg•h/mL (95% CI)	C_{max}, pg/mL (95% CI)
6 to <12 Months	Yes	17	141 (88, 227)	19 (13, 29)
1 to <4 Years	Yes	164	143 (131, 157)	20 (18, 21)
4 to 11 Years	No	14	68 (48, 97)	11 (8, 16)
≥12 Years	No	20	149 (106, 210)	20 (15, 27)

The lower exposure to fluticasone propionate in children aged 4 to 11 years who did not use a VHC may reflect the inability to coordinate actuation and inhalation of the metered-dose inhaler. The impact of the use of a VHC on exposure to fluticasone propionate in patients aged 4 to 11 years was evaluated in a single-dose crossover trial with FLOVENT HFA 44 mcg given as 264 mcg. In this trial, use of a VHC increased systemic exposure to fluticasone propionate (Table 5), possibly correcting for the inability to coordinate actuation and inhalation.

Table 5. Systemic Exposure to Fluticasone Propionate following a Single Dose of FLOVENT HFA 264 mcg

Age	Valved Holding Chamber	N	$AUC_{(0-\infty)}$, pg•h/mL (95% CI)	C_{max}, pg/mL (95% CI)
4 to 11 Years	Yes	22	373 (297, 468)	61 (51, 73)
4 to 11 Years	No	21	141 (111, 178)	23 (19, 28)

There was a dose-related increase in systemic exposure in subjects aged 12 years and older receiving higher doses of fluticasone propionate (220 and 440 mcg twice daily). The $AUC_{0-\tau}$ in pg•h/mL was 358 (95% CI: 272, 473) and 640 (95% CI: 477, 858), and C_{max} in pg/mL was 47.3 (95% CI: 37, 61) and 87 (95% CI: 68, 112) following fluticasone propionate 220 and 440 mcg, respectively.

Hepatic and Renal Impairment: Formal pharmacokinetic studies using FLOVENT HFA 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.

Race: No significant difference in clearance (CL/F) of fluticasone propionate in Caucasian, African-American, Asian, or Hispanic populations was observed.

Drug Interactions

Inhibitors of Cytochrome P450 3A4: Ritonavir: Fluticasone propionate is a substrate of CYP3A4. Coadministration of fluticasone propionate and the strong CYP3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction trial in 18 healthy

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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 (less than 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•h/mL (range: 4.2 to 18.8 pg•h/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•h/mL (range: 1,207.1 to 5,662.0 pg•h/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.

Ketoconazole: In a placebo-controlled crossover trial 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•h/mL (range: 0.555 to 2.906 ng•h/mL) and $AUC_{(2-\infty)}$ averaged 2.269 ng•h/mL (range: 0.836 to 3.707 ng•h/mL). Fluticasone propionate $AUC_{(2\text{-last})}$ and $AUC_{(2-\infty)}$ increased to 2.781 ng•h/mL (range: 2.489 to 8.486 ng•h/mL) and 4.317 ng•h/mL (range: 3.256 to 9.408 ng•h/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 trial, 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 MRHDID for 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 MRHDID for 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.

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 0.3 times the MRHDID for adults on a mg/m^2 basis).

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13.2 Animal Toxicology and/or Pharmacology

Propellant HFA-134a

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.

14 CLINICAL STUDIES

14.1 Adult and Adolescent Subjects Aged 12 Years and Older

Three randomized, double-blind, parallel-group, placebo-controlled, U.S. clinical trials were conducted in 980 adult and adolescent subjects (aged 12 years and older) 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. Subjects in these trials included those inadequately controlled with bronchodilators alone (Trial 1), those already receiving inhaled corticosteroids (Trial 2), and those requiring oral corticosteroid therapy (Trial 3). In all 3 trials, subjects were allowed to use VENTOLIN® (albuterol, USP) Inhalation Aerosol as needed for relief of acute asthma symptoms. In Trials 1 and 2, other maintenance asthma therapies were discontinued.

Trial 1 enrolled 397 subjects 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 demonstrated a statistically significant improvement in lung function as measured by improvement in AM pre-dose FEV_1 compared with placebo. This improvement was observed after the first week of treatment, and 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 statistically significant, and the corresponding 95% confidence intervals were (2.2%, 9.2%), (2.8%, 9.9%), and (4.3%,

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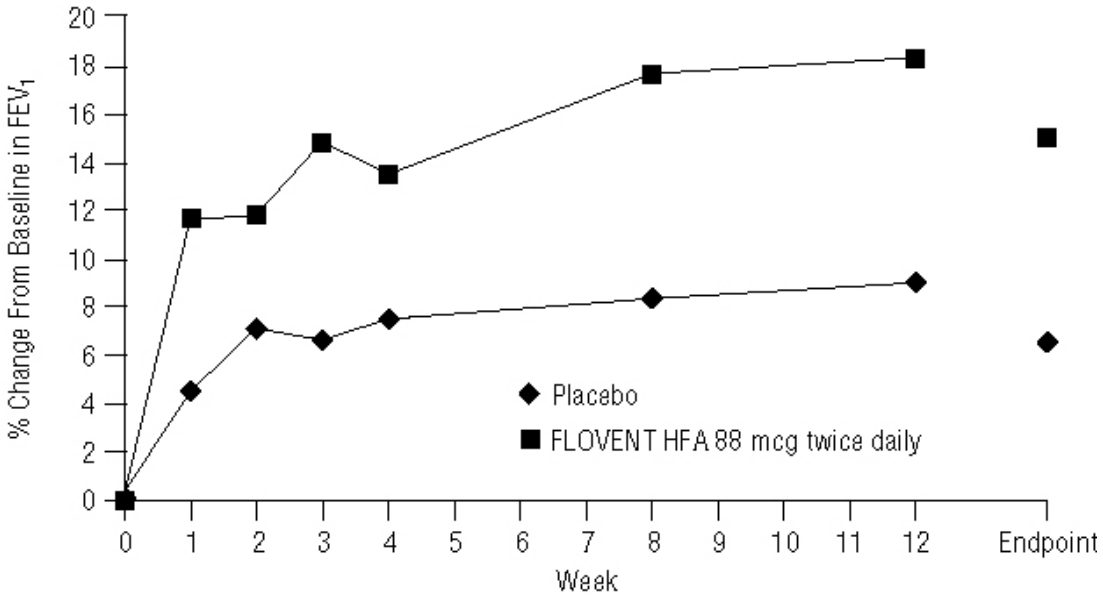
11.3%), respectively.

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 Trial 1. This trial used predetermined criteria for lack of efficacy (indicators of worsening asthma), resulting in withdrawal of more subjects in the placebo group. Therefore, pulmonary function results at Endpoint (the last evaluable FEV_1 result, including most subjects' lung function data) are also displayed.

Figure 1. A 12-Week Clinical Trial in Subjects Aged 12 Years and Older Inadequately Controlled on Bronchodilators Alone: Mean Percent Change from Baseline in FEV_1 Prior to AM Dose (Trial 1)



In Trial 2, FLOVENT HFA at dosages of 88, 220, and 440 mcg twice daily was evaluated over 12 weeks of treatment in 415 subjects 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 demonstrated a statistically significant improvement in lung function, as measured by improvement in FEV_1, compared with placebo. This improvement was observed after the first week of treatment and was maintained over the 12-week treatment period. Discontinuations from the trial for lack of efficacy (defined by a pre-specified decrease in FEV_1 or 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 with placebo (50%).

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

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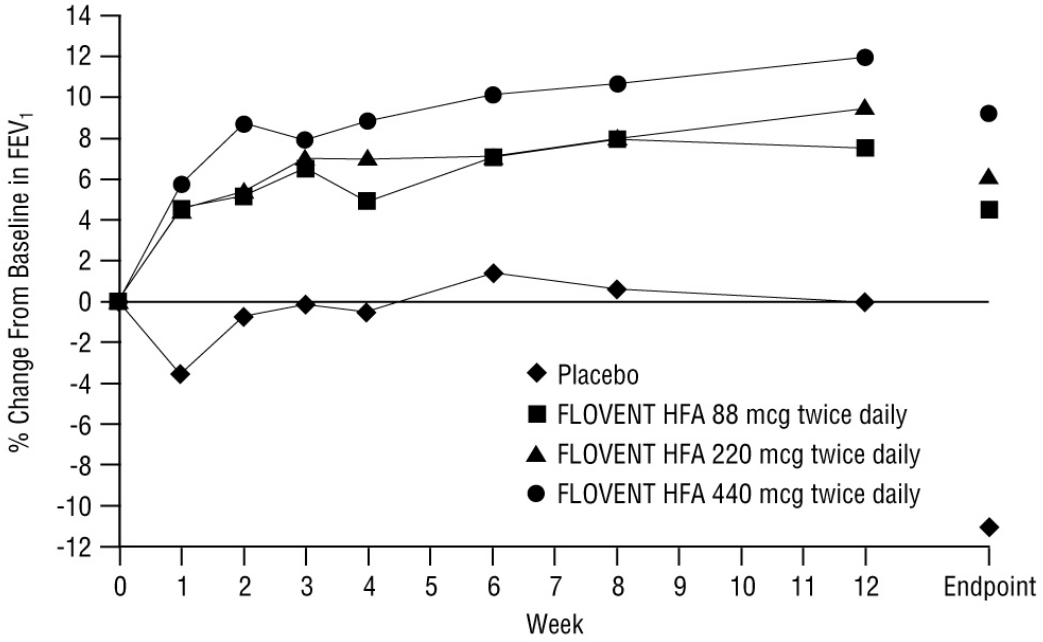
the placebo group (-8.3%). The mean differences between the groups treated with FLOVENT HFA 88, 220, and 440 mcg and the placebo group were statistically significant, and the corresponding 95% confidence intervals were (7.1%, 13.8%), (8.2%, 14.9%), and (9.6%, 16.4%), respectively.

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

Figure 2. A 12-Week Clinical Trial in Subjects Aged 12 Years and Older Already Receiving Daily Inhaled Corticosteroids: Mean Percent Change from Baseline in FEV_1 Prior to AM Dose (Trial 2)



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

Trial 3 enrolled 168 subjects 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 trial, subjects treated with either dosage of FLOVENT HFA required a statistically significantly lower mean daily oral prednisone dose (6 mg) compared with placebo-treated subjects (15 mg). Both dosages of FLOVENT HFA enabled a larger percentage of subjects (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

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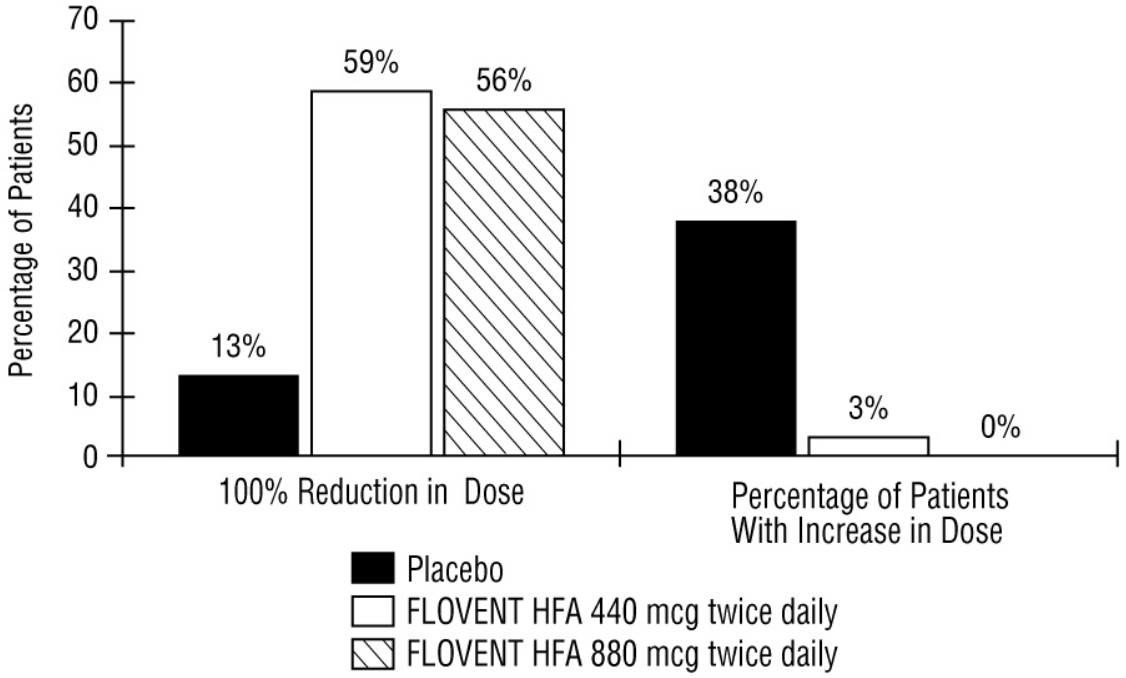
FLOVENT HFA 880 mcg twice daily compared with 440 mcg twice daily. Accompanying the reduction in oral corticosteroid use, subjects treated with either dosage of FLOVENT HFA had statistically significantly improved lung function, fewer asthma symptoms, and less use of VENTOLIN Inhalation Aerosol compared with the placebo-treated subjects.

Figure 3. A 16-Week Clinical Trial in Subjects Aged 12 Years and Older Requiring Chronic Oral Prednisone Therapy: Change in Maintenance Prednisone Dose



Two long-term safety trials (Trial 4 and Trial 5) of greater than or equal to 6 months' duration were conducted in 507 adult and adolescent subjects with asthma. Trial 4 was designed to monitor the safety of 2 doses of FLOVENT HFA, while Trial 5 compared fluticasone propionate HFA with fluticasone propionate CFC. Trial 4 enrolled 182 subjects 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 subjects, respectively. Trial 5 enrolled 325 subjects 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 subjects, 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 with baseline. In both trials, none of

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the subjects were withdrawn due to lack of efficacy.

14.2 Pediatric Subjects Aged 4 to 11 Years

A 12-week clinical trial conducted in 241 pediatric subjects with asthma was supportive of efficacy but inconclusive due to measurable levels of fluticasone propionate in 6/48 (13%) of the plasma samples from subjects randomized to placebo. Efficacy in subjects aged 4 to 11 years is extrapolated from adult data with FLOVENT HFA and other supporting data *[see Use in Specific Populations (8.4)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

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 counter and supplied with a dark orange actuator with a peach strapcap. Each inhaler is packaged with a Patient Information 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 canister into fire or incinerator.

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. SHAKE WELL BEFORE EACH SPRAY.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

<u>Local Effects</u>

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Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, treat it with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with FLOVENT HFA, but at times therapy with FLOVENT HFA may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.

Status Asthmaticus and Acute Asthma Symptoms

Inform patients that FLOVENT HFA is not a bronchodilator and is not intended for use as rescue medicine for acute asthma exacerbations. Advise patients to treat acute asthma symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Instruct patients to contact their physicians immediately if there is deterioration of their asthma.

Immunosuppression

Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Hypercorticism and Adrenal Suppression

Advise patients that FLOVENT HFA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients 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 HFA.

Immediate Hypersensitivity Reactions

Advise patients that immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of FLOVENT HFA. Patients should discontinue FLOVENT HFA if such reactions occur.

Reduction in Bone Mineral Density

Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Reduced Growth Velocity

Inform patients that orally inhaled corticosteroids, including FLOVENT HFA, 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.

Ocular Effects

Inform patients that long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

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Use Daily for Best Effect

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. Patients should not increase the prescribed dosage but should contact their physicians if symptoms do not improve or if the condition worsens. Instruct patients not to stop use of FLOVENT HFA abruptly. Patients should contact their physicians immediately if they discontinue use of FLOVENT HFA.

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Reference ID: 3995104

PHARMACIST—DETACH HERE AND GIVE LEAFLET TO PATIENT

PATIENT INFORMATION

FLOVENT® [*flō′vent*] HFA 44 mcg
(fluticasone propionate HFA 44 mcg)
Inhalation Aerosol
FLOVENT® HFA 110 mcg
(fluticasone propionate HFA 110 mcg)
Inhalation Aerosol
FLOVENT® HFA 220 mcg
(fluticasone propionate HFA 220 mcg)
Inhalation Aerosol
for oral inhalation

What is FLOVENT HFA?

FLOVENT HFA is a prescription inhaled corticosteroid (ICS) medicine for the long-term treatment of asthma in people aged 4 years and older.

- ICS medicines such as fluticasone propionate help to decrease inflammation in the lungs. Inflammation in the lungs can lead to breathing problems.
- FLOVENT HFA is not used to relieve sudden breathing problems.
- It is not known if FLOVENT HFA is safe and effective in children younger than 4 years of age.

Who should not use FLOVENT HFA?

Do not use FLOVENT HFA:

- to relieve sudden breathing problems.
- if you are allergic to fluticasone propionate or any of the ingredients in FLOVENT HFA. See “What are the ingredients in FLOVENT HFA?” below for a complete list of ingredients.

What should I tell my healthcare provider before using FLOVENT HFA?

Tell your healthcare provider about all of your health conditions, including if you:

- have liver problems.
- have weak bones (osteoporosis).
- have an immune system problem.
- have eye problems such as glaucoma or cataracts.
- are allergic to any of the ingredients in FLOVENT HFA, any other medicines, or food products. See “What are the ingredients in FLOVENT HFA?” below for a complete list of ingredients.
- have any type of viral, bacterial, or fungal infection.
- are exposed to chickenpox or measles.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if FLOVENT HFA may harm your unborn baby.
- are breastfeeding. It is not known if the medicine in FLOVENT HFA passes into your milk and if it can harm your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. FLOVENT HFA and certain other medicines may interact with each other. This may

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cause serious side effects. Especially, tell your healthcare provider if you take antifungal or anti-HIV medicines.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use FLOVENT HFA?

Read the step-by-step instructions for using FLOVENT HFA at the end of this Patient Information.

- **Do not** use FLOVENT HFA unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly.
- Children should use FLOVENT HFA with an adult's help, as instructed by the child's healthcare provider.
- FLOVENT HFA comes in 3 different strengths. Your healthcare provider prescribed the strength that is best for you.
- Use FLOVENT HFA exactly as your healthcare provider tells you to use it. **Do not** use FLOVENT HFA more often than prescribed.
- It may take 1 to 2 weeks or longer after you start FLOVENT HFA for your asthma symptoms to get better. You must use FLOVENT HFA regularly.
- **Do not** stop using FLOVENT HFA, even if you are feeling better, unless your healthcare provider tells you to.
- Talk to your healthcare provider right away if you stop using FLOVENT HFA.
- If you miss a dose of FLOVENT HFA, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at 1 time.
- **FLOVENT HFA does not relieve sudden breathing problems.** Always have a rescue inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- Call your healthcare provider or get medical care right away if:
  - your breathing problems get worse.
  - you need to use your rescue inhaler more often than usual.
  - your rescue inhaler does not work as well to relieve your symptoms.
  - you need to use 4 or more inhalations of your rescue inhaler in 24 hours for 2 or more days in a row.
  - you use 1 whole canister of your rescue inhaler in 8 weeks.
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.

What are the possible side effects of FLOVENT HFA?

FLOVENT HFA can cause serious side effects, including:

- **fungal infection in your mouth or throat (thrush).** Rinse your mouth with water without swallowing after using FLOVENT HFA to help reduce your chance of getting thrush.
- **weakened immune system and increased chance of getting infections (immunosuppression).**
- **reduced adrenal function (adrenal insufficiency).** Adrenal insufficiency is a condition where the adrenal glands do not make enough steroid hormones. This can happen when you stop taking oral corticosteroid medicines (such as prednisone) and start taking a medicine containing an inhaled steroid (such as FLOVENT HFA). During this transition period, when your body is under stress such as from fever, trauma (such as a car accident), infection, or surgery, adrenal insufficiency can get worse and may cause death.

  Symptoms of adrenal insufficiency include:
  - feeling tired
  - lack of energy
  - weakness
  - nausea and vomiting
  - low blood pressure

- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling of your face, mouth, and tongue
  - breathing problems
- **bone thinning or weakness (osteoporosis).**
- **slowed growth in children.** A child's growth should be checked often.
- **eye problems including glaucoma and cataracts.** You should have regular eye exams while using FLOVENT HFA.
- **increased wheezing (bronchospasm).** Increased wheezing can happen right away after using FLOVENT HFA. Always have a rescue inhaler with you to treat sudden wheezing.

Common side effects of FLOVENT HFA include:

- a cold or upper respiratory tract infection
- throat irritation
- headache
- fever
- diarrhea
- ear infection

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with FLOVENT HFA. Ask your healthcare provider or pharmacist for more information.

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

How should I store FLOVENT HFA?

- Store FLOVENT HFA at room temperature between 68°F and 77°F (20°C and 25°C) with the mouthpiece down.
- **The contents of your FLOVENT HFA inhaler are under pressure. Do not** puncture. **Do not** use or store near heat or open flame. Temperatures above 120°F may cause the canister to burst.
- **Do not** throw into fire or an incinerator.
- Safely throw away FLOVENT HFA in the trash when the counter reads **000**.
- **Keep FLOVENT HFA and all medicines out of the reach of children.**

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

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

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

What are the ingredients in FLOVENT HFA?

Active ingredient: fluticasone propionate

Inactive ingredient: propellant HFA-134a

For more information about FLOVENT HFA, call 1-888-825-5249 or visit our website at www.flovent.com.

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GlaxoSmithKline

Research Triangle Park, NC 27709

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This Patient Information has been approved by the U.S. Food and Drug Administration Revised: July 2016

INSTRUCTIONS FOR USE

FLOVENT® [*flō′vent*] HFA 44 mcg
(fluticasone propionate HFA 44 mcg)
Inhalation Aerosol
FLOVENT® HFA 110 mcg
(fluticasone propionate HFA 110 mcg)
Inhalation Aerosol
FLOVENT® HFA 220 mcg
(fluticasone propionate HFA 220 mcg)
Inhalation Aerosol
for oral inhalation

Your FLOVENT HFA inhaler

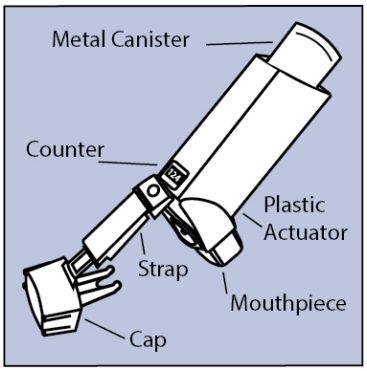

Figure A

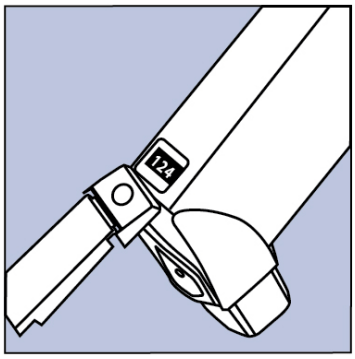

Figure B

- The metal canister holds the medicine. **See Figure A.**
- 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. **See Figure B.**
- 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**.
- **Do not 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 dark orange plastic actuator sprays the medicine from the canister. The actuator has a protective cap that covers the mouthpiece. **See Figure A.** Keep the protective cap on the mouthpiece when the canister is not in use. The strap keeps the cap attached to the actuator.
- **Do not** use the actuator with a canister of medicine from any other inhaler.
- **Do not** use a FLOVENT HFA canister with an actuator from any other inhaler.

Before using your FLOVENT HFA inhaler

- The inhaler should be at room temperature before you use it.

- If a child needs help using the inhaler, an adult should help the child use the inhaler with or without a valved holding chamber, which may also be attached to a mask. The adult should follow the instructions that came with the valved holding chamber. An adult should watch a child use the inhaler to be sure it is used correctly.

Priming your FLOVENT HFA inhaler

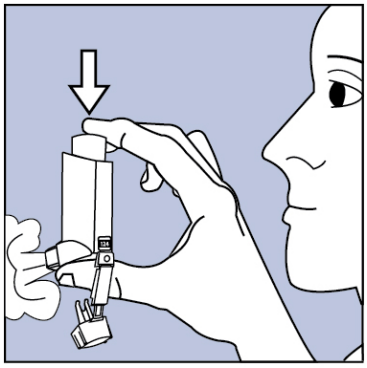

Figure C

- **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 1 time into the air away from your face. **See Figure C. Avoid spraying in eyes.**

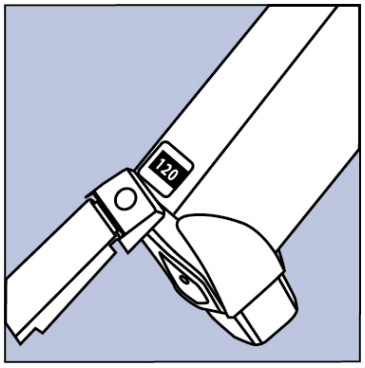

Figure D

- Shake and spray the inhaler like this 3 more times to finish priming it. The counter should now read **120**. **See Figure D.**
- You must prime your 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.

How to use your FLOVENT HFA inhaler

Follow these steps every time you use FLOVENT HFA.

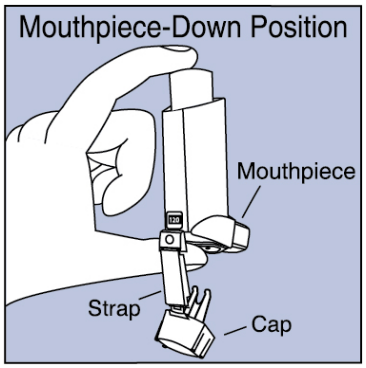

Figure E

Step 1. Make sure the canister fits firmly in the actuator. The counter should show through the window in the actuator.

Shake the inhaler well for 5 seconds before each spray.

Take the cap off the mouthpiece of the actuator. Look inside the mouthpiece for foreign objects, and take out any you see.

Step 2. Hold the inhaler with the mouthpiece down. **See Figure E.**

Step 3. 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. **See Figure F.**

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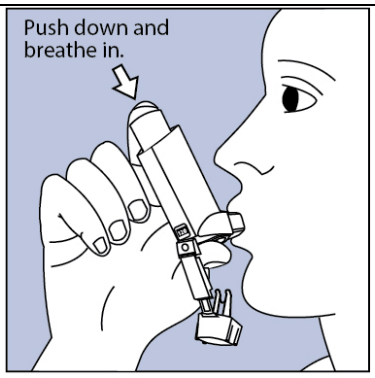

Figure F

Figure G

Step 4. Push the top of the canister **all the way down** while you breathe in deeply and slowly through your mouth. **See Figure F.**

Step 5. 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.

Step 6. **Hold your breath for about 10 seconds,** or for as long as is comfortable. **Breathe out slowly as long as you can.**

Wait about 30 seconds and shake the inhaler well for 5 seconds. Repeat steps 2 through 6.

Step 7. **Rinse your mouth with water after breathing in the medicine.** Spit out the water. Do not swallow it. **See Figure G.**

Step 8. Put the cap back on the mouthpiece after every time you use the inhaler. Make sure it snaps firmly into place.

Cleaning your FLOVENT HFA inhaler

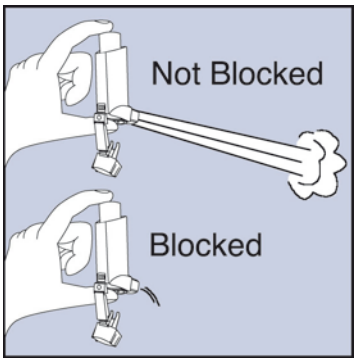

Figure H

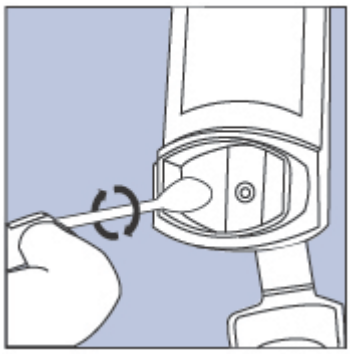

Figure I

Clean your inhaler at least 1 time each week after your evening dose. You may not see any medicine build-up on the inhaler, but it is important to keep it clean so medicine build-up will not block the spray. **See Figure H.**

Step 9. 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.

Step 10. 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 I.** Repeat with a new swab dampened with water to take off any medicine still at the opening.

Step 11. Wipe the inside of the mouthpiece with a clean tissue dampened with water. Let the actuator air-dry overnight.

Step 12. Put the cap back on the mouthpiece after the actuator has dried.

Replacing your FLOVENT HFA inhaler

- **When the counter reads 020**, you should refill your prescription or ask your healthcare provider if you need another prescription for FLOVENT HFA.
- **When the counter reads 000, throw the inhaler away.** You should not keep using the inhaler when the counter reads **000** because you may 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 correct use of your FLOVENT HFA inhaler, remember:

- The canister should always fit firmly in the actuator.
- Breathe in deeply and slowly to make sure you get all the medicine.
- Hold your breath for about 10 seconds after breathing in the medicine. Then breathe out fully.
- After each dose, rinse your mouth with water and spit it out. **Do not** swallow the water.
- **Do not** take the inhaler apart.
- Always keep the protective cap on the mouthpiece when your inhaler is not in use.
- Always store your inhaler with the mouthpiece pointing down.
- Clean your inhaler at least 1 time each week.

If you have questions about FLOVENT HFA or how to use your inhaler, call GlaxoSmithKline (GSK) at 1-888-825-5249 or visit www.flovent.com.

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