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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 (fluticasone propionate inhalation aerosol), for oral inhalation use
Initial U.S. Approval: 1994

INDICATIONS AND USAGE

FLOVENT HFA is an inhaled corticosteroid indicated for:

- Maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients aged 4 years and older. (1)

Limitations of use: Not indicated for relief of acute bronchospasm. (1)

DOSAGE AND ADMINISTRATION

- For oral inhalation only. (2.1)
- Starting dosage is based on prior asthma therapy and disease severity. (2.2)
- Adult and adolescent patients aged 12 years and older: 88 mcg twice daily up to a maximum dosage of 880 mcg twice daily. (2.2)
- Pediatric patients aged 4 to 11 years: 88 mcg twice daily. (2.2)

DOSAGE FORMS AND STRENGTHS

Inhalation aerosol:

- 44 mcg fluticasone propionate per actuation (3)
- 110 mcg fluticasone propionate per actuation (3)
- 220 mcg fluticasone propionate per actuation (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 infections; 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)
- Glaucoma and cataracts may occur with long-term use of ICS. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use FLOVENT HFA long term. (5.9)

ADVERSE REACTIONS

Most common adverse reactions (incidence >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: 8/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Administration Information
2.2 Recommended Dosage
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Oropharyngeal Candidiasis
5.2 Acute Asthma Episodes
5.3 Immunosuppression and Risk of Infections
5.4 Transferring Patients from Systemic Corticosteroid Therapy
5.5 Hypercorticism and Adrenal Suppression
5.6 Hypersensitivity Reactions, including Anaphylaxis
5.7 Reduction in Bone Mineral Density
5.8 Effect on Growth
5.9 Glaucoma and Cataracts
5.10 Paradoxical Bronchospasm
5.11 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors
5.12 Eosinophilic Conditions and Churg-Strauss Syndrome
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Inhibitors of Cytochrome P450 3A4
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
8.7 Renal Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Adult and Adolescent Subjects Aged 12 Years and Older
14.2 Pediatric Subjects Aged 4 to 11 Years
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

Reference ID: 4843467

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLOVENT HFA is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients aged 4 years and older.

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Administration Information

FLOVENT HFA should be administered by the orally inhaled route only. After inhalation, rinse mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

A valved holding chamber and mask may be used to deliver FLOVENT HFA to young patients.

Priming

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. Avoid spraying in eyes.

2.2 Recommended Dosage

Adult and Adolescent Patients Aged 12 Years and Older

The recommended starting dosage for patients aged 12 years and older who are not on an inhaled corticosteroid (ICS): 88 mcg (2 inhalations of 44 mcg fluticasone propionate) twice daily by oral inhalation, approximately 12 hours apart.

- The maximum recommended dosage for patients aged 12 years and older is 880 mcg twice daily.

Pediatric Patients Aged 4 to 11 Years

The recommended dosage for patients aged 4 to 11 years: 88 mcg (2 inhalations of 44 mcg fluticasone propionate) twice daily by oral inhalation, approximately 12 hours apart.

General Dosing Recommendations

The starting dosage is based on previous asthma therapy and asthma severity, including consideration of patients' current control of asthma symptoms and risk of future exacerbation.

If symptoms arise between doses, an inhaled short-acting beta$_2$-agonist should be used for immediate relief.

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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.

For other patients, and for patients who do not respond adequately to the starting dosage after 2 weeks of therapy, higher dosages may provide additional asthma control.

If a dosage regimen fails to provide adequate control of asthma, the therapeutic regimen should be re-evaluated and additional therapeutic options, e.g., replacing the current strength with a higher strength, initiating an ICS and long-acting beta$_2$-agonist (LABA) combination product, or initiating oral corticosteroids, should be considered.

After asthma stability has been achieved, titrate to the lowest effective dosage to reduce the possibility of side effects.

3 DOSAGE FORMS AND STRENGTHS

Inhalation aerosol: dark orange plastic inhaler with a peach cap containing a pressurized metered-dose aerosol canister containing 120 metered inhalations and fitted with a counter.

- 44 mcg of fluticasone propionate from the mouthpiece per actuation
- 110 mcg of fluticasone propionate from the mouthpiece per actuation
- 220 mcg of fluticasone propionate from the mouthpiece per actuation

4 CONTRAINDICATIONS

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 Oropharyngeal Candidiasis

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 and Risk of Infections

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.

ICS 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

HPA Suppression/Adrenal Insufficiency

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. 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

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corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to 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.

Unmasking of Allergic Conditions Previously Suppressed by Systemic Corticosteroids

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).

Corticosteroid Withdrawal Symptoms

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 ICS 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.

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5.6 Hypersensitivity Reactions, including Anaphylaxis

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

5.7 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. 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 (2.2), 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 ICS, including fluticasone propionate. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use FLOVENT HFA long term.

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,

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telithromycin) with FLOVENT HFA is not recommended because increased systemic corticosteroid adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

5.12 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other ICS 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

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Oropharyngeal candidiasis infection *[see Warnings and Precautions (5.1)]*
- Immunosuppression and risk of infections *[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 1 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 ICS were treated twice daily for up to 12 weeks with 2 inhalations of FLOVENT HFA 44 mcg, FLOVENT HFA 110 mcg, FLOVENT HFA 220 mcg (dosages of 88, 220, or 440 mcg twice daily), or placebo.

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Table 1. 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 1 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

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not 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.

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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.

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 insufficient data on the use 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, was observed with subcutaneously

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administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mcg/m^2 basis. *(See Data.)* However, fluticasone propionate administered via inhalation to rats decreased fetal body weight but did not induce teratogenicity at a maternal toxic dose less than the MRHDID on a mcg/m^2 basis. *(See 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 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

Human Data: Following inhaled administration, fluticasone propionate was detected in the neonatal cord blood after delivery.

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 mcg/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 mcg/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 mcg/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 mcg/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 mcg/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 mcg/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

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weights, in the presence of maternal toxicity, at doses approximately 0.006 times the MRHDID and higher (on a mcg/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 a dose approximately 0.04 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.001 times the MRHDID (on a mcg/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 mcg/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 of 10 mcg/kg/day to lactating rats resulted in measurable levels in milk.

8.4 Pediatric Use

The safety and effectiveness of FLOVENT HFA in pediatric patients aged 4 years and older have been established *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*. 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.

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The safety and effectiveness of FLOVENT HFA in pediatric patients younger than 4 years have not been established.

Effects on Growth

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

Controlled clinical trials have shown that ICS 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

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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 growth data is not certain.

Pediatric Patients 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 >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

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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 2 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, 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 2. 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

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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, 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

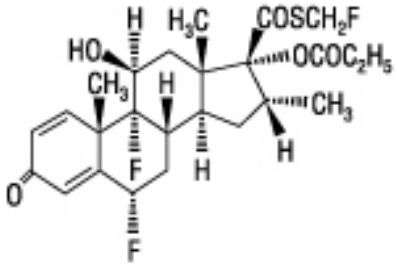
Formal pharmacokinetic studies using FLOVENT HFA have not been conducted in patients with renal impairment.

10 OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.5)]*.

11 DESCRIPTION

FLOVENT HFA is a pressurized metered dose inhaler for oral inhalation. The active component of FLOVENT HFA 44 mcg, FLOVENT HFA 110 mcg, and FLOVENT HFA 220 mcg is fluticasone propionate, a corticosteroid having the chemical name *S*-(fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



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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 is a dark orange plastic inhaler with a peach cap 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. Avoid spraying in eyes.

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

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activity and systemic corticosteroid effects with recommended doses of orally inhaled fluticasone propionate. This is explained by a combination of a relatively high local anti-inflammatory effect, negligible oral systemic bioavailability (<1%), and the minimal pharmacological activity of the only metabolite detected in man.

12.2 Pharmacodynamics

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 <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 <18 mcg/dL.

12.3 Pharmacokinetics

Absorption

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 (<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.

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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.

Elimination

Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for <0.02% of the total. 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.

Metabolism: 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.

Specific Populations

Male and Female Patients: No significant difference in clearance (CL/F) of fluticasone propionate was observed.

Pediatric Patients: 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

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VHC, as shown in Table 3.

Table 3. 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 4), possibly correcting for the inability to coordinate actuation and inhalation.

Table 4. 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.

Patients with 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.

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

Drug Interaction Studies

Inhibitors of Cytochrome P450 3A4: Ritonavir: Fluticasone propionate is a substrate of

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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 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•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 3 and 10 times the MRHDID for adults and children aged 4 to 11 years, respectively, on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately 0.3 times and approximately equivalent to the MRHDID for adults and children aged 4 to 11 years, 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 in vivo mouse micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous

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doses up to 50 mcg/kg (approximately 0.3 times the MRHDID for adults on a mcg/m^2 basis).

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 ICS (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%, 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.

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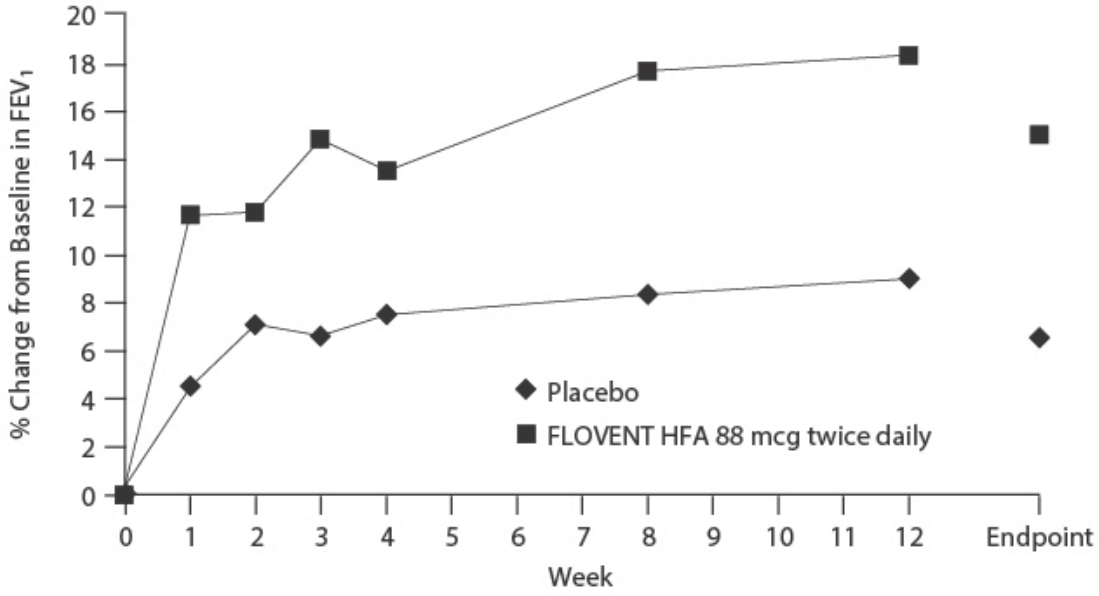
Figure 1. A 12-Week Clinical Trial in Subjects Aged 12 Years and Older Inadequately Controlled on Bronchodilators Alone: Mean Percent Change from Baseline in FEV_1 Prior to AM Dose (Trial 1)



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 ICS 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 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.

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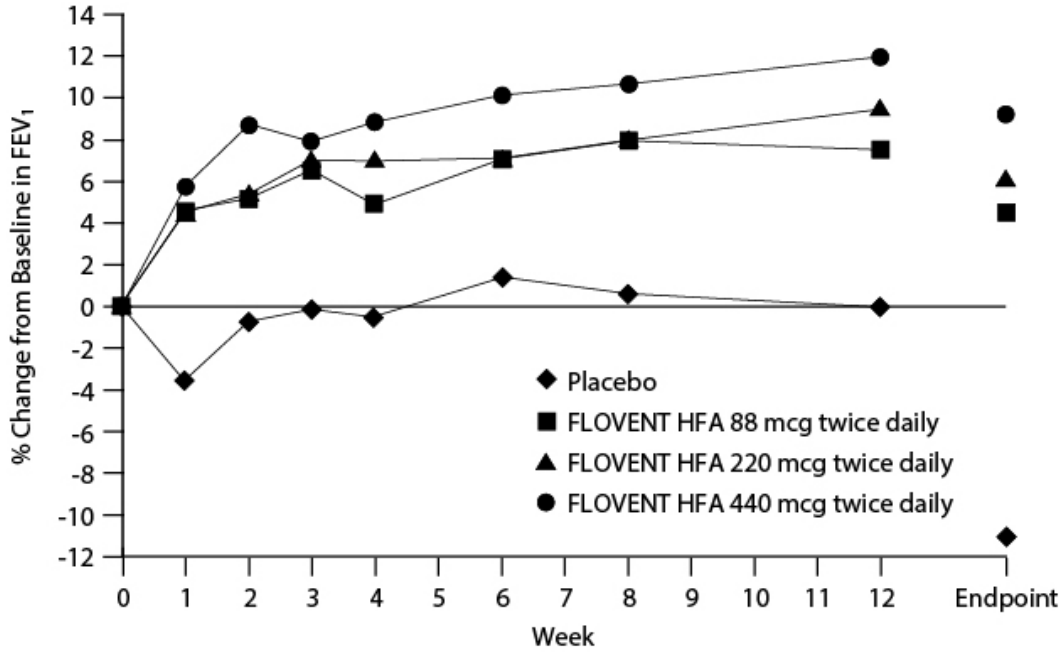
Figure 2. A 12-Week Clinical Trial in Subjects Aged 12 Years and Older Already Receiving Daily Inhaled Corticosteroids: Mean Percent Change from Baseline in FEV_1 Prior to AM Dose (Trial 2)



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 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.

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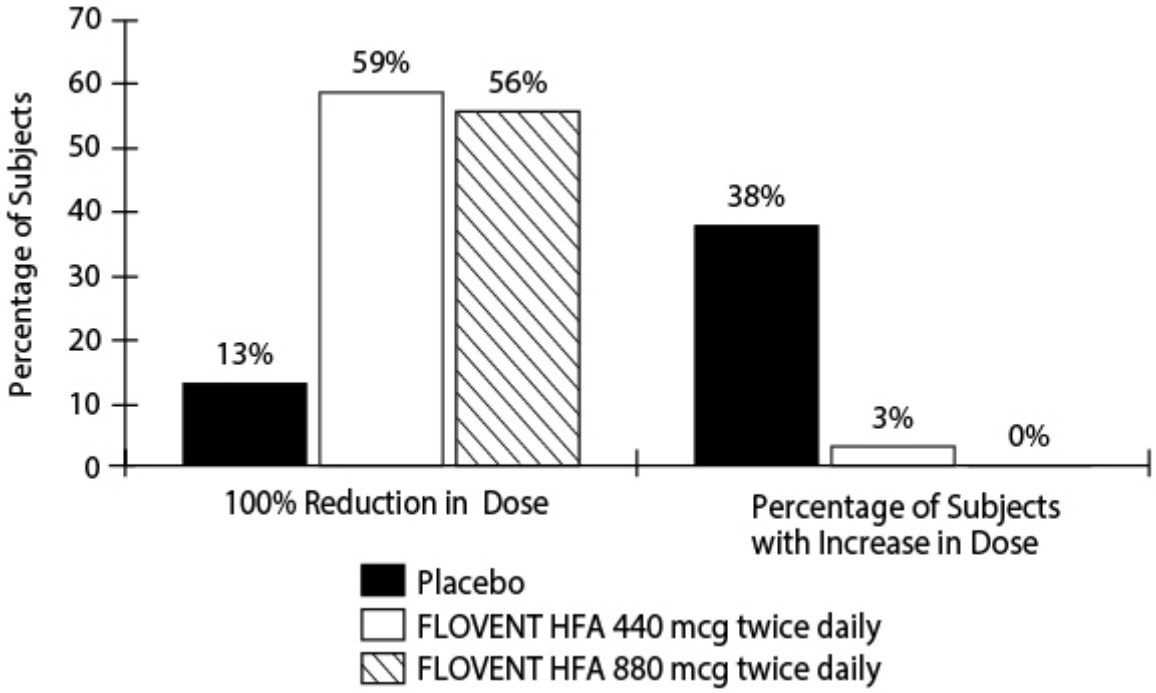
Figure 3. A 16-Week Clinical Trial in Subjects Aged 12 Years and Older Requiring Chronic Oral Prednisone Therapy: Change in Maintenance Prednisone Dose



Two long-term safety trials (Trial 4 and Trial 5) of ≥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 ICS, 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 ICS, 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 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

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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 is supplied in the following boxes of 1 as a pressurized aluminum canister fitted with a counter and supplied with a dark orange actuator with a peach cap:

- FLOVENT HFA 44 mcg: 10.6-g canister containing 120 actuations (NDC 0173-0718-20)
- FLOVENT HFA 110 mcg: 12-g canister containing 120 actuations (NDC 0173-0719-20)
- FLOVENT HFA 220 mcg: 12-g canister containing 120 actuations (NDC 0173-0720-20)

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.

Counter

FLOVENT HFA has a counter attached to the canister. The counter starts at 124 and counts down each time a spray is released. 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.

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.

Storage

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.

17 PATIENT COUNSELING INFORMATION

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

Oropharyngeal Candidiasis

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

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medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush. *[See Warnings and Precautions (5.1).]*

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. *[See Warnings and Precautions (5.2).]*

Immunosuppression and Risk of Infections

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. *[See Warnings and Precautions (5.3).]*

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. *[See Warnings and Precautions (5.5).]*

Hypersensitivity Reactions, including Anaphylaxis

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. *[See Warnings and Precautions (5.6).]*

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. *[See Warnings and Precautions (5.7).]*

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. *[See Warnings and Precautions (5.8).]*

Glaucoma and Cataracts

Advise patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations. *[See Warnings and Precautions (5.9).]*

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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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PHARMACIST—DETACH HERE AND GIVE LEAFLET TO PATIENT

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PATIENT INFORMATION

FLOVENT (FLO vent) HFA
(fluticasone propionate inhalation aerosol)
for oral inhalation use

What is FLOVENT HFA?

FLOVENT HFA is a prescription inhaled corticosteroid (ICS) medicine used 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** and will not replace a rescue inhaler.
- It is not known if FLOVENT HFA is safe and effective in children younger than 4 years of age.

Do not use FLOVENT HFA:

- to relieve sudden breathing problems.
- as a rescue inhaler.
- if you are allergic to fluticasone propionate or any of the ingredients in FLOVENT HFA. See the end of this leaflet for a complete list of ingredients in FLOVENT HFA.

Before using FLOVENT HFA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems.
- have weak bones (osteoporosis).
- have an immune system problem.
- have or have had eye problems such as glaucoma, increased pressure in your eye, cataracts, or other changes in vision.
- have any type of viral, bacterial, or fungal infection.
- are exposed to chickenpox or measles.
- are pregnant or plan 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 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.

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- 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.
- 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.
- Rinse your mouth with water **without swallowing** after each dose of FLOVENT HFA. This will help lessen the chance of getting a yeast infection (thrush) in your mouth and throat.
- 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 (hypotension)
- **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.** Your child's growth should be checked regularly by the healthcare provider while using FLOVENT HFA.

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- **eye problems** including glaucoma, increased pressure in your eye, cataracts, or other changes in vision**.** 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:

- upper respiratory tract infection
- throat irritation
- headache
- diarrhea
- difficulty speaking
- sinus irritation
- cough
- persistent cough

These are not all the possible side effects of FLOVENT HFA.

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

You can ask your healthcare provider or pharmacist for information about FLOVENT HFA that was written for health 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.

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INSTRUCTIONS FOR USE

FLOVENT (FLO vent) HFA

(fluticasone propionate inhalation aerosol)

for oral inhalation use

Your FLOVENT HFA inhaler

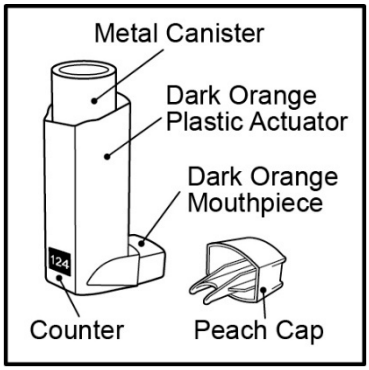

Figure A

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

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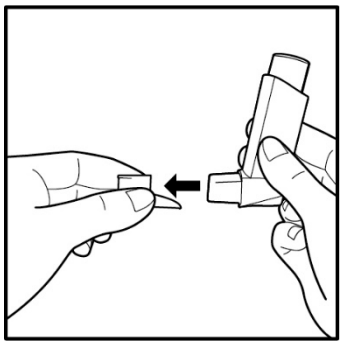

Figure B

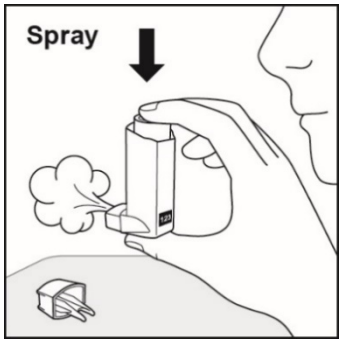

Figure C

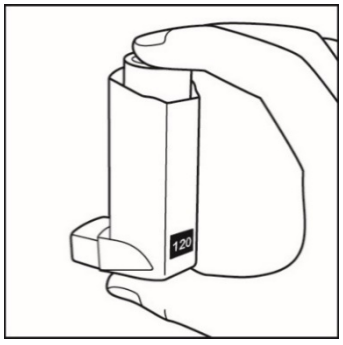

Figure D

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 take the cap off the mouthpiece, squeeze the sides of the cap and pull it straight out. **See Figure B.**
- Shake the inhaler well for 5 seconds.
- Spray the inhaler 1 time into the air away from your face. **Avoid spraying in eyes. See Figure C.**
- 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 have dropped it. To take the cap off the mouthpiece, squeeze the sides of the cap and pull it straight out. 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.

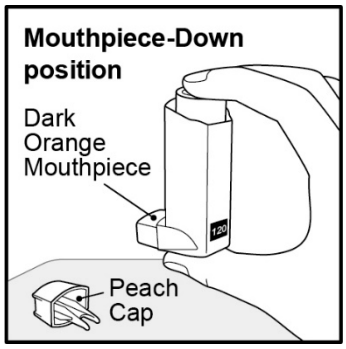

Figure E

Step 1. Make sure the metal canister fits firmly in the plastic actuator. The counter should show through the window in the plastic actuator. To take the cap off the mouthpiece, squeeze the sides of the cap and pull it straight out. Look inside the mouthpiece for foreign objects and take out any you see.

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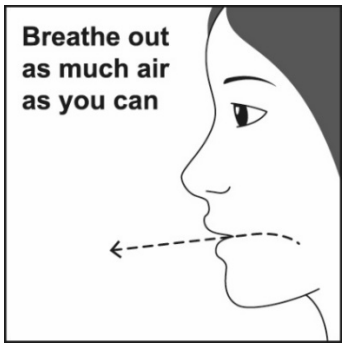

Figure F

Figure G

Figure H

Step 2. Hold the inhaler with the mouthpiece down and **shake it well for 5 seconds**. **See Figure E.**

Step 3. Breathe out through your mouth and push as much air from your lungs as you can. **See Figure F.**

Step 4. Put the mouthpiece in your mouth and close your lips around it. Push the top of the metal canister firmly **all the way down** while you breathe in deeply and slowly through your mouth. **See Figure G.**

Step 5. After the spray comes out, take your finger off the metal 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 Step 2 through Step 6.

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

Step 8. Put the cap back on the mouthpiece after you finish using the inhaler. Make sure it snaps firmly into place.

Cleaning your FLOVENT HFA inhaler

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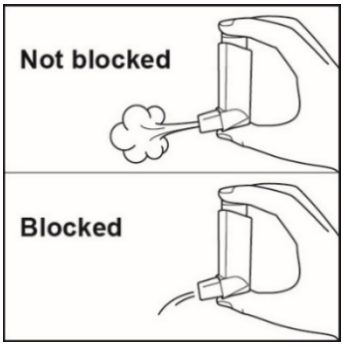

Figure I

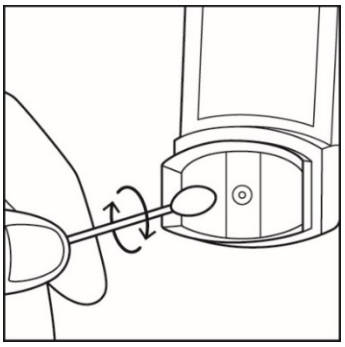

Figure J

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 I.**

Step 9. Take the cap off the mouthpiece by squeezing the sides of the cap and pulling it straight out. Do not take the metal 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 metal canister. Gently twist the swab in a circular motion to take off any medicine. **See Figure J.** 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 plastic actuator air-dry overnight.

Step 12. Put the cap back on the mouthpiece after the plastic 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 metal canister should always fit firmly in the plastic actuator.
- **Shake the inhaler well** for 5 seconds before each spray.

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- 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.

For more information about FLOVENT HFA or how to use your inhaler, call 1-888-825-5249.
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Revised: August 2021

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VENTOLIN HFA (albuterol sulfate inhalation aerosol), for oral inhalation use
Initial U.S. Approval: 1981

INDICATIONS AND USAGE

VENTOLIN HFA is a beta$_2$-adrenergic agonist indicated for:

- Treatment or prevention of bronchospasm in adult and pediatric patients aged 4 years and older with reversible obstructive airway disease. (1.1)
- Prevention of exercise-induced bronchospasm in adult and pediatric patients aged 4 years and older. (1.2)

DOSAGE AND ADMINISTRATION

- For oral inhalation only. (2)
- Treatment or prevention of bronchospasm in adult and pediatric patients aged 4 years and older: 2 inhalations by oral inhalation every 4 to 6 hours. For some patients, 1 inhalation every 4 hours may be sufficient. (2.1)
- Prevention of exercise-induced bronchospasm in adult and pediatric patients aged 4 years and older: 2 inhalations by oral inhalation 15 to 30 minutes before exercise. (2.2)
- Priming information: Prime VENTOLIN HFA before using for the first time, when the inhaler has not been used for more than 2 weeks, or when the inhaler has been dropped. To prime VENTOLIN HFA, release 4 sprays into the air away from the face, shaking well before each spray. (2.3)
- Cleaning information: At least once a week, wash the actuator with warm water and let it air-dry completely. (2.3)

DOSAGE FORMS AND STRENGTHS

Inhalation aerosol: 108 mcg albuterol sulfate (90 mcg albuterol base) per actuation. (3)

CONTRAINDICATIONS

Hypersensitivity to any ingredient. (4)

WARNINGS AND PRECAUTIONS

- Life-threatening paradoxical bronchospasm may occur. Discontinue VENTOLIN HFA immediately and institute alternative therapy. (5.1)
- Need for more doses of VENTOLIN HFA than usual may be a sign of deterioration of asthma and requires reevaluation of treatment. (5.2)
- VENTOLIN HFA is not a substitute for corticosteroids. (5.3)
- Cardiovascular effects may occur. Use with caution in patients sensitive to sympathomimetic drugs and patients with cardiovascular or convulsive disorders. (5.4, 5.7)
- Excessive use may be fatal. Do not exceed recommended dose. (5.5)
- Immediate hypersensitivity reactions may occur. Discontinue VENTOLIN HFA immediately. (5.6)
- Hypokalemia and changes in blood glucose may occur. (5.7, 5.8)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥3%) are throat irritation, viral respiratory infections, upper respiratory inflammation, cough, and musculoskeletal pain. (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

- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.1)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists. (7.2)
- Digoxin: May decrease serum digoxin levels. Consider monitoring digoxin levels. (7.3)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of albuterol on vascular system. (7.4)

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

Revised: 8/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Bronchospasm
1.2 Exercise-Induced Bronchospasm
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage for Bronchospasm (Acute Episodes or Symptoms Associated with Bronchospasm)
2.2 Recommended Dosage for Prevention of Exercise-Induced Bronchospasm
2.3 Administration Information
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Paradoxical Bronchospasm
5.2 Deterioration of Asthma
5.3 Use of Anti-inflammatory Agents
5.4 Cardiovascular Effects
5.5 Do Not Exceed Recommended Dose
5.6 Hypersensitivity Reactions, including Anaphylaxis
5.7 Coexisting Conditions
5.8 Hypokalemia
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Beta-Adrenergic Receptor Blocking Agents
7.2 Non–Potassium-Sparing Diuretics
7.3 Digoxin
7.4 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Bronchospasm Associated with Asthma
14.2 Exercise-Induced Bronchospasm
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bronchospasm

VENTOLIN HFA is indicated for the treatment or prevention of bronchospasm in adult and pediatric patients aged 4 years and older with reversible obstructive airway disease.

1.2 Exercise-Induced Bronchospasm

VENTOLIN HFA is indicated for the prevention of exercise-induced bronchospasm in adult and pediatric patients aged 4 years and older.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Bronchospasm (Acute Episodes or Symptoms Associated with Bronchospasm)

Adult and pediatric patients aged 4 years and older: 2 inhalations by oral inhalation repeated every 4 to 6 hours; in some patients, 1 inhalation every 4 hours may be sufficient. More frequent administration or a greater number of inhalations is not recommended.

2.2 Recommended Dosage for Prevention of Exercise-Induced Bronchospasm

Adult and pediatric patients aged 4 years and older: 2 inhalations by oral inhalation 15 to 30 minutes before exercise.

2.3 Administration Information

VENTOLIN HFA should be administered by the orally inhaled route only.

Priming

Priming VENTOLIN HFA is essential to ensure appropriate albuterol content in each actuation. Prime VENTOLIN HFA before using for the first time, when the inhaler has not been used for more than 2 weeks, or when the inhaler has been dropped. To prime VENTOLIN HFA, release 4 sprays into the air away from the face, shaking well before each spray. Avoid spraying in eyes.

Cleaning

To ensure proper dosing and to prevent actuator orifice blockage, wash the actuator with warm water and let it air-dry completely at least once a week.

3 DOSAGE FORMS AND STRENGTHS

Inhalation aerosol: 108 mcg of albuterol sulfate (90 mcg of albuterol base) from the mouthpiece per actuation. Blue plastic inhaler with a blue cap containing a pressurized metered-dose aerosol canister containing 60 or 200 metered inhalations and fitted with a counter.

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4 CONTRAINDICATIONS

VENTOLIN HFA is contraindicated in patients with a history of hypersensitivity to any of the ingredients *[see Warnings and Precautions (5.6), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Paradoxical Bronchospasm

VENTOLIN HFA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with VENTOLIN HFA, it should be discontinued immediately and alternative therapy should be instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

5.2 Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of VENTOLIN HFA than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

5.3 Use of Anti-inflammatory Agents

The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

5.4 Cardiovascular Effects

VENTOLIN HFA, like all other beta$_2$-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients such as changes in pulse rate or blood pressure. If such effects occur, VENTOLIN HFA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical relevance of these findings is unknown. Therefore, VENTOLIN HFA, like all other sympathomimetic amines, should be used with caution in patients with underlying cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.5 Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

5.6 Hypersensitivity Reactions, including Anaphylaxis

Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm,

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hypotension), including anaphylaxis, may occur after administration of VENTOLIN HFA *[see Contraindications (4)]*.

5.7 Coexisting Conditions

VENTOLIN HFA, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus and in patients who are unusually responsive to sympathomimetic amines. Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.8 Hypokalemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.1)]*. The decrease in serum potassium is usually transient, not requiring supplementation.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.1)]*
- Cardiovascular effects *[see Warnings and Precautions (5.4)]*
- Hypersensitivity reactions, including anaphylaxis *[see Warnings and Precautions (5.6)]*
- Hypokalemia *[see Warnings and Precautions (5.8)]*

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 safety data described below reflects exposure to VENTOLIN HFA in 248 subjects treated with VENTOLIN HFA in 3 placebo-controlled clinical trials of 2 to 12 weeks' duration. The data from adults and adolescents is based upon 2 clinical trials in which 202 subjects with asthma aged 12 years and older were treated with VENTOLIN HFA 2 inhalations 4 times daily for 12 weeks' duration. The adult/adolescent population was 92 female, 110 male and 163 white, 19 black, 18 Hispanic, 2 other. The data from pediatric subjects are based upon 1 clinical trial in which 46 subjects with asthma aged 4 to 11 years were treated with VENTOLIN HFA 2 inhalations 4 times daily for 2 weeks' duration. The population was 21 female, 25 male and 25 white, 17 black, 3 Hispanic, 1 other.

Adult and Adolescent Subjects Aged 12 Years and Older

The two 12-week, randomized, double-blind trials in 610 adult and adolescent subjects with asthma that compared VENTOLIN HFA, a CFC 11/12-propelled albuterol inhaler, and an

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HFA-134a placebo inhaler. Overall, the incidence and nature of the adverse reactions reported for VENTOLIN HFA and a CFC 11/12-propelled albuterol inhaler were comparable. Table 1 lists the incidence of all adverse reactions (whether considered by the investigator to be related or unrelated to drug) from these trials that occurred at a rate of ≥3% in the group treated with VENTOLIN HFA and more frequently in the group treated with VENTOLIN HFA than in the HFA-134a placebo inhaler group.

Table 1. Adverse Reactions with VENTOLIN HFA with ≥3% Incidence and More Common than Placebo in Adult and Adolescent Subjects

	Percent of Subjects		
Adverse Reaction	**VENTOLIN HFA (n = 202) %**	**CFC 11/12-Propelled Albuterol Inhaler (n = 207) %**	**Placebo HFA-134a (n = 201) %**
Ear, nose, and throat			
Throat irritation	10	6	7
Upper respiratory inflammation	5	5	2
Lower respiratory			
Viral respiratory infections	7	4	4
Cough	5	2	2
Musculoskeletal			
Musculoskeletal pain	5	5	4

Adverse reactions reported by <3% of the adult and adolescent subjects receiving VENTOLIN HFA and by a greater proportion of subjects receiving VENTOLIN HFA than receiving HFA-134a placebo inhaler and that have the potential to be related to VENTOLIN HFA include diarrhea, laryngitis, oropharyngeal edema, cough, lung disorders, tachycardia, and extrasystoles. Palpitations and dizziness have also been observed with VENTOLIN HFA.

Pediatric Subjects Aged 4 to 11 Years

Results from the 2-week clinical trial in pediatric subjects with asthma aged 4 to 11 years showed that this pediatric population had an adverse reaction profile similar to that of the adult and adolescent populations.

Three trials have been conducted to evaluate the safety and efficacy of VENTOLIN HFA in subjects between birth and 4 years of age. The results of these trials did not establish the efficacy of VENTOLIN HFA in this age group *[see Use in Specific Populations (8.4)]*. Since the efficacy of VENTOLIN HFA has not been demonstrated in children between birth and 48 months of age, the safety of VENTOLIN HFA in this age group cannot be established. However, the safety profile observed in the pediatric population younger than 4 years was comparable to that observed in the older pediatric subjects and in adults and adolescents. Where adverse reaction

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incidence rates were greater in subjects younger than 4 years compared with older subjects, the higher incidence rates were noted in all treatment arms, including placebo. These adverse reactions included upper respiratory tract infection, nasopharyngitis, pyrexia, and tachycardia.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of albuterol sulfate. 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 albuterol or a combination of these factors.

Cases of paradoxical bronchospasm, hoarseness, arrhythmias (including atrial fibrillation, supraventricular tachycardia), and hypersensitivity reactions (including urticaria, angioedema, rash) have been reported after the use of VENTOLIN HFA.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypokalemia, hypertension, peripheral vasodilatation, angina, tremor, central nervous system stimulation, hyperactivity, sleeplessness, headache, muscle cramps, drying or irritation of the oropharynx, and metabolic acidosis.

7 DRUG INTERACTIONS

Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

7.1 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as VENTOLIN HFA, but may also produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.2 Non–Potassium-Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of VENTOLIN HFA with non–potassium-sparing diuretics.

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7.3 Digoxin

Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical relevance of these findings for patients with obstructive airway disease who are receiving inhaled albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

7.4 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

VENTOLIN HFA should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to asthma medications during pregnancy. For more information, contact the MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists at 1-877-311-8972 or visit https://mothertobaby.org/ongoing-study/asthma/.

Risk Summary

There are no randomized clinical studies of use of albuterol sulfate during pregnancy. Available data from epidemiological studies and postmarketing case reports of pregnancy outcomes following inhaled albuterol use do not consistently demonstrate a risk of major birth defects or miscarriage. There are, however, clinical considerations in pregnant women with asthma. *(See Clinical Considerations.)*

Administration of VENTOLIN HFA to mice and rabbits during the period of organogenesis revealed evidence of adverse developmental outcomes (cleft palate in mice, delayed ossification in rabbits) at less than the maximum recommended human daily inhaled dose (MRHDID). *(See Data.)*

The estimated background risk of major birth defects and miscarriage for the indicated population(s) 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

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preeclampsia 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.

Labor or Delivery: Because of the potential for beta-agonist interference with uterine contractility, use of VENTOLIN HFA during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. VENTOLIN HFA has not been approved for the management of pre-term labor. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol.

Data

Human Data: While available studies cannot definitively establish the absence of risk, published data from epidemiological studies and case reports have not consistently demonstrated an association with use of VENTOLIN HFA during pregnancy and major birth defects, specific birth defects, or miscarriage. The available studies have methodologic limitations, including inconsistent comparator groups, definitions of outcomes, and assessment of disease impact.

Animal Data: In a study in pregnant mice, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure less than the MRHDID for adults (on a mg/m^2 basis at a maternal dose of 0.25 mg/kg) and in 10 of 108 (9.3%) fetuses at approximately 9 times the MRHDID (on a mg/m^2 basis at a maternal dose of 2.5 mg/kg). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol, another beta$_2$-agonist.

In a study in pregnant rabbits, orally administered albuterol sulfate produced cranioschisis in 7 of 19 fetuses (37%) at approximately 750 times the MRHDID (on a mg/m^2 basis at a maternal dose of 50 mg/kg).

In a study in pregnant rabbits, an albuterol/HFA-134a formulation administered by inhalation produced enlargement of the frontal portion of the fetal fontanelles at approximately one third of the MRHDID on a mg/m^2 basis.

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

8.2 Lactation

Risk Summary

There are no available data on the presence of albuterol or the components of VENTOLIN HFA in human milk, the effects on the breastfed child, or the effects on milk production. However, plasma levels of albuterol after inhaled therapeutic doses are low in humans, and if present in 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

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clinical need for VENTOLIN HFA and any potential adverse effects on the breastfed child from VENTOLIN HFA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of VENTOLIN HFA for treatment or prevention of bronchospasm and for prevention of exercised-induced bronchospasm in pediatric patients aged 4 years and older have been established. Use of VENTOLIN HFA for this indication is supported by evidence from adequate and well-controlled studies of two 12-week clinical trials in subjects aged 12 years and older with asthma and one 2-week clinical trial in subjects aged 4 to 11 years with asthma *[see Adverse Reactions (6.1), Clinical Studies (14.1)]*.

The safety and effectiveness of VENTOLIN HFA in pediatric patients younger than 4 years have not been established. Three trials have been conducted to evaluate the safety and efficacy of VENTOLIN HFA in subjects younger than 4 years and the findings are described below.

Two 4-week randomized, double-blind, placebo-controlled trials were conducted in 163 pediatric subjects aged from birth to 48 months with symptoms of bronchospasm associated with obstructive airway disease (presenting symptoms included: wheeze, cough, dyspnea, or chest tightness). VENTOLIN HFA or placebo HFA was delivered with either an AeroChamber Plus Valved Holding Chamber or an Optichamber Valved Holding Chamber with mask 3 times daily. In one trial, VENTOLIN HFA 90 mcg (n = 26), VENTOLIN HFA 180 mcg (n = 25), and placebo HFA (n = 26) were administered to children aged between 24 and 48 months. In the second trial, VENTOLIN HFA 90 mcg (n = 29), VENTOLIN HFA 180 mcg (n = 29), and placebo HFA (n = 28) were administered to children aged between birth and 24 months. Over the 4-week treatment period, there were no treatment differences in asthma symptom scores between the groups receiving VENTOLIN HFA 90 mcg, VENTOLIN HFA 180 mcg, and placebo in either trial.

In a third trial, VENTOLIN HFA was evaluated in 87 pediatric subjects younger than 24 months for the treatment of acute wheezing. VENTOLIN HFA was delivered with an AeroChamber Plus Valved Holding Chamber in this trial. There were no significant differences in asthma symptom scores and mean change from baseline in an asthma symptom score between VENTOLIN HFA 180 mcg and VENTOLIN HFA 360 mcg.

In vitro dose characterization studies were performed to evaluate the delivery of VENTOLIN HFA via holding chambers with attached masks. The studies were conducted with 2 different holding chambers with masks (small and medium size). The in vitro study data when simulating patient breathing suggest that the dose of VENTOLIN HFA presented for inhalation via a valved holding chamber with mask will be comparable to the dose delivered in adults without a spacer and mask per kilogram of body weight (Table 2). However, clinical trials in children younger than 4 years described above suggest that either the optimal dose of VENTOLIN HFA has not been defined in this age group or VENTOLIN HFA is not effective in this age group. The safety and effectiveness of VENTOLIN HFA administered with or without a spacer device in children

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younger than 4 years have not been demonstrated.

Table 2. 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 (mcg/actuation)	Body Weight 50th Percentile (kg)[a]	Medication Delivered per Actuation (mcg/kg)[b]
6 to 12 Months	Small	4.9	0	18.2	7.5-9.9	1.8-2.4
			2	19.8		2.0-2.6
			5	13.8		1.4-1.8
			10	15.4		1.6-2.1
2 to 5 Years	Small	8.0	0	17.8	12.3-18.0	1.0-1.4
			2	16.0		0.9-1.3
			5	16.3		0.9-1.3
			10	18.3		1.0-1.5
2 to 5 Years	Medium	8.0	0	21.1	12.3-18.0	1.2-1.7
			2	15.3		0.8-1.2
			5	18.3		1.0-1.5
			10	18.2		1.0-1.5
>5 Years	Medium	12.0	0	26.8	18.0	1.5
			2	20.9		1.2
			5	19.6		1.1
			10	20.3		1.1

[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 VENTOLIN HFA in a 70-kg adult without use of a valved holding chamber and mask delivers approximately 90 mcg, or 1.3 mcg/kg.

8.5 Geriatric Use

Clinical trials of VENTOLIN HFA did not include sufficient numbers of subjects aged 65 years and older to determine whether older subjects respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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10 OVERDOSAGE

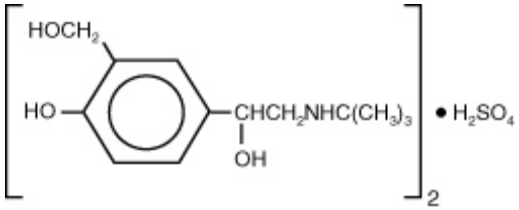
The expected signs and symptoms with overdosage of albuterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis).

As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of VENTOLIN HFA.

Treatment consists of discontinuation of VENTOLIN HFA together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of VENTOLIN HFA.

11 DESCRIPTION

The active component of VENTOLIN HFA is albuterol sulfate, USP, the racemic form of albuterol and a relatively selective beta$_2$-adrenergic bronchodilator. Albuterol sulfate has the chemical name α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α, α'-diol sulfate (2:1)(salt) and the following chemical structure:



Albuterol sulfate is a white crystalline powder with a molecular weight of 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$. It is soluble in water and slightly soluble in ethanol.

The World Health Organization recommended name for albuterol base is salbutamol.

VENTOLIN HFA is a blue plastic inhaler with a blue cap containing a pressurized metered-dose aerosol canister fitted with a counter. Each canister contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

After priming, each actuation of the inhaler delivers 120 mcg of albuterol sulfate, USP in 75 mg of suspension from the valve and 108 mcg of albuterol sulfate, USP from the mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece).

Prime VENTOLIN HFA before using for the first time, when the inhaler has not been used for more than 2 weeks, or when the inhaler has been dropped. To prime VENTOLIN HFA, release 4 sprays into the air away from the face, shaking well before each spray. Avoid spraying in eyes.

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

In vitro studies and in vivo pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. Although beta$_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$-adrenoceptors are the predominant receptors in the heart, there are also beta$_2$-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective beta$_2$-agonists may have cardiac effects.

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenyl cyclase and to an increase in the intracellular concentration of cyclic-3′,5′-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Albuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes *[see Warnings and Precautions (5.4)]*.

12.3 Pharmacokinetics

The systemic levels of albuterol are low after inhalation of recommended doses. A trial conducted in 12 healthy male and female subjects using a higher dose (1,080 mcg of albuterol base) showed that mean peak plasma concentrations of approximately 3 ng/mL occurred after dosing when albuterol was delivered using propellant HFA-134a. The mean time to peak concentrations (T_{max}) was delayed after administration of VENTOLIN HFA (T_{max} = 0.42 hours) as compared with CFC-propelled albuterol inhaler (T_{max} = 0.17 hours). Apparent terminal plasma half-life of albuterol is approximately 4.6 hours. No further pharmacokinetic trials for VENTOLIN HFA were conducted in neonates, children, or elderly subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the

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incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 15 and 6 times the MRHDID for adults and children, respectively, on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1,900 and 740 times the MRHDID for adults and children, respectively, on a mg/m^2 basis). In a 22-month study in Golden hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 250 and 100 times the MRHDID for adults and children, respectively, on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Fertility and reproductive performance in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 380 times the MRHDID for adults on a mg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical relevance of these findings is unknown.

14 CLINICAL STUDIES

14.1 Bronchospasm Associated with Asthma

Adult and Adolescent Subjects Aged 12 Years and Older

The efficacy of VENTOLIN HFA was evaluated in two 12-week, randomized, double-blind, placebo-controlled trials in subjects aged 12 years and older with mild to moderate asthma. These trials included a total of 610 subjects (323 males, 287 females). In each trial, subjects received 2 inhalations of VENTOLIN HFA, CFC 11/12-propelled albuterol, or HFA-134a placebo 4 times daily for 12 weeks' duration. Subjects taking the HFA-134a placebo inhaler also took VENTOLIN HFA for asthma symptom relief on an as-needed basis. Some subjects who participated in these clinical trials were using concomitant inhaled steroid therapy. Efficacy was assessed by serial forced expiratory volume in 1 second (FEV_1). In each of these trials, 2 inhalations of VENTOLIN HFA produced significantly greater improvement in FEV_1 over the pretreatment value than placebo. Results from the 2 clinical trials are described below.

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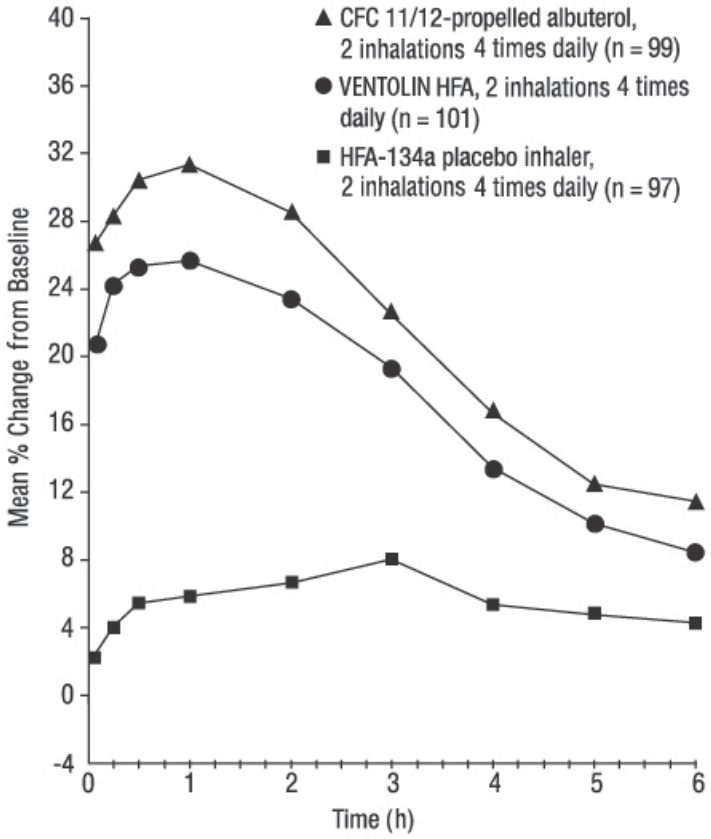
In a 12-week, randomized, double-blind trial, VENTOLIN HFA (101 subjects) was compared with CFC 11/12-propelled albuterol (99 subjects) and an HFA-134a placebo inhaler (97 subjects) in adolescent and adult subjects aged 12 to 76 years with mild to moderate asthma. Serial FEV_1 measurements [shown below as percent change from test-day baseline at Day 1 (n = 297) and at Week 12 (n = 249)] demonstrated that 2 inhalations of VENTOLIN HFA produced significantly greater improvement in FEV_1 over the pretreatment value than placebo.

FEV_1 as Percent Change from Predose in a Large, 12-Week Clinical Trial

Day 1



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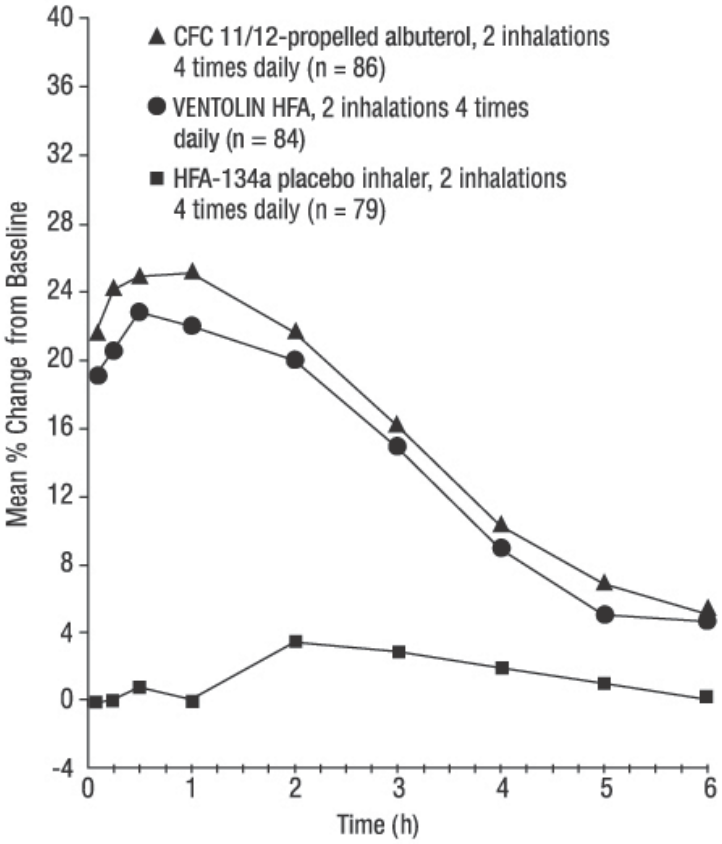
Week 12



In the responder population (≥15% increase in FEV_1 within 30 minutes postdose) treated with VENTOLIN HFA, the mean time to onset of a 15% increase in FEV_1 over the pretreatment value was 5.4 minutes, and the mean time to peak effect was 56 minutes. The mean duration of effect as measured by a 15% increase in FEV_1 over the pretreatment value was approximately 4 hours. In some subjects, duration of effect was as long as 6 hours.

The second 12-week randomized, double-blind trial was conducted to evaluate the efficacy and safety of switching subjects from CFC 11/12-propelled albuterol to VENTOLIN HFA. During the 3-week run-in phase of the trial, all subjects received CFC 11/12-propelled albuterol. During the double-blind treatment phase, VENTOLIN HFA (91 subjects) was compared to CFC 11/12-propelled albuterol (100 subjects) and an HFA-134a placebo inhaler (95 subjects) in adult and adolescent subjects with mild to moderate asthma. Serial FEV_1 measurements demonstrated that 2 inhalations of VENTOLIN HFA produced significantly greater improvement in pulmonary function than placebo. The switching from CFC 11/12-propelled albuterol inhaler to VENTOLIN HFA did not reveal any clinically significant changes in the efficacy profile.

In the 2 adult trials, the efficacy results from VENTOLIN HFA were significantly greater than placebo and were clinically comparable to those achieved with CFC 11/12-propelled albuterol, although small numerical differences in mean FEV_1 response and other measures were observed.

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Physicians should recognize that individual responses to beta-adrenergic agonists administered via different propellants may vary and that equivalent responses in individual patients should not be assumed.

Pediatric Subjects Aged 4 to 11 Years

The efficacy of VENTOLIN HFA was evaluated in one 2-week, randomized, double-blind, placebo-controlled trial in 135 pediatric subjects aged 4 to 11 years with mild to moderate asthma. In this trial, subjects received VENTOLIN HFA, CFC 11/12-propelled albuterol, or HFA-134a placebo. Serial pulmonary function measurements demonstrated that 2 inhalations of VENTOLIN HFA produced significantly greater improvement in pulmonary function than placebo and that there were no significant differences between the groups treated with VENTOLIN HFA and CFC 11/12-propelled albuterol. In the responder population treated with VENTOLIN HFA, the mean time to onset of a 15% increase in peak expiratory flow rate (PEFR) over the pretreatment value was 7.8 minutes, and the mean time to peak effect was approximately 90 minutes. The mean duration of effect as measured by a 15% increase in PEFR over the pretreatment value was greater than 3 hours. In some subjects, duration of effect was as long as 6 hours.

14.2 Exercise-Induced Bronchospasm

One controlled clinical trial in adult subjects with asthma (N = 24) demonstrated that 2 inhalations of VENTOLIN HFA taken approximately 30 minutes prior to exercise significantly prevented exercise-induced bronchospasm (as measured by maximum percentage fall in FEV_1 following exercise) compared with an HFA-134a placebo inhaler. In addition, VENTOLIN HFA was shown to be clinically comparable to a CFC 11/12-propelled albuterol inhaler for this indication.

16 HOW SUPPLIED/STORAGE AND HANDLING

VENTOLIN HFA is supplied in the following boxes of 1 as a pressurized aluminum canister fitted with a counter and supplied with a blue plastic actuator with a blue cap:

NDC 0173-0682-20 18-g canister containing 200 actuations

NDC 0173-0682-24 8-g canister containing 60 actuations

Each inhaler is packaged with a Patient Information leaflet.

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

Counter

VENTOLIN HFA has a counter attached to the canister. The counter starts at 204 or 064 and counts down each time a spray is released. The correct amount of medication in each actuation

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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.

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.

Storage

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.

17 PATIENT COUNSELING INFORMATION

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

Frequency of Use

Inform patients that the action of VENTOLIN HFA should last up to 4 to 6 hours. Do not use VENTOLIN HFA more frequently than recommended. Instruct patients not to increase the dose or frequency of doses of VENTOLIN HFA without consulting the physician. Instruct patients to seek medical attention immediately if treatment with VENTOLIN HFA becomes less effective for symptomatic relief, symptoms become worse, and/or they need to use the product more frequently than usual.

Priming

Instruct patients to prime VENTOLIN HFA before using for the first time, when the inhaler has not been used for more than 2 weeks, or when the inhaler has been dropped. To prime VENTOLIN HFA, release 4 sprays into the air away from the face, shaking well before each spray. Avoid spraying in eyes.

Cleaning

To ensure proper dosing and to prevent actuator orifice blockage, instruct patients to wash the actuator with warm water and let it air-dry completely at least once a week. Inform patients that detailed cleaning instructions are included in the Patient Information leaflet.

Paradoxical Bronchospasm

Inform patients that VENTOLIN HFA can produce paradoxical bronchospasm. Instruct them to discontinue VENTOLIN HFA if paradoxical bronchospasm occurs *[see Warnings and Precautions (5.1)]*.

Concomitant Drug Use

Advise patients that while they are using VENTOLIN HFA, other inhaled drugs and asthma

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medications should be taken only as directed by the physician.

Common Adverse Effects

Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, and nervousness.

Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to asthma medications, including VENTOLIN HFA, during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting https://mothertobaby.org/ongoing-study/asthma *[see Use in Specific Populations (8.1)]*.

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VNT:14PI

PHARMACIST—DETACH HERE AND GIVE LEAFLET TO PATIENT

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PATIENT INFORMATION

VENTOLIN (VENT o lin) HFA
(albuterol sulfate inhalation aerosol)
for oral inhalation use

What is VENTOLIN HFA?

- VENTOLIN HFA is a prescription inhaled medicine used in people aged 4 years and older to:
  - treat or prevent bronchospasm in people who have reversible obstructive airway disease.
  - prevent exercise-induced bronchospasm.
- It is not known if VENTOLIN HFA is safe and effective in children younger than 4 years of age.

Do not use VENTOLIN HFA:

- if you are allergic to albuterol sulfate propionate or any of the ingredients in VENTOLIN HFA. See the end of this Patient Information for a complete list of ingredients in VENTOLIN HFA.

Before using VENTOLIN HFA, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems.
- have high blood pressure.
- have seizures.
- have thyroid problems.
- have diabetes.
- have low potassium levels in your blood.
- are pregnant or plan to become pregnant. It is not known if VENTOLIN HFA may harm your unborn baby.
  - **Pregnancy Registry.** There is a pregnancy registry for women with asthma who receive asthma medications, including VENTOLIN HFA, while pregnant. The purpose of the registry is to collect information about the health of you and your baby. You can talk to your healthcare provider about how to take part in this registry or you can get more information and register by calling 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/asthma.
- are breastfeeding. It is not known if the medicine in VENTOLIN 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. VENTOLIN HFA and certain other medicines may interact with each other. This may cause serious side effects. Especially tell your healthcare provider if you take:

- other inhaled medicines or asthma medicines
- beta-blocker medicines
- diuretics
- digoxin
- monoamine oxidase inhibitors
- tricyclic antidepressants

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

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How should I use VENTOLIN HFA?

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

- **Do not** use VENTOLIN HFA unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly.
- Children should use VENTOLIN HFA with an adult's help, as instructed by the child's healthcare provider.
- Use VENTOLIN HFA exactly as your healthcare provider tells you to use it. **Do not** use VENTOLIN HFA more often than prescribed.
- **Do not** increase your dose or take extra doses of VENTOLIN HFA without first talking to your healthcare provider.
- Each dose of VENTOLIN HFA should last up to 4 hours to 6 hours.
- Get medical help right away if VENTOLIN HFA no longer helps your symptoms.
- Get medical help right away if your symptoms get worse or if you need to use your inhaler more often.
- While you are using VENTOLIN HFA, use other inhaled medicines and asthma medicines only as directed by your healthcare provider.
- Call your healthcare provider if your asthma symptoms like wheezing and trouble breathing become worse over a few hours or days. Your healthcare provider may need to give you another medicine to treat your symptoms.

What are the possible side effects of VENTOLIN HFA?

VENTOLIN HFA can cause serious side effects, including:

- **worsening trouble breathing, coughing, and wheezing (paradoxical bronchospasm).** If this happens, stop using VENTOLIN HFA and call your healthcare provider or get emergency help right away. Paradoxical bronchospasm is more likely to happen with your first use of a new canister of medicine.
- **heart problems, including faster heart rate and higher blood pressure.**
- **possible death in people with asthma who use too much VENTOLIN HFA.**
- **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
- **changes in laboratory blood levels (sugar, potassium).**

Common side effects of VENTOLIN HFA include:

- sore throat
- upper respiratory tract infection, including viral infection
- cough
- muscle pain
- your heart feels like it is pounding or racing (palpitations)
- chest pain
- fast heart rate
- shakiness
- nervousness
- dizziness

These are not all the possible side effects of VENTOLIN HFA.

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 VENTOLIN HFA?

- Store VENTOLIN HFA at room temperature between 68°F and 77°F (20°C and 25°C) with the mouthpiece down.
- **The contents of your VENTOLIN HFA 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.

Keep VENTOLIN HFA and all medicines out of the reach of children.

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

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

You can ask your healthcare provider or pharmacist for information about VENTOLIN HFA that was written for health professionals.

What are the ingredients in VENTOLIN HFA?

Active ingredient: albuterol sulfate

Inactive ingredient: propellant HFA-134a

For more information about VENTOLIN HFA, call 1-888-825-5249.
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This Patient Information has been approved by the U.S. Food and Drug Administration Revised: January 2020

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INSTRUCTIONS FOR USE

VENTOLIN (VENT o lin) HFA
(albuterol sulfate inhalation aerosol)
for oral inhalation use

Your VENTOLIN HFA inhaler

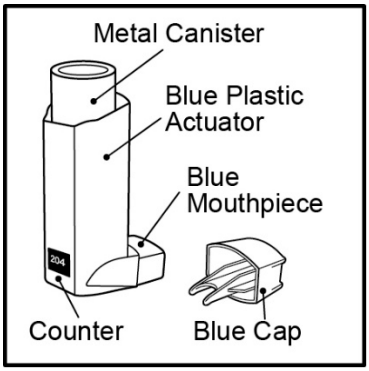

Figure A

- The metal canister holds the medicine. **See Figure A.**
- The metal 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 blue plastic actuator. **See Figure A.**
- The counter starts at either **204** or **064**, depending on which size inhaler you have. 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 metal canister.
- The blue plastic actuator sprays the medicine from the metal canister. The plastic actuator has a blue protective cap that covers the mouthpiece. **See Figure A.** Keep the protective cap on the mouthpiece when the metal canister is not in use.
- **Do not** use the plastic actuator with a canister of medicine from any other inhaler.
- **Do not** use a VENTOLIN HFA metal canister with an actuator from any other inhaler.

Before using your VENTOLIN HFA inhaler

- The inhaler should be at room temperature before you use it.
- If your child needs to use VENTOLIN HFA, watch your child closely to make sure your child uses the inhaler correctly. Your healthcare provider will show you how your child should use VENTOLIN HFA.

Priming your VENTOLIN HFA inhaler

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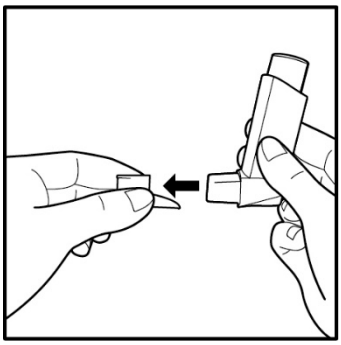

Figure B

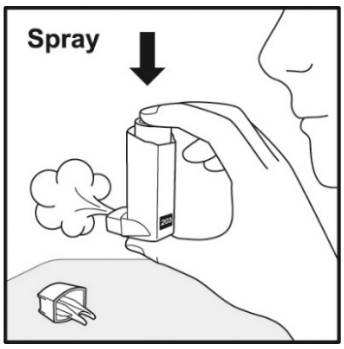

Figure C

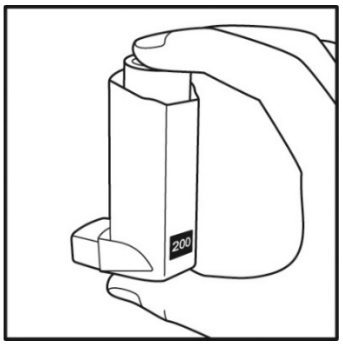

Figure D

Before you use VENTOLIN 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 take the cap off the mouthpiece, squeeze the sides of the cap and pull it straight out. **See Figure B.**
- Shake the inhaler well.
- Spray the inhaler 1 time into the air away from your face. **Avoid spraying in eyes. See Figure C.**
- Shake and spray the inhaler like this 3 more times to finish priming it. The counter should now read **200** or **060**, depending on which size inhaler you have. **See Figure D.**
- You must prime your inhaler again if you have not used it in more than 14 days or if you have dropped it. To take the cap off the mouthpiece, squeeze the sides of the cap and pull it straight out. Shake and spray the inhaler 4 times into the air away from your face.

How to use your VENTOLIN HFA inhaler

Follow these steps every time you use VENTOLIN HFA.

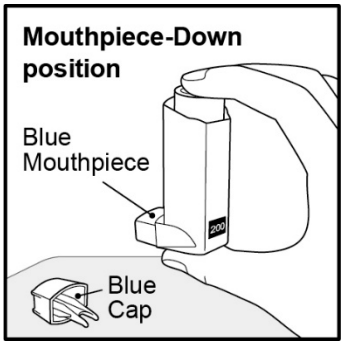

Figure E

Step 1. Make sure the metal canister fits firmly in the plastic actuator. The counter should show through the window in the actuator.
To take the cap off the mouthpiece, squeeze the sides of the cap and pull it straight out.
Look inside the mouthpiece for

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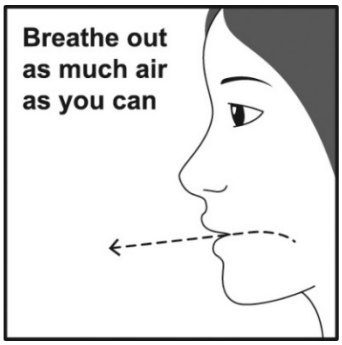

Figure F

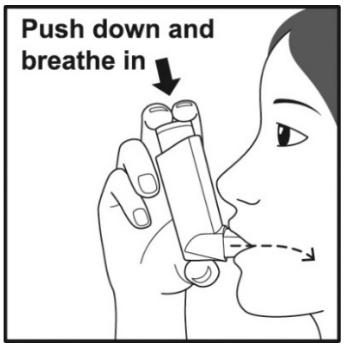

Figure G

foreign objects and take out any you see.

Step 2. Hold the inhaler with the mouthpiece down and **shake it well**. **See Figure E.**

Step 3. Breathe out through your mouth and push as much air from your lungs as you can. **See Figure F.**

Step 4. Put the mouthpiece in your mouth and close your lips around it. Push the top of the metal canister firmly **all the way down** while you breathe in deeply and slowly through your mouth. **See Figure G.**

Step 5. After the spray comes out, take your finger off the metal 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.**

If your healthcare provider has told you to use more sprays, wait 1 minute and shake the inhaler again. Repeat Step 2 through Step 6.

Put the cap back on the mouthpiece after you finish using the inhaler. Make sure it snaps firmly into place.

Cleaning your VENTOLIN HFA inhaler

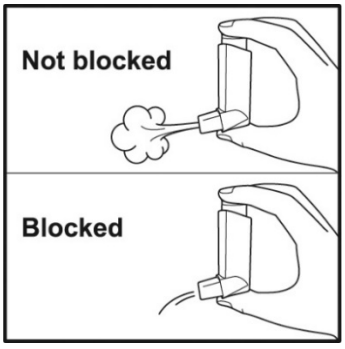

Figure H

Clean your inhaler at least 1 time each week. 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 7. Take the canister out of the plastic actuator and take the cap off the mouthpiece by squeezing the sides of the cap and pulling it straight out.

Step 8. Hold the plastic actuator under

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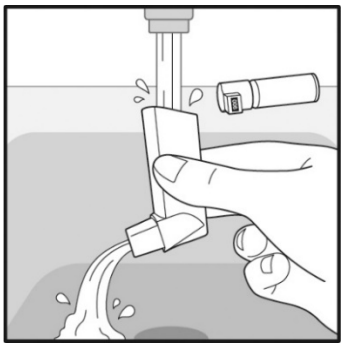

Figure I

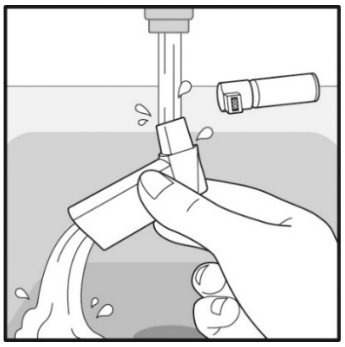

Figure J

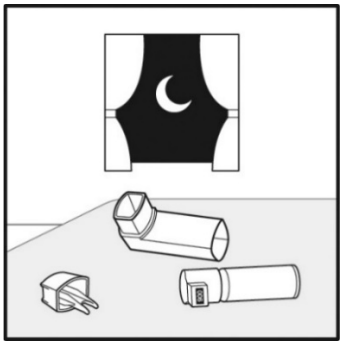

Figure K

the faucet and run warm water through it for about 30 seconds. **See Figure I.**

Step 9. Turn the plastic actuator upside down and run warm water through the mouthpiece for about 30 seconds. **See Figure J.**

Step 10. Shake off as much water from the plastic actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat Step 8 and Step 9.

Step 11. Let the plastic actuator air-dry overnight. **See Figure K.**

Step 12. When the plastic actuator is dry, put the protective cap on the mouthpiece and then put the canister in the plastic actuator and make sure it fits firmly. Shake the inhaler well, remove the cap, and spray the inhaler 1 time into the air away from your face. (The counter will count down by 1 number.) Put the cap back on the mouthpiece.

If you need to use your inhaler before the plastic actuator is completely dry:

- Shake as much water off the plastic actuator as you can.
- Put the cap on the mouthpiece and then put the canister in the plastic actuator and make sure it fits firmly.
- Shake the inhaler well, remove the cap, and spray it 1 time into the air away from your face.
- Take your VENTOLIN HFA dose as prescribed.
- Follow cleaning Step 7 through Step 12 above.

Replacing your VENTOLIN HFA inhaler

- **When the counter reads 020**, you should refill your prescription or ask your

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healthcare provider if you need another prescription for VENTOLIN HFA.

- **When the counter reads 000, throw the inhaler away.** You should not keep using the inhaler when the counter reads **000** 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 correct use of your VENTOLIN HFA inhaler, remember:

- The metal canister should always fit firmly in the plastic 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.
- 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.

For more information about VENTOLIN HFA or how to use your inhaler, call 1-888-825-5249.
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This Instructions for Use has been approved by
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