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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ADVAIR HFA 45/21 (fluticasone propionate 45 mcg and salmeterol 21 mcg) Inhalation Aerosol
ADVAIR HFA 115/21 (fluticasone propionate 115 mcg and salmeterol 21 mcg) Inhalation Aerosol
ADVAIR HFA 230/21 (fluticasone propionate 230 mcg and salmeterol 21 mcg) Inhalation Aerosol
FOR ORAL INHALATION

Initial U.S. Approval: 2000

WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- **Long-acting beta$_2$-adrenergic agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR HFA, increase the risk of asthma-related death. A US study showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients. (5.1)**
- **When treating patients with asthma, only prescribe ADVAIR HFA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR HFA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. (1, 5.1)**

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

ADVAIR HFA is a combination product containing a corticosteroid and a LABA indicated for treatment of asthma in patients aged 12 years and older.
Important limitation:

- Not indicated for the relief of acute bronchospasm. (1)

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

For oral inhalation only.
Treatment of asthma in patients ≥12 years: 2 inhalations of ADVAIR HFA 45/21, 115/21, or 230/21 twice daily. Starting dosage is based on asthma severity. (2)

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

Inhalation aerosol: delivers a combination of fluticasone propionate (45, 115, or 230 mcg) and salmeterol (21 mcg) from mouthpiece 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----------

- Asthma-related death: LABAs increase the risk. Prescribe only for recommended patient populations. (5.1)
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms. (5.2)
- Use with additional LABA: Do not use in combination because of risk of overdose. (5.3)
- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth following inhalation. (5.4)
- Pneumonia: Increased risk in patients with COPD. Monitor patients for signs and symptoms of pneumonia. (5.5)
- Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infection; ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to ADVAIR HFA. (5.7)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue ADVAIR HFA slowly. (5.8)
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid and cardiovascular effects. Use not recommended with ADVAIR HFA. (5.9)
- Paradoxical bronchospasm: Discontinue ADVAIR HFA and institute alternative therapy if paradoxical bronchospasm occurs. (5.10)
- Patients with cardiovascular or central nervous system disorders: Use with caution because of beta-adrenergic stimulation. (5.12)
- Decreases in bone mineral density: Assess bone mineral density initially and periodically thereafter. (5.13)
- Effects on growth: Monitor growth of pediatric patients. (5.14)
- Glaucoma and cataracts: Close monitoring is warranted. (5.15)
- Metabolic effects: Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.16, 5.18)
- Coexisting conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.17)

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

Most common adverse reactions (incidence ≥3%) are: upper respiratory tract infection or inflammation, throat irritation, dysphonia, headache, dizziness, nausea and vomiting. (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): Use not recommended. May cause systemic corticosteroid and cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of salmeterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: December 2012

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FULL PRESCRIBING INFORMATION: CONTENTS*

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

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FULL PRESCRIBING INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR® HFA, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR HFA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

ADVAIR HFA is indicated for the treatment of asthma in patients aged 12 years and older.

Long-acting beta$_2$-adrenergic agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR HFA, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients *[see Warnings and Precautions (5.1)]*. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control

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medication, such as an inhaled corticosteroid. Do not use ADVAIR HFA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Important Limitation of Use: ADVAIR HFA is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

ADVAIR HFA should be administered twice daily every day by the orally inhaled route only. After inhalation, the patient should rinse the mouth with water without swallowing *[see Patient Counseling Information (17.4)]*.

More frequent administration or a higher number of inhalations (more than 2 inhalations twice daily) of the prescribed strength of ADVAIR HFA is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. Patients using ADVAIR HFA should not use additional LABAs for any reason. *[See Warnings and Precautions (5.3, 5.12).]*

If asthma symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

For patients aged 12 years and older, the dosage is 2 inhalations twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for ADVAIR HFA for patients aged 12 years and older are based upon patients' asthma severity.

The maximum recommended dosage is 2 inhalations of ADVAIR HFA 230/21 twice daily.

Improvement in asthma control following inhaled administration of ADVAIR HFA can occur within 30 minutes of beginning treatment, although maximum benefit may not be achieved for 1 week or longer after starting treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, replacing the current strength of ADVAIR HFA with a higher strength may provide additional improvement in asthma control.

If a previously effective dosage regimen of ADVAIR HFA fails to provide adequate improvement in asthma control, the therapeutic regimen should be reevaluated and additional therapeutic options (e.g., replacing the current strength of ADVAIR HFA with a higher strength, adding additional inhaled corticosteroid, initiating oral corticosteroids) should be considered.

ADVAIR HFA should be primed before using for the first time by releasing 4 test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 4 weeks or when it has been dropped, prime the inhaler again by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before each spray.

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3 DOSAGE FORMS AND STRENGTHS

ADVAIR HFA is an inhalation aerosol. Each actuation delivers a combination of fluticasone propionate (45, 115, or 230 mcg) and salmeterol (21 mcg) from the actuator. ADVAIR HFA is supplied in 8- and 12-g pressurized aluminum canisters containing 60 and 120 metered inhalations, respectively. Each canister is fitted with a counter and a purple actuator with a light purple strapcap.

4 CONTRAINDICATIONS

The use of ADVAIR HFA is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.
- Hypersensitivity to any of the ingredients of these preparations contraindicates their use *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

LABAs, such as salmeterol, one of the active ingredients in ADVAIR HFA, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on a long-term asthma control medication such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR HFA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

A large placebo-controlled US study that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized double-blind study that enrolled LABA-naive patients with asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared with placebo when added to usual asthma therapy. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355), which led to premature termination of the study. The results of the interim analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events (see Table 3 and Figure 5). In the total population, a higher rate of asthma-related death occurred in

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patients treated with salmeterol than those treated with placebo (0.10% versus 0.02%; relative risk: 4.37 [95% CI: 1.25, 15.34]).

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo (0.07% versus 0.01%; relative risk: 5.82 [95% CI: 0.70, 48.37]). In African Americans also, asthma-related death occurred at a higher rate in patients treated with salmeterol than those treated with placebo (0.31% versus 0.04%; relative risk: 7.26 [95% CI: 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American patients (see Table 3). Given the similar basic mechanisms of action of $beta_2$-agonists, the findings seen in the SMART study are considered a class effect.

Post-hoc analyses in pediatric patients aged 12 to 18 years were also performed. Pediatric patients accounted for approximately 12% of patients in each treatment arm. Respiratory-related death or life-threatening experience occurred at a similar rate in the salmeterol group (0.12% [2/1,653]) and the placebo group (0.12% [2/1,622]; relative risk: 1.0 [95% CI: 0.1, 7.2]). All-cause hospitalization, however, was increased in the salmeterol group (2% [35/1,653]) versus the placebo group (<1% [16/1,622]; relative risk: 2.1 [95% CI: 1.1, 3.7]).

The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other active ingredient in ADVAIR HFA, or other long-term asthma control therapy mitigates the risk of asthma-related death.

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Table 1. Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)

	Salmeterol n (%[a])	Placebo n (%[a])	Relative Risk[b] (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients[c] (95% Confidence Interval)
Total Population[d] Salmeterol: n = 13,176 Placebo: n = 13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Salmeterol: n = 9,281 Placebo: n = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Salmeterol: n = 2,366 Placebo: n = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

[a] Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

[b] Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week treatment period.

[c] Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

[d] The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those patients whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma-related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n = 130, placebo n = 127).

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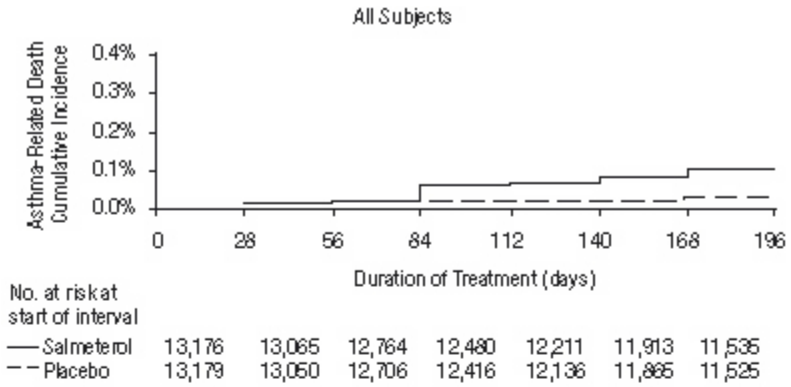
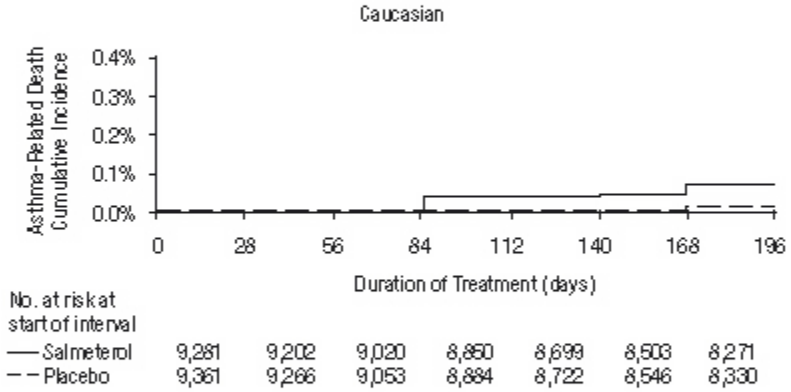
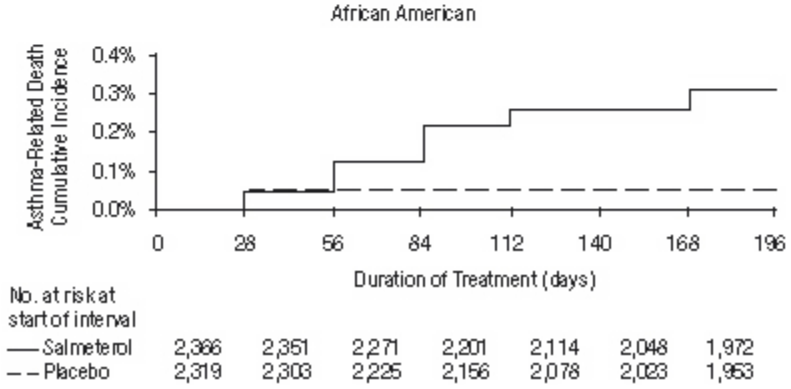
Figure 1. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART), by Duration of Treatment







A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate of asthma-related death was numerically, though not statistically significantly, greater in patients

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with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol (180 mcg 4 times daily) added to usual asthma therapy.

5.2 Deterioration of Disease and Acute Episodes

ADVAIR HFA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. ADVAIR HFA has not been studied in patients with acutely deteriorating asthma. The initiation of ADVAIR HFA in this setting is not appropriate.

Serious acute respiratory events, including fatalities, have been reported when salmeterol, a component of ADVAIR HFA, has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, previous life-threatening acute asthma exacerbations) and in some patients with acutely deteriorating asthma (e.g., patients with significantly increasing symptoms; increasing need for inhaled, short-acting beta$_2$-agonists; decreasing response to usual medications; increasing need for systemic corticosteroids; recent emergency room visits; deteriorating lung function). However, these events have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of ADVAIR HFA with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of ADVAIR HFA.

ADVAIR HFA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta$_2$-agonist, not ADVAIR HFA, should be used to relieve acute symptoms such as shortness of breath. When prescribing ADVAIR HFA, the physician must also provide the patient with an inhaled, short-acting beta$_2$-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily (morning and evening) use of ADVAIR HFA.

When beginning treatment with ADVAIR HFA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

5.3 Excessive Use of ADVAIR HFA and Use With Other Long-Acting Beta$_2$-Agonists

As with other inhaled drugs containing beta$_2$-adrenergic agents, ADVAIR HFA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ADVAIR HFA should not use an additional

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LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma.

5.4 Local Effects

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

5.5 Pneumonia

Lower respiratory tract infections, including pneumonia, have been reported in patients with chronic obstructive pulmonary disease (COPD) following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder). In 2 replicate 1-year studies of 1,579 patients with COPD, there was a higher incidence of pneumonia reported in patients receiving ADVAIR DISKUS 250/50 (7%) than in those receiving salmeterol 50 mcg (3%). The incidence of pneumonia in the patients treated with ADVAIR DISKUS was higher in patients over 65 years of age (9%) compared with the incidence in patients less than 65 years of age (4%).

In a 3-year study of 6,184 patients with COPD, there was a higher incidence of pneumonia reported in patients receiving ADVAIR DISKUS 500/50 compared with placebo (16% with ADVAIR DISKUS 500/50, 14% with fluticasone propionate 500 mcg, 11% with salmeterol 50 mcg, and 9% with placebo). Similar to what was seen in the 1-year studies with ADVAIR DISKUS 250/50, the incidence of pneumonia was higher in patients over 65 years of age (18% with ADVAIR DISKUS 500/50 versus 10% with placebo) compared with patients less than 65 years of age (14% with ADVAIR DISKUS 500/50 versus 8% with placebo).

5.6 Immunosuppression

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

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

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5.7 Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although ADVAIR HFA may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiologic amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

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

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to ADVAIR HFA. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with ADVAIR HFA. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

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

5.8 Hypercorticism and Adrenal Suppression

Fluticasone propionate, a component of ADVAIR HFA, 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 ADVAIR HFA in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are

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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 ADVAIR HFA.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with ADVAIR HFA should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when fluticasone propionate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of ADVAIR HFA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

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

5.10 Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, ADVAIR HFA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ADVAIR HFA, it should be treated immediately with an inhaled, short-acting bronchodilator; ADVAIR HFA should be discontinued immediately; and alternative therapy should be instituted. Upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving fluticasone propionate and salmeterol.

5.11 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of ADVAIR HFA, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm *[see Adverse Reactions (6.2)]*.

5.12 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia *[see Overdosage (10)]*. Therefore, ADVAIR HFA, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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Salmeterol, a component of ADVAIR HFA, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug 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 significance of these findings is unknown. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.13 Reduction in Bone Mineral Density

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

2-Year Fluticasone Propionate Study: A 2-year study of 160 patients (females aged 18 to 40 years, males 18 to 50) with asthma receiving 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.

5.14 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 ADVAIR HFA routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR HFA, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Use in Specific Populations (8.4)]*.

5.15 Glaucoma and Cataracts

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

5.16 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled fluticasone propionate, a component of ADVAIR HFA, 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

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the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

5.17 Coexisting Conditions

ADVAIR HFA, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.18 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2)]*. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with ADVAIR HFA at recommended doses.

6 ADVERSE REACTIONS

LABAs, such as salmeterol, one of the active ingredients in ADVAIR HFA, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol *[see Warnings and Precautions (5.1)]*. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.4)]*
- Pneumonia in patients with COPD *[see Warnings and Precautions (5.5)]*
- Immunosuppression *[see Warnings and Precautions (5.6)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*
- Growth effects *[see Warnings and Precautions (5.14)]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

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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.

Adult and Adolescent Patients Aged 12 Years and Older: The incidence of adverse reactions associated with ADVAIR HFA in Table 2 is based upon 2 placebo-controlled 12-week US clinical studies (Studies 1 and 3) and 1 active-controlled 12-week US clinical study (Study 2). A total of 1,008 adult and adolescent patients with asthma (556 females and 452 males) previously treated with albuterol alone, salmeterol, or inhaled corticosteroids were treated twice daily with 2 inhalations of ADVAIR HFA 45/21 or ADVAIR HFA 115/21, fluticasone propionate chlorofluorocarbon (CFC) inhalation aerosol (44- or 110-mcg doses), salmeterol CFC inhalation aerosol 21 mcg, or placebo HFA inhalation aerosol. The average duration of exposure was 71 to 81 days in the active treatment groups compared with 51 days in the placebo group.

Table 2. Adverse Reactions With ≥3% Incidence With ADVAIR HFA Inhalation Aerosol in Adult and Adolescent Patients With Asthma

	ADVAIR HFA Inhalation Aerosol		Fluticasone Propionate CFC Inhalation Aerosol		Salmeterol CFC Inhalation Aerosol	Placebo HFA Inhalation Aerosol
Adverse Event	45/21 (n = 187) %	115/21 (n = 94) %	44 mcg (n = 186) %	110 mcg (n = 91) %	21 mcg (n = 274) %	(n = 176) %
Ear, nose, & throat						
Upper respiratory tract infection	16	24	13	15	17	13
Throat irritation	9	7	12	13	9	7
Upper respiratory inflammation	4	4	3	7	5	3
Hoarseness/dysphonia	3	1	2	0	1	0
Lower respiratory						
Viral respiratory infection	3	5	4	5	3	4
Neurology						
Headache	21	15	24	16	20	11
Dizziness	4	1	1	0	<1	0
Gastrointestinal						
Nausea & vomiting	5	3	4	2	2	3
Viral gastrointestinal infection	4	2	2	0	1	2

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Gastrointestinal signs & symptoms	3	2	2	1	1	1
Musculoskeletal						
Musculoskeletal pain	5	7	8	2	4	4
Muscle pain	4	1	1	1	3	<1

The incidence of common adverse reactions reported in Study 4, a 12-week non-US clinical study of 509 patients previously treated with inhaled corticosteroids who were treated twice daily with 2 inhalations of ADVAIR HFA 230/21, fluticasone propionate CFC inhalation aerosol 220 mcg, or 1 inhalation of ADVAIR DISKUS 500/50 was similar to the incidences reported in Table 2.

Additional Adverse Reactions: Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that occurred in the groups receiving ADVAIR HFA with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo include the following: tachycardia, arrhythmias, myocardial infarction, postoperative complications, wounds and lacerations, soft tissue injuries, ear signs and symptoms, rhinorrhea/postnasal drip, epistaxis, nasal congestion/blockage, laryngitis, unspecified oropharyngeal plaques, dryness of nose, weight gain, allergic eye disorders, eye edema and swelling, gastrointestinal discomfort and pain, dental discomfort and pain, candidiasis mouth/throat, hyposalivation, gastrointestinal infections, disorders of hard tissue of teeth, abdominal discomfort and pain, oral abnormalities, arthralgia and articular rheumatism, muscle cramps and spasms, musculoskeletal inflammation, bone and skeletal pain, muscle injuries, sleep disorders, migraines, allergies and allergic reactions, viral infections, bacterial infections, candidiasis unspecified site, congestion, inflammation, bacterial reproductive infections, lower respiratory signs and symptoms, lower respiratory infections, lower respiratory hemorrhage, eczema, dermatitis and dermatosis, urinary infections.

Laboratory Test Abnormalities: In Study 3, there were more reports of hyperglycemia among adults and adolescents receiving ADVAIR HFA, but this was not seen in Studies 1 and 2.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use of any formulation of ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. 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 ADVAIR, fluticasone propionate, and/or salmeterol or a combination of these factors.

Cardiovascular: Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular tachycardia), hypertension, ventricular tachycardia.

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Ear, Nose, and Throat: Aphonia, earache, facial and oropharyngeal edema, paranasal sinus pain, rhinitis, throat soreness, tonsillitis.

Endocrine and Metabolic: Cushing's syndrome, Cushingoid features, growth velocity reduction in children/adolescents, hypercorticism, osteoporosis.

Eye: Cataracts, glaucoma.

Gastrointestinal: Dyspepsia, xerostomia.

Hepatobiliary Tract and Pancreas: Abnormal liver function tests.

Immune System: Immediate and delayed hypersensitivity reactions, including rash and rare events of angioedema, bronchospasm, and anaphylaxis.

Musculoskeletal: Back pain, myositis.

Neurology: Paresthesia, restlessness.

Non-Site Specific: Fever, pallor.

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

Respiratory: Asthma; asthma exacerbation; chest congestion; chest tightness; cough; dyspnea; immediate bronchospasm; influenza; paradoxical bronchospasm; tracheitis; wheezing; pneumonia; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

Skin: Contact dermatitis, contusions, ecchymoses, photodermatitis, pruritus.

Urogenital: Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal candidiasis, vaginitis, vulvovaginitis.

7 DRUG INTERACTIONS

ADVAIR HFA has been used concomitantly with other drugs, including short-acting beta$_2$-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma, without adverse drug reactions *[see Clinical Pharmacology (12.2)]*. No formal drug interaction studies have been performed with ADVAIR HFA.

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate and salmeterol, the individual components of ADVAIR HFA, are substrates of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with ADVAIR HFA is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

Ritonavir: *Fluticasone Propionate:* A drug interaction study 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.

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Ketoconazole: *Fluticasone Propionate:* Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate exposure and reduced plasma cortisol area under the curve (AUC), but had no effect on urinary excretion of cortisol.

Salmeterol: In a drug interaction study in 20 healthy subjects, coadministration of inhaled salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold). Three (3) subjects were withdrawn due to beta$_2$-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

ADVAIR 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 salmeterol, a component of ADVAIR HFA, on the vascular system may be potentiated by these agents.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR HFA, but may produce severe bronchospasm in patients with reversible obstructive airways disease. 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.

7.4 Diuretics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies with ADVAIR HFA in pregnant women. The combination of fluticasone propionate and salmeterol was teratogenic in mice and rats. Fluticasone propionate alone was teratogenic in mice, rats, and rabbits, and salmeterol alone was teratogenic in rabbits and not in rats. From the reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using combinations of fluticasone propionate and salmeterol when compared with toxicity data from the components administered separately.

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ADVAIR HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Combination of Fluticasone Propionate and Salmeterol: In the mouse reproduction assay, fluticasone propionate by the subcutaneous route at a dose approximately equivalent to the maximum recommended human daily inhalation dose (MRHD) (on a mcg/m^2 basis at a maternal dose of 150 mcg/kg) combined with oral salmeterol at a dose approximately 580 times the MRHD (on a mg/m^2 basis at a maternal dose of 10 mg/kg) produced cleft palate, fetal death, increased implantation loss, and delayed ossification. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses of fluticasone propionate subcutaneously up to approximately 1/5 the MRHD (on a mcg/m^2 basis at a maternal dose of 40 mcg/kg) and oral doses of salmeterol up to approximately 80 times the MRHD (on a mg/m^2 basis at a maternal dose of 1.4 mg/kg). In rats, combining fluticasone propionate subcutaneously at a dose equivalent to the MRHD (on a mcg/m^2 basis at a maternal dose of 100 mcg/kg) and an oral dose of salmeterol at approximately 1,200 times the MRHD (on a mg/m^2 basis at a maternal dose of 10 mg/kg) produced decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. No such effects were seen when combining fluticasone propionate subcutaneously at a dose less than the MRHD (on a mcg/m^2 basis at a maternal dose of 30 mcg/kg) and an oral dose of salmeterol at approximately 120 times the MRHD (on a mg/m^2 basis at a maternal dose of 1 mg/kg).

Fluticasone Propionate: Subcutaneous studies in mice at a dose less than the MRHD (on a mcg/m^2 basis at a maternal dose of 45 mcg/kg) and in rats at a dose equivalent to the MRHD (on a mcg/m^2 basis at a maternal dose of 100 mcg/kg) revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification. No teratogenicity was seen in rats at inhalation doses approximately equivalent to the MRHD (on a mcg/m^2 basis at maternal doses up to 68.7 mg/kg).

In rabbits, fetal weight reduction and cleft palate were observed at a subcutaneous dose less than the MRHD (on a mcg/m^2 basis at a maternal dose of 4 mcg/kg). However, no teratogenic effects were reported at oral doses up to approximately 6 times the MRHD (on a mcg/m^2 basis at maternal doses up to 300 mcg/kg). No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration *[see Clinical Pharmacology (12.3)]*.

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

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

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Salmeterol: No teratogenic effects occurred in rats at oral doses approximately 230 times the MRHD (on a mg/m^2 basis at maternal doses up to 2 mg/kg). In Dutch rabbits administered oral doses approximately 25 times the MRHD (on an AUC basis at maternal doses of 1 mg/kg and higher), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at an oral dose approximately 10 times the MRHD (on an AUC basis at a maternal dose of 0.6 mg/kg).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at an oral dose approximately 2,300 times the MRHD (on a mg/m^2 basis at a maternal dose of 10 mg/kg). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans.

Salmeterol xinafoate crossed the placenta following oral administration to mice and rats.

8.2 Labor and Delivery

There are no well-controlled human studies that have investigated effects of ADVAIR HFA on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of ADVAIR HFA during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

8.3 Nursing Mothers

Plasma levels of salmeterol, a component of ADVAIR HFA, after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known whether fluticasone propionate is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of tritiated fluticasone propionate resulted in measurable radioactivity in milk.

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

8.4 Pediatric Use

Thirty-eight (38) patients aged 12 to 17 years were treated with ADVAIR HFA in US pivotal clinical trials. Patients in this age-group demonstrated efficacy results similar to those observed in patients aged 18 years and older. There were no obvious differences in the type or frequency of adverse events reported in this age-group compared with patients aged 18 years and older.

In a 12-week study, the safety of ADVAIR HFA 45/21 given as 2 inhalations twice daily was compared with that of fluticasone propionate 44 mcg HFA (FLOVENT® HFA) 2 inhalations twice daily in 350 subjects aged 4 to 11 years with persistent asthma currently being treated with inhaled corticosteroids. No new safety concerns were observed in children aged 5 to 11 years treated for 12 weeks with ADVAIR HFA 45/21 compared with adults and adolescents aged 12 years and older. Common adverse reactions (≥3%) seen in children aged 5 to 11 years treated with ADVAIR HFA 45/21 but not reported in the adult and adolescent clinical trials of ADVAIR

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HFA include: pyrexia, cough, pharyngolaryngeal pain, rhinitis, and sinusitis *[see Adverse Reactions (6.1)]*.This study was not designed to assess the effect of salmeterol, a component of ADVAIR HFA, on asthma hospitalizations and death in patients aged 4 to 11 years.

The pharmacokinetics and pharmacodynamic effect on serum cortisol of 21 days of treatment with ADVAIR HFA 45/21 (2 inhalations twice daily with or without a spacer) or ADVAIR DISKUS 100/50 (1 inhalation twice daily) was evaluated in a study of 31 children aged 4 to 11 years with mild asthma. Systemic exposure to salmeterol xinafoate was similar for ADVAIR HFA, ADVAIR HFA delivered with a spacer, and ADVAIR DISKUS while the systemic exposure to fluticasone propionate was lower with ADVAIR HFA compared with that of ADVAIR HFA delivered with a spacer or ADVAIR DISKUS. There were reductions in serum cortisol from baseline in all treatment groups (14%, 22%, and 13% for ADVAIR HFA, ADVAIR HFA delivered with a spacer, and ADVAIR DISKUS, respectively) *[see Clinical Pharmacology (12.2, 12.3)]*.

The safety and effectiveness of ADVAIR HFA in children less than 12 years have not been established.

Effects on Growth: Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR HFA, may cause a reduction in growth velocity in children and adolescents *[see Warnings and Precautions (5.14)]*. The growth of pediatric patients receiving orally inhaled corticosteroids, including ADVAIR HFA, should be monitored.

A 52-week placebo-controlled study to assess the potential growth effects of fluticasone propionate inhalation powder (FLOVENT® ROTADISK®) at 50 and 100 mcg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and 5.66 cm/year in the 100-mcg group (n = 89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the 100-mcg group (n = 79). In children aged 8.5 years, the mean age of children in this study, the range for expected growth velocity is: boys – 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year. The clinical relevance of these growth data is not certain.

If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR HFA, each patient should be titrated to the lowest strength that effectively controls his/her asthma.

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8.5 Geriatric Use

Clinical studies of ADVAIR HFA did not include sufficient numbers of patients aged 65 years and older to determine whether older patients respond differently than 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. In addition, as with other products containing beta$_2$-agonists, special caution should be observed when using ADVAIR HFA in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta$_2$-agonists.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using ADVAIR HFA have not been conducted in patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

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

10 OVERDOSAGE

Fluticasone Propionate: Chronic overdosage with fluticasone propionate may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.7)]*. Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate CFC inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at dosages of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups.

Salmeterol: The expected signs and symptoms with overdosage of salmeterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the following: 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, and insomnia. Overdosage with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of salmeterol.

Treatment consists of discontinuation of salmeterol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be

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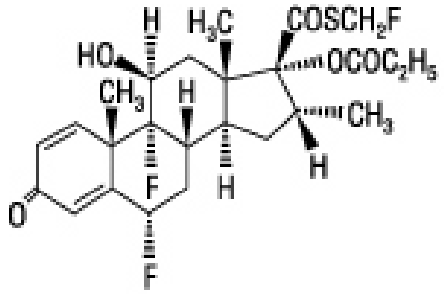
considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is recommended in cases of overdosage.

11 DESCRIPTION

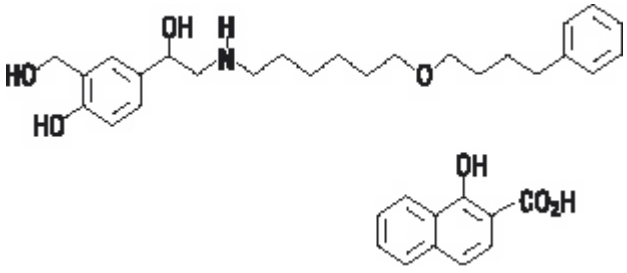
ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR HFA 115/21 Inhalation Aerosol, and ADVAIR HFA 230/21 Inhalation Aerosol are combinations of fluticasone propionate and salmeterol xinafoate.

One active component of ADVAIR HFA is fluticasone propionate, a corticosteroid having the chemical name *S*-(fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of ADVAIR HFA is salmeterol xinafoate, a beta$_2$-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:



Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

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ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR HFA 115/21 Inhalation Aerosol, and ADVAIR HFA 230/21 Inhalation Aerosol are pressurized metered-dose aerosol units fitted with a counter. ADVAIR HFA is intended for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) and salmeterol xinafoate (micronized) in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

After priming, each actuation of the inhaler delivers 50, 125, or 250 mcg of fluticasone propionate and 25 mcg of salmeterol in 75 mg of suspension from the valve. Each actuation delivers 45, 115, or 230 mcg of fluticasone propionate and 21 mcg of salmeterol from the actuator. Twenty-one micrograms (21 mcg) of salmeterol base is equivalent to 30.45 mcg of salmeterol xinafoate. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the device and inspiration through the delivery system.

Each 8-g canister contains 60 inhalations. Each 12-g canister provides 120 inhalations.

ADVAIR HFA should be primed before using for the first time by releasing 4 test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 4 weeks or when it has been dropped, prime the inhaler again by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before each spray.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ADVAIR HFA: Since ADVAIR HFA contains both fluticasone propionate and salmeterol, the mechanisms of action described below for the individual components apply to ADVAIR HFA. These drugs represent 2 classes of medications (a synthetic corticosteroid and a selective LABA) that have different effects on clinical, physiologic, and inflammatory indices of asthma.

Fluticasone Propionate: Fluticasone propionate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Salmeterol Xinafoate: Salmeterol is a selective LABA. In vitro studies show salmeterol to be at least 50 times more selective for beta$_2$-adrenoceptors than albuterol. Although

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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.

The pharmacologic effects of beta$_2$-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D_2, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor–induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

12.2 Pharmacodynamics

ADVAIR HFA: *Healthy Subjects: Cardiovascular Effects:* Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four (4) placebo-controlled crossover studies were conducted in healthy subjects: (1) a cumulative-dose study using 42 to 336 mcg of salmeterol CFC inhalation aerosol given alone or as ADVAIR HFA 115/21, (2) a single-dose study using 4 inhalations of ADVAIR HFA 230/21, salmeterol CFC inhalation aerosol 21 mcg, or fluticasone propionate CFC inhalation aerosol 220 mcg, (3) a single-dose study using 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, or ADVAIR HFA 230/21, and (4) a single-dose study using 4 inhalations of ADVAIR HFA 230/21; 2 inhalations of ADVAIR DISKUS 500/50; 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg; or 1,010 mcg of fluticasone propionate given intravenously. In these studies pulse rate, blood pressure, QTc interval, glucose, and/or potassium were measured. Comparable or lower effects were observed for ADVAIR HFA compared with ADVAIR DISKUS or salmeterol alone. The effect of salmeterol on pulse rate and potassium was not altered by the presence of different amounts of fluticasone propionate in ADVAIR HFA.

Hypothalamic-Pituitary-Adrenal Axis Effects: The potential effect of salmeterol on the effects of fluticasone propionate on the HPA axis was also evaluated in 3 of these studies. Compared with fluticasone propionate CFC inhalation aerosol, ADVAIR HFA had less effect on 24-hour urinary cortisol excretion and less or comparable effect on 24-hour serum cortisol. In these crossover studies in healthy subjects, ADVAIR HFA and ADVAIR DISKUS had similar effects on urinary and serum cortisol.

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Patients With Asthma: Cardiovascular Effects: In clinical studies with ADVAIR HFA in adult and adolescent patients aged 12 years and older with asthma, systemic pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) were similar to or slightly lower in patients treated with ADVAIR HFA compared with patients treated with salmeterol CFC inhalation aerosol 21 mcg. In 61 adult and adolescent patients with asthma given ADVAIR HFA (45/21 or 115/21 mcg), continuous 24-hour electrocardiographic monitoring was performed after the first dose and after 12 weeks of twice-daily therapy, and no clinically significant dysrhythmias were noted.

The effect of 21 days of treatment with ADVAIR HFA 45/21 (2 inhalations twice daily with or without a spacer) or ADVAIR DISKUS 100/50 (1 inhalation twice daily) was evaluated in 31 children aged 4 to 11 years with mild asthma. There were no notable changes from baseline for QTc, heart rate, or systolic and diastolic blood pressure.

Hypothalamic-Pituitary-Adrenal Axis Effects: A 4-way crossover study in 13 patients with asthma compared pharmacodynamics at steady state following 4 weeks of twice-daily treatment with 2 inhalations of ADVAIR HFA 115/21, 1 inhalation of ADVAIR DISKUS 250/50 mcg, 2 inhalations of fluticasone propionate HFA inhalation aerosol 110 mcg, and placebo. No significant differences in serum cortisol AUC were observed between active treatments and placebo. Mean 12-hour serum cortisol AUC ratios comparing active treatment with placebo ranged from 0.9 to 1.2. No statistically or clinically significant increases in heart rate or QTc interval were observed for any active treatment compared with placebo.

In a 12-week study in adult and adolescent patients with asthma, ADVAIR HFA 115/21 was compared with the individual components, fluticasone propionate CFC inhalation aerosol 110 mcg and salmeterol CFC inhalation aerosol 21 mcg, and placebo *[see Clinical Studies (14.1)]*. All treatments were administered as 2 inhalations twice daily. After 12 weeks of treatment with these therapeutic doses, the geometric mean ratio of urinary cortisol excretion compared with baseline was 0.9 for ADVAIR HFA and fluticasone propionate and 1.0 for placebo and salmeterol. In addition, the ability to increase cortisol production in response to stress, as assessed by 30-minute cosyntropin stimulation in 23 to 32 patients per treatment group, remained intact for the majority of patients and was similar across treatments. Three patients who received ADVAIR HFA 115/21 had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing, compared with 1 patient who received placebo, 2 patients who received fluticasone propionate 110 mcg, and 1 patient who received salmeterol.

In another 12-week study in adult and adolescent patients with asthma, ADVAIR HFA 230/21 (2 inhalations twice daily) was compared with ADVAIR DISKUS 500/50 (1 inhalation twice daily) and fluticasone propionate CFC inhalation aerosol 220 mcg (2 inhalations twice daily) *[see Clinical Studies (14.1)]*. The geometric mean ratio of 24-hour urinary cortisol excretion at week 12 compared with baseline was 0.9 for all 3 treatment groups.

The effect of 21 days of treatment with ADVAIR HFA 45/21 (2 inhalations twice daily with or without a spacer) or ADVAIR DISKUS 100/50 (1 inhalation twice daily) on serum cortisol was evaluated in 31 children aged 4 to 11 years with mild asthma. There were reductions

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in serum cortisol from baseline in all treatment groups (14%, 22%, and 13% for ADVAIR HFA, ADVAIR HFA with spacer, and ADVAIR DISKUS, respectively).

Other Fluticasone Propionate Products: *Patients With Asthma: Hypothalamic-Pituitary-Adrenal Axis Effects:* In clinical trials with fluticasone propionate inhalation powder using dosages up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out with the DISKHALER® inhalation device in 64 patients with mild, persistent asthma (mean FEV_1 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

Other Salmeterol Xinafoate Products: *Patients With Asthma: Cardiovascular Effects:* Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium *[see Warnings and Precautions (5.12, 5.18)]*. The cardiovascular effects (heart rate, blood pressure) associated with salmeterol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). In 2 double-blind asthma studies, patients receiving either 42 mcg of salmeterol inhalation aerosol twice daily (n = 81) or 180 mcg of albuterol inhalation aerosol 4 times daily (n = 80) underwent continuous electrocardiographic monitoring during four 24-hour periods; no clinically significant dysrhythmias were noted.

Concomitant Use of ADVAIR HFA With Other Respiratory Medications: *Short-Acting Beta$_2$-Agonists:* In three 12-week US clinical trials, the mean daily need for additional beta$_2$-agonist use in 277 patients receiving ADVAIR HFA was approximately 1.2 inhalations/day and ranged from 0 to 9 inhalations/day. Two percent (2%) of patients receiving ADVAIR HFA in these trials averaged 6 or more inhalations per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations per day.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving ADVAIR HFA has not been completely evaluated. In five 12-week clinical trials (3 US and 2 non-US), 45 patients receiving ADVAIR HFA 45/21, 115/21, or 230/21 twice daily concurrently with a theophylline

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product had adverse event rates similar to those in 577 patients receiving ADVAIR HFA without theophylline.

Fluticasone Propionate Nasal Spray: In patients receiving ADVAIR HFA in three 12-week US clinical trials, no difference in the profile of adverse events or HPA axis effects was noted between patients receiving FLONASE® (fluticasone propionate) Nasal Spray, 50 mcg concurrently (n = 89) and those who were not (n = 192).

12.3 Pharmacokinetics

Absorption: *Fluticasone Propionate: Healthy Subjects:* Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed.

Three single-dose placebo-controlled crossover studies were conducted in healthy subjects: (1) a study using 4 inhalations of ADVAIR HFA 230/21, salmeterol CFC inhalation aerosol 21 mcg, or fluticasone propionate CFC inhalation aerosol 220 mcg, (2) a study using 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, or ADVAIR HFA 230/21, and (3) a study using 4 inhalations of ADVAIR HFA 230/21; 2 inhalations of ADVAIR DISKUS 500/50; 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg; or 1,010 mcg of fluticasone propionate given intravenously. Peak plasma concentrations of fluticasone propionate were achieved in 0.33 to 1.5 hours and those of salmeterol were achieved in 5 to 10 minutes.

Peak plasma concentrations of fluticasone propionate (N = 20 subjects) following 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, and ADVAIR HFA 230/21 averaged 41, 108, and 173 pg/mL, respectively.

Systemic exposure (N = 20 subjects) from 4 inhalations of ADVAIR HFA 230/21 was 53% of the value from the individual inhaler for fluticasone propionate CFC inhalation aerosol and 42% of the value from the individual inhaler for salmeterol CFC inhalation aerosol. Peak plasma concentrations from ADVAIR HFA for fluticasone propionate (86 versus 120 pg/mL) and salmeterol (170 versus 510 pg/mL) were significantly lower compared with individual inhalers.

In 15 healthy subjects, systemic exposure (AUC) to fluticasone propionate from 4 inhalations of ADVAIR HFA 230/21 (920/84 mcg) and 2 inhalations of ADVAIR DISKUS 500/50 (1,000/100 mcg) were similar between the 2 inhalers (i.e., 799 versus 832 pg•hr/mL, respectively) but approximately half the systemic exposure from 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg (880 mcg, AUC = 1,543 pg•hr/mL). Similar results were observed for peak fluticasone propionate plasma concentrations (186 and 182 pg/mL from ADVAIR HFA and ADVAIR DISKUS, respectively, and 307 pg/mL from the fluticasone propionate CFC inhalation aerosol). Absolute bioavailability of fluticasone propionate was 5.3% and 5.5% following administration of ADVAIR HFA and ADVAIR DISKUS, respectively.

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Patients With Asthma: A double-blind crossover study was conducted in 13 adult patients with asthma to evaluate the steady-state pharmacokinetics of fluticasone propionate and salmeterol following administration of 2 inhalations of ADVAIR HFA 115/21 twice daily or 1 inhalation of ADVAIR DISKUS 250/50 twice daily for 4 weeks. Systemic exposure (AUC) to fluticasone propionate was similar for ADVAIR HFA (274 pg•hr/mL [95% CI: 150, 502]) and ADVAIR DISKUS (338 pg•hr/mL [95% CI: 197, 581]).

The effect of 21 days of treatment with ADVAIR HFA 45/21 (2 inhalations twice daily with or without a spacer) or ADVAIR DISKUS 100/50 (1 inhalation twice daily) was evaluated in a study of 31 children aged 4 to 11 years with mild asthma. Systemic exposure to fluticasone propionate was similar with ADVAIR DISKUS and ADVAIR HFA with a spacer (138 pg•hr/mL [95% CI: 69, 273] and 107 pg•hr/mL [95% CI: 46, 252], respectively) and lower with ADVAIR HFA without a spacer (24 pg•hr/mL [95% CI: 10, 60]).

Salmeterol: Healthy Subjects: Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Peak plasma concentrations of salmeterol (N = 20 subjects) following 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, and ADVAIR HFA 230/21 ranged from 220 to 470 pg/mL.

In 15 healthy subjects receiving ADVAIR HFA 230/21 (920/84 mcg) and ADVAIR DISKUS 500/50 (1,000/100 mcg), systemic exposure to salmeterol was higher (317 versus 169 pg•hr/mL) and peak salmeterol concentrations were lower (196 versus 223 pg/mL) following ADVAIR HFA compared with ADVAIR DISKUS, although pharmacodynamic results were comparable.

Patients With Asthma: Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended dosages (42 mcg of salmeterol inhalation aerosol twice daily). Following chronic administration of an inhaled dosage of 42 mcg of salmeterol inhalation aerosol twice daily, salmeterol was detected in plasma within 5 to 10 minutes in 6 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 150 pg/mL at 20 minutes and no accumulation with repeated doses.

A double-blind crossover study was conducted in 13 adult patients with asthma to evaluate the steady-state pharmacokinetics of fluticasone propionate and salmeterol following administration of 2 inhalations of ADVAIR HFA 115/21 twice daily or 1 inhalation of ADVAIR DISKUS 250/50 twice daily for 4 weeks. Systemic exposure to salmeterol was similar for ADVAIR HFA (53 pg•hr/mL [95% CI: 17, 164]) and ADVAIR DISKUS (70 pg•hr/mL [95% CI: 19, 254]).

The effect of 21 days of treatment with ADVAIR HFA 45/21 (2 inhalations twice daily with or without a spacer) or ADVAIR DISKUS 100/50 (1 inhalation twice daily) was evaluated in 31 children aged 4 to 11 years with mild asthma. Systemic exposure to salmeterol was similar for ADVAIR HFA, ADVAIR HFA with spacer, and ADVAIR DISKUS (126 pg•hr/mL [95%

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CI: 70, 225], 103 pg•hr/mL [95% CI: 54, 200], and 110 pg•hr/mL [95% CI: 55, 219], respectively).

Distribution: *Fluticasone Propionate:* 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.

Salmeterol: The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism: *Fluticasone Propionate:* The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the CYP3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Salmeterol: Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to α-hydroxysalmeterol (aliphatic oxidation) by CYP3A4. Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of α-hydroxysalmeterol in vitro.

Elimination: *Fluticasone Propionate:* Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites. Terminal half-life estimates of fluticasone propionate for ADVAIR HFA, ADVAIR DISKUS, and fluticasone propionate CFC inhalation aerosol were similar and averaged 5.6 hours.

Salmeterol: In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days. No terminal half-life estimates were calculated for salmeterol following administration of ADVAIR HFA.

Special Populations: A population pharmacokinetic analysis was performed for fluticasone propionate and salmeterol utilizing data from 9 controlled clinical trials that included

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350 patients with asthma aged 4 to 77 years who received treatment with ADVAIR DISKUS, ADVAIR HFA, fluticasone propionate inhalation powder (FLOVENT® DISKUS®), HFA-propelled fluticasone propionate inhalation aerosol (FLOVENT HFA), or CFC-propelled fluticasone propionate inhalation aerosol. The population pharmacokinetic analyses for fluticasone propionate and salmeterol showed no clinically relevant effects of age, gender, race, body weight, body mass index, or percent of predicted FEV_1 on apparent clearance and apparent volume of distribution.

Hepatic and Renal Impairment: Formal pharmacokinetic studies using ADVAIR HFA have not been conducted in patients with hepatic or renal impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Drug Interactions: In the repeat- and single-dose studies, there was no evidence of significant drug interaction in systemic exposure between fluticasone propionate and salmeterol when given alone or in combination via the DISKUS. Similar definitive studies have not been performed with ADVAIR HFA. The population pharmacokinetic analysis from 9 controlled clinical trials in 350 patients with asthma showed no significant effects on fluticasone propionate or salmeterol pharmacokinetics following co-administration with $beta_2$-agonists, corticosteroids, antihistamines, or theophyllines.

Inhibitors of Cytochrome P450 3A4: Ritonavir: Fluticasone Propionate: Fluticasone propionate is a substrate of CYP3A4. Coadministration of fluticasone propionate and the strong CYP3A4 inhibitor ritonavir is not recommended based upon a multiple-dose crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{max}) averaged 11.9 pg/mL (range: 10.8 to 14.1 pg/mL) and $AUC_{(0-\tau)}$ averaged 8.43 pg•hr/mL (range: 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range: 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range: 1,207.1 to 5,662.0 pg•hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

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

Salmeterol: In a placebo-controlled crossover drug interaction study in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant

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increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76 [90% CI: 10.66, 23.31]) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist–mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

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

Salmeterol: In a repeat-dose study in 13 healthy subjects, concomitant administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with and without erythromycin 1.4 [90% CI: 0.96, 2.03], p = 0.12), a 3.6-beat/min increase in heart rate ([95% CI: 0.19, 7.03], p<0.04), a 5.8-msec increase in QTc interval ([95% CI: -6.14, 17.77], p = 0.34), and no change in plasma potassium.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone Propionate: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 5 times the MRHD on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than the MRHD 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.

No evidence of impairment of fertility was observed in reproductive studies conducted in rats at subcutaneous doses up to 50 mcg/kg (less than the MRHD on a mcg/m^2 basis). Prostate weight was significantly reduced.

Salmeterol: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 10 times the MRHD based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at 0.2 mg/kg (approximately 2 times the MRHD for adults based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 80 times the MRHD on a mg/m^2

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basis). No tumors were seen at 0.21 mg/kg (approximately 25 times the MRHD on a mg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 230 times the MRHD on a mg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: 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.

Propellant HFA-134a: In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to 7 minutes in humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (i.e., 380 to 1,300 times the maximum human exposure based on comparisons of area under the plasma concentration versus time curve [AUC] values), primarily producing ataxia, tremors, dyspnea, or salivation. These events are similar to effects produced by the structurally related CFCs, which have been used extensively in metered-dose inhalers. In drug interaction studies in male and female dogs, there was a slight increase in the salmeterol-related effect on heart rate (a known effect of beta$_2$-agonists) when given in combination with high doses of fluticasone propionate. This effect was not observed in clinical studies.

14 CLINICAL STUDIES

ADVAIR HFA has been studied in patients with asthma aged 12 years and older. ADVAIR HFA has not been studied in patients less than 12 years of age or in patients with COPD. In clinical trials comparing ADVAIR HFA Inhalation Aerosol with its individual components, improvements in most efficacy endpoints were greater with ADVAIR HFA than with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed comparable results between ADVAIR HFA and ADVAIR DISKUS.

14.1 Studies Comparing ADVAIR HFA With Fluticasone Propionate Alone or Salmeterol Alone

Four (4) double-blind parallel-group clinical trials were conducted with ADVAIR HFA in 1,517 adult and adolescent patients (≥12 years, mean baseline FEV_1 65% to 75% of predicted normal) with asthma that was not optimally controlled on their current therapy. All metered-dose inhaler treatments were inhalation aerosols given as 2 inhalations twice daily, and other maintenance therapies were discontinued.

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Study 1: Clinical Trial With ADVAIR HFA 45/21 Inhalation Aerosol: This placebo-controlled 12-week US study compared ADVAIR HFA 45/21 with fluticasone propionate CFC inhalation aerosol 44 mcg or salmeterol CFC inhalation aerosol 21 mcg, each given as 2 inhalations twice daily. The primary efficacy endpoints were predose FEV_1 and withdrawals due to worsening asthma. This study was stratified according to baseline asthma therapy: patients using beta-agonists (albuterol alone [n = 142], salmeterol [n = 84], or inhaled corticosteroids [n = 134] [daily doses of beclomethasone dipropionate 252 to 336 mcg; budesonide 400 to 600 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol 176 mcg; fluticasone propionate inhalation powder 200 mcg; or triamcinolone acetonide 600 to 800 mcg]). Baseline FEV_1 measurements were similar across treatments: ADVAIR HFA 45/21, 2.29 L; fluticasone propionate 44 mcg, 2.20 L; salmeterol, 2.33 L; and placebo, 2.27 L.

Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were utilized for this placebo-controlled study. Worsening asthma was defined as a clinically important decrease in FEV_1 or PEF, increase in use of VENTOLIN® (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. As shown in Table 4, statistically significantly fewer patients receiving ADVAIR HFA 45/21 were withdrawn due to worsening asthma compared with salmeterol and placebo. Fewer patients receiving ADVAIR HFA 45/21 were withdrawn due to worsening asthma compared with fluticasone propionate 44 mcg; however, the difference was not statistically significant.

Table 4. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously Treated With $Beta_2$-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)

ADVAIR HFA 45/21 Inhalation Aerosol (n = 92)	Fluticasone Propionate CFC Inhalation Aerosol 44 mcg (n = 89)	Salmeterol CFC Inhalation Aerosol 21 mcg (n = 92)	Placebo HFA Inhalation Aerosol (n = 87)
2%	8%	25%	28%

The FEV_1 results are displayed in Figure 2. Because this trial used predetermined criteria for worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV_1 results at Endpoint (last available FEV_1 result) are also provided. Patients receiving ADVAIR HFA 45/21 had significantly greater improvements in FEV_1 (0.58 L, 27%) compared with fluticasone propionate 44 mcg (0.36 L, 18%), salmeterol (0.25 L, 12%), and placebo (0.14 L, 5%). These improvements in FEV_1 with ADVAIR HFA 45/21 were achieved regardless of baseline asthma therapy (albuterol alone, salmeterol, or inhaled corticosteroids).

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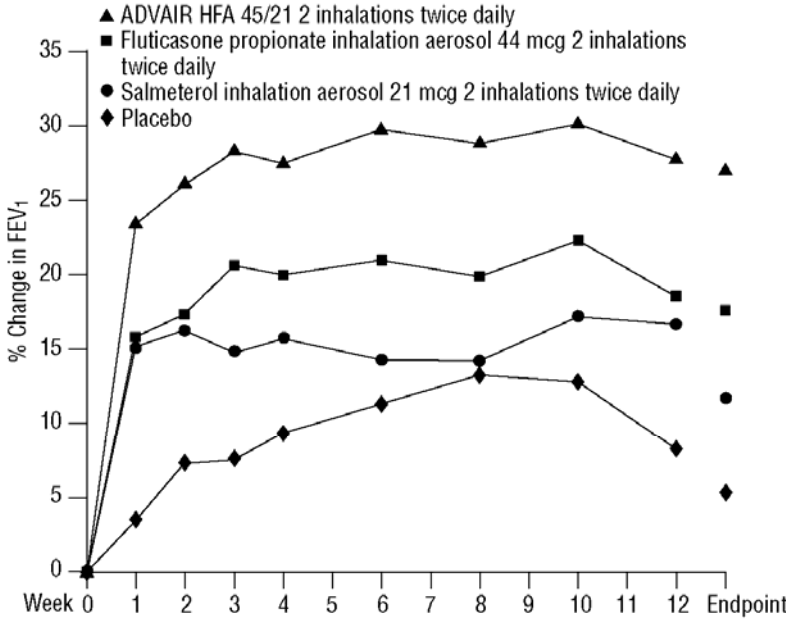
Figure 2. Mean Percent Change From Baseline in FEV_1 in Patients Previously Treated With Either $Beta_2$-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)



	N		N		N
ADVAIR HFA 45/21	92		88		85
Fluticasone propionate inhalation aerosol 44 mcg	89		84		76
Salmeterol inhalation aerosol 21 mcg	92		72		65
Placebo	87		63		58

The effect of ADVAIR HFA 45/21 on the secondary efficacy parameters, including morning and evening PEF, usage of VENTOLIN Inhalation Aerosol, and asthma symptoms over 24 hours on a scale of 0 to 5 is shown in Table 5.

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Table 5. Secondary Efficacy Variable Results for Patients Previously Treated With Beta$_2$-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)

Efficacy Variable[a]	ADVAIR HFA 45/21 Inhalation Aerosol (n = 92)	Fluticasone Propionate CFC Inhalation Aerosol 44 mcg (n = 89)	Salmeterol CFC Inhalation Aerosol 21 mcg (n = 92)	Placebo HFA Inhalation Aerosol (n = 87)
AM PEF (L/min)				
Baseline	377	369	381	382
Change from baseline	58	27	25	1
PM PEF (L/min)				
Baseline	397	387	402	407
Change from baseline	48	20	16	3
Use of VENTOLIN Inhalation Aerosol (inhalations/day)				
Baseline	3.1	2.4	2.7	2.7
Change from baseline	-2.1	-0.4	-0.8	0.2
Asthma symptom score/day				
Baseline	1.8	1.6	1.7	1.7
Change from baseline	-1.0	-0.3	-0.4	0

[a] Change from baseline = change from baseline at Endpoint (last available data).

The subjective impact of asthma on patients' perceptions of health was evaluated through use of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR HFA 45/21 had clinically meaningful improvements in overall asthma-specific quality of life as defined by a difference between groups of ≥0.5 points in change from baseline AQLQ scores (difference in AQLQ score of 1.14 [95% CI: 0.85, 1.44] compared with placebo).

Study 2: Clinical Trial With ADVAIR HFA 45/21 Inhalation Aerosol: This active-controlled 12-week US study compared ADVAIR HFA 45/21 with fluticasone propionate CFC inhalation aerosol 44 mcg and salmeterol CFC inhalation aerosol 21 mcg, each given as 2 inhalations twice daily, in 283 patients using as-needed albuterol alone. The primary efficacy endpoint was predose FEV_1. Baseline FEV_1 measurements were similar across treatments: ADVAIR HFA 45/21, 2.37 L; fluticasone propionate 44 mcg, 2.31 L; and salmeterol, 2.34 L.

Efficacy results in this study were similar to those observed in Study 1. Patients receiving ADVAIR HFA 45/21 had significantly greater improvements in FEV_1 (0.69 L, 33%) compared with fluticasone propionate 44 mcg (0.51 L, 25%) and salmeterol (0.47 L, 22%).

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Study 3: Clinical Trial With ADVAIR HFA 115/21 Inhalation Aerosol: This placebo-controlled 12-week US study compared ADVAIR HFA 115/21 with fluticasone propionate CFC inhalation aerosol 110 mcg or salmeterol CFC inhalation aerosol 21 mcg, each given as 2 inhalations twice daily, in 365 patients using inhaled corticosteroids (daily doses of beclomethasone dipropionate 378 to 840 mcg; budesonide 800 to 1,200 mcg; flunisolide 1,250 to 2,000 mcg; fluticasone propionate inhalation aerosol 440 to 660 mcg; fluticasone propionate inhalation powder 400 to 600 mcg; or triamcinolone acetonide 900 to 1,600 mcg). The primary efficacy endpoints were predose FEV_1 and withdrawals due to worsening asthma. Baseline FEV_1 measurements were similar across treatments: ADVAIR HFA 115/21, 2.23 L; fluticasone propionate 110 mcg, 2.18 L; salmeterol, 2.22 L; and placebo, 2.17 L.

Efficacy results in this study were similar to those observed in Studies 1 and 2. Patients receiving ADVAIR HFA 115/21 had significantly greater improvements in FEV_1 (0.41 L, 20%) compared with fluticasone propionate 110 mcg (0.19 L, 9%), salmeterol (0.15 L, 8%), and placebo (-0.12 L, -6%). Significantly fewer patients receiving ADVAIR HFA 115/21 were withdrawn from this study for worsening asthma (7%) compared with salmeterol (24%) and placebo (54%). Fewer patients receiving ADVAIR HFA 115/21 were withdrawn due to worsening asthma (7%) compared with fluticasone propionate 110 mcg (11%); however, the difference was not statistically significant.

Study 4: Clinical Trial With ADVAIR HFA 230/21 Inhalation Aerosol: This active-controlled 12-week non-US study compared ADVAIR HFA 230/21 with fluticasone propionate CFC inhalation aerosol 220 mcg, each given as 2 inhalations twice daily, and with ADVAIR DISKUS 500/50 given as 1 inhalation twice daily in 509 patients using inhaled corticosteroids (daily doses of beclomethasone dipropionate CFC inhalation aerosol 1,500 to 2,000 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; fluticasone propionate inhalation aerosol 660 to 880 mcg; or fluticasone propionate inhalation powder 750 to 1,000 mcg). The primary efficacy endpoint was morning PEF.

Baseline morning PEF measurements were similar across treatments: ADVAIR HFA 230/21, 327 L/min; ADVAIR DISKUS 500/50, 341 L/min; and fluticasone propionate 220 mcg, 345 L/min. As shown in Figure 3, morning PEF improved significantly with ADVAIR HFA 230/21 compared with fluticasone propionate 220 mcg over the 12-week treatment period. Improvements in morning PEF observed with ADVAIR HFA 230/21 were similar to improvements observed with ADVAIR DISKUS 500/50.

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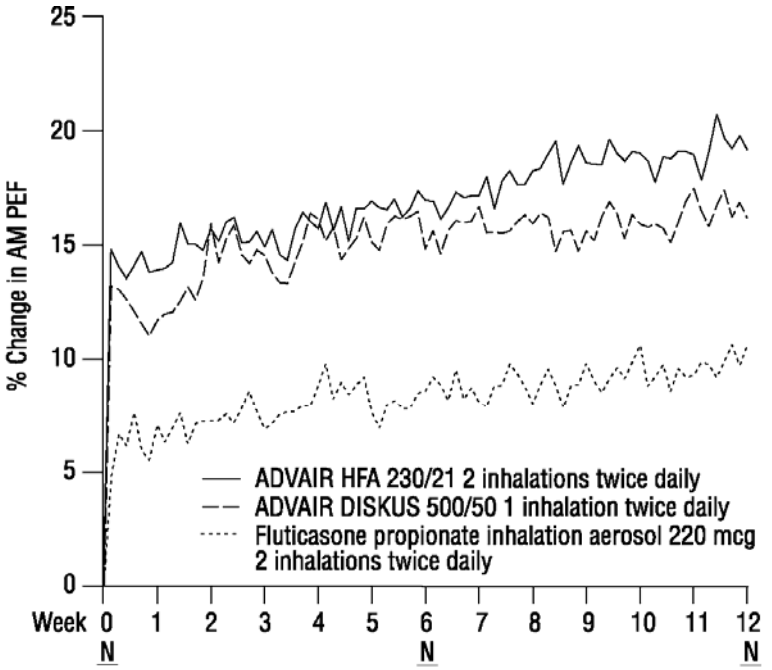
Figure 3. Mean Percent Change From Baseline in Morning Peak Expiratory Flow in Patients Previously Treated With Inhaled Corticosteroids (Study 4)



	N			N			N
ADVAIR HFA 230/21	176			159			130
ADVAIR DISKUS 500/50	161			147			119
Fluticasone propionate inhalation aerosol 220 mcg	172			155			133

14.2 One-Year Safety Study

Clinical Trial With ADVAIR HFA 45/21, 115/21, and 230/21 Inhalation Aerosol:

This 1-year open-label non-US study evaluated the safety of ADVAIR HFA 45/21, 115/21, and 230/21 given as 2 inhalations twice daily in 325 patients. This study was stratified into 3 groups according to baseline asthma therapy: patients using short-acting beta$_2$-agonists alone (n = 42), salmeterol (n = 91), or inhaled corticosteroids (n = 277). Patients treated with short-acting beta$_2$-agonists alone, salmeterol, or low doses of inhaled corticosteroids with or without concurrent salmeterol received ADVAIR HFA 45/21. Patients treated with moderate doses of inhaled corticosteroids with or without concurrent salmeterol received ADVAIR HFA 115/21. Patients treated with high doses of inhaled corticosteroids with or without concurrent salmeterol received ADVAIR HFA 230/21. Baseline FEV_1 measurements ranged from 2.3 to 2.6 L.

Improvements in FEV_1 (0.17 to 0.35 L at 4 weeks) were seen across all 3 treatments and were sustained throughout the 52-week treatment period. Few patients (3%) were withdrawn due to worsening asthma over 1 year.

14.3 Onset of Action and Progression of Improvement in Control

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The onset of action and progression of improvement in asthma control were evaluated in 2 placebo-controlled US trials and 1 active-controlled US trial. Following the first dose, the median time to onset of clinically significant bronchodilatation (≥15% improvement in FEV_1) in most patients was seen within 30 to 60 minutes. Maximum improvement in FEV_1 occurred within 4 hours, and clinically significant improvement was maintained for 12 hours (see Figure 4).

Following the initial dose, predose FEV_1 relative to Day 1 baseline improved markedly over the first week of treatment and continued to improve over the 12 weeks of treatment in all 3 studies.

No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR HFA 45/21 (Figures 4 and 5) or ADVAIR HFA 230/21 as assessed by FEV_1 following 12 weeks of therapy.

Figure 4. Percent Change in Serial 12-Hour FEV_1 in Patients Previously Using Either $Beta_2$-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)

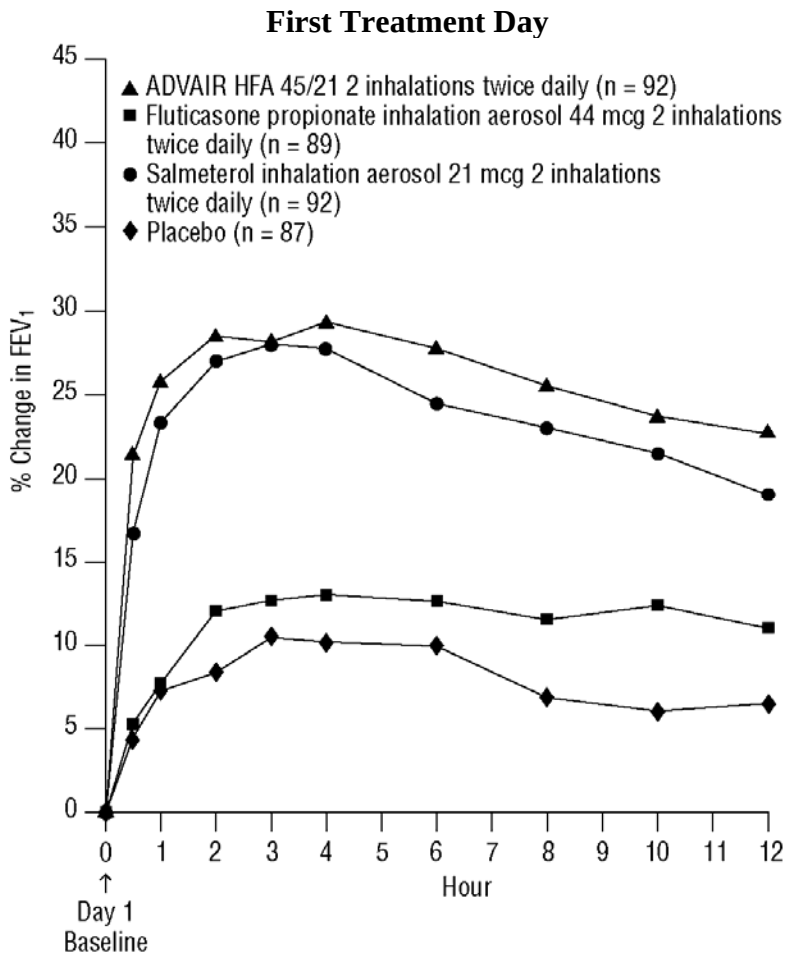

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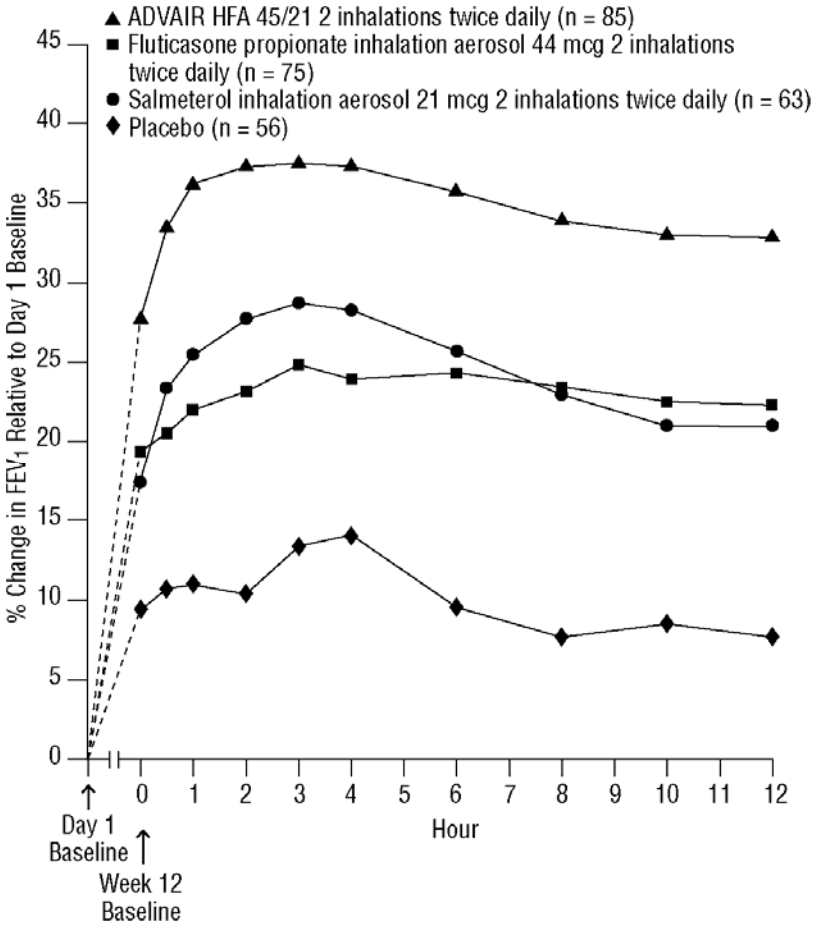
Figure 5. Percent Change in Serial 12-Hour FEV_1 in Patients Previously Using Either $Beta_2$-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)

Last Treatment Day (Week 12)



Reduction in asthma symptoms and use of rescue VENTOLIN Inhalation Aerosol and improvement in morning and evening PEF also occurred within the first day of treatment with ADVAIR HFA, and continued to improve over the 12 weeks of therapy in all 3 studies.

16 HOW SUPPLIED/STORAGE AND HANDLING

ADVAIR HFA 45/21 Inhalation Aerosol is supplied in 12-g pressurized aluminum canisters containing 120 metered actuations in boxes of 1 (NDC 0173-0715-20) and 8-g pressurized aluminum canisters containing 60 metered actuations in institutional pack boxes of 1 (NDC 0173-0715-22).

ADVAIR HFA 115/21 Inhalation Aerosol is supplied in 12-g pressurized aluminum canisters containing 120 metered actuations in boxes of 1 (NDC 0173-0716-20) and 8-g

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pressurized aluminum canisters containing 60 metered actuations in institutional pack boxes of 1 (NDC 0173-0716-22).

ADVAIR HFA 230/21 Inhalation Aerosol is supplied in 12-g pressurized aluminum canisters containing 120 metered actuations in boxes of 1 (NDC 0173-0717-20) and 8-g pressurized aluminum canisters containing 60 metered actuations in institutional pack boxes of 1 (NDC 0173-0717-22).

Each canister is fitted with a counter, supplied with a purple actuator with a light purple strapcap, and sealed in a plastic-coated, moisture-protective foil pouch with a desiccant that should be discarded when the pouch is opened. Each canister is packaged with a Medication Guide leaflet.

The purple actuator supplied with ADVAIR HFA Inhalation Aerosol should not be used with any other product canisters, and actuators from other products should not be used with an ADVAIR HFA Inhalation Aerosol canister.

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

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

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Asthma-Related Death

Patients should be informed that salmeterol, one of the active ingredients in ADVAIR HFA, increases the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. They should also be informed that currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs.

17.2 Not for Acute Symptoms

ADVAIR HFA is not meant to relieve acute asthma symptoms, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist such as albuterol. The healthcare provider should provide the patient with such medication and instruct the patient in how it should be used.

Patients should be instructed to seek medical attention immediately if they experience any of the following:

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- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Patients should not stop therapy with ADVAIR HFA without physician/provider guidance since symptoms may recur after discontinuation.

17.3 Do Not Use Additional Long-Acting Beta$_2$-Agonists

When patients are prescribed ADVAIR HFA, other LABAs for asthma should not be used.

17.4 Risks Associated With Corticosteroid Therapy

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

Pneumonia: Patients with COPD have a higher risk of pneumonia and should be instructed to contact their healthcare provider if they develop symptoms of pneumonia.

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

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

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk.

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

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

17.5 Risks Associated With Beta-Agonist Therapy

Patients should be informed of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

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Research Triangle Park, NC 27709

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December 2012
ADH:XPI

PHARMACIST—DETACH HERE AND GIVE MEDICATION GUIDE TO PATIENT

MEDICATION GUIDE

ADVAIR® HFA [*ad′vair*] 45/21 Inhalation Aerosol
(fluticasone propionate 45 mcg and salmeterol 21 mcg)

ADVAIR® HFA 115/21 Inhalation Aerosol
(fluticasone propionate 115 mcg and salmeterol 21 mcg)

ADVAIR® HFA 230/21 Inhalation Aerosol
(fluticasone propionate 230 mcg and salmeterol 21 mcg)

Read the Medication Guide that comes with ADVAIR HFA Inhalation Aerosol before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about ADVAIR HFA?

ADVAIR HFA can cause serious side effects, including:

1. **People with asthma who take long-acting beta$_2$-adrenergic agonist (LABA) medicines, such as salmeterol (one of the medicines in ADVAIR HFA), have an increased risk of death from asthma problems.** It is not known whether fluticasone propionate, the other medicine in ADVAIR HFA, reduces the risk of death from asthma problems seen with salmeterol.

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- **Call your healthcare provider if breathing problems worsen over time while using ADVAIR HFA.** You may need different treatment.
- **Get emergency medical care if:**
  - breathing problems worsen quickly and
  - you use your rescue inhaler medicine, but it does not relieve your breathing problems.

2. ADVAIR HFA should be used only if your healthcare provider decides that your asthma is not well controlled with a long-term asthma control medicine, such as inhaled corticosteroids.
3. When your asthma is well controlled, your healthcare provider may tell you to stop taking ADVAIR HFA. Your healthcare provider will decide if you can stop ADVAIR HFA without loss of asthma control. Your healthcare provider may prescribe a different long-term asthma control medicine for you, such as an inhaled corticosteroid.
4. Children and adolescents who take LABA medicines may have an increased risk of being hospitalized for asthma problems.

What is ADVAIR HFA?

- ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate (the same medicine found in FLOVENT®), and a LABA medicine, salmeterol (the same medicine found in SEREVENT®).
  - Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
  - LABA medicines are used in people with asthma and chronic obstructive pulmonary disease (COPD). LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.
- ADVAIR HFA is used to control symptoms of asthma and to prevent symptoms such as wheezing in adults and adolescents aged 12 years and older.
- ADVAIR HFA should not be used as a rescue inhaler.
- ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). LABA medicines, such as salmeterol, increase the risk of death from asthma problems.

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ADVAIR HFA is not for adults and adolescents with asthma who are well controlled with an asthma control medicine, such as a low to medium dose of an inhaled corticosteroid medicine.

Who should not use ADVAIR HFA?

Do not use ADVAIR HFA:

- to treat sudden, severe symptoms of asthma and
- if you are allergic to any of the ingredients in ADVAIR HFA. See the end of this Medication Guide for a list of ingredients in ADVAIR HFA.

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

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

- **have heart problems**
- **have high blood pressure**
- **have seizures**
- **have thyroid problems**
- **have diabetes**
- **have liver problems**
- **have osteoporosis**
- **have an immune system problem**
- **have eye problems such as increased pressure in the eye (glaucoma) or cataracts**
- **are pregnant or planning to become pregnant.** It is not known if ADVAIR HFA may harm your unborn baby.
- **are breastfeeding.** It is not known if ADVAIR HFA passes into your milk and if it can harm your baby.
- **are allergic to ADVAIR HFA or any other medicines**
- **are exposed to chickenpox or measles**

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. ADVAIR HFA and certain other medicines may interact with each other. This may cause serious side effects. Especially, tell your healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR® (ritonavir capsules) Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA® (lopinavir/ritonavir) Tablets contain ritonavir.

Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist each time you get a new medicine.

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How do I use ADVAIR HFA?

See the step-by-step instructions for using ADVAIR HFA at the end of this Medication Guide. Do not use ADVAIR HFA unless your healthcare provider has taught you and you understand everything. Ask your healthcare provider or pharmacist if you have any questions.

- Use ADVAIR HFA exactly as prescribed. **Do not use ADVAIR HFA more often than prescribed.** ADVAIR HFA comes in 3 strengths. Your healthcare provider has prescribed the one that is best for your condition.
- The usual dosage of ADVAIR HFA is 2 inhalations 2 times each day (morning and evening). The 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR HFA.
- If you take more ADVAIR HFA than your doctor has prescribed, get medical help right away if you have any unusual symptom, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.
- If you miss a dose of ADVAIR HFA, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.
- **While you are using ADVAIR HFA 2 times each day, do not use other medicines that contain a LABA for any reason.** Ask your healthcare provider or pharmacist if any of your other medicines are LABA medicines.
- Do not stop using ADVAIR HFA or other asthma medicines unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- ADVAIR HFA does not relieve sudden symptoms. Always have a rescue inhaler medicine with you to treat sudden symptoms. If you do not have a short-acting bronchodilator rescue inhaler, call your healthcare provider to have one prescribed for you.
- Call your healthcare provider or get medical care right away if:
  - your breathing problems worsen with ADVAIR HFA
  - you need to use your rescue inhaler medicine more often than usual
  - your rescue inhaler medicine does not work as well for you at relieving symptoms
  - you need to use 4 or more inhalations of your rescue inhaler medicine for 2 or more days in a row
  - you use 1 whole canister of your rescue inhaler medicine in 8 weeks' time
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.

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- your asthma symptoms do not improve after using ADVAIR HFA regularly for 1 week

What are the possible side effects with ADVAIR HFA?

ADVAIR HFA can cause serious side effects, including:

- **See "What is the most important information I should know about ADVAIR 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 the face, mouth, and tongue
  - breathing problems
- **sudden breathing problems immediately after inhaling your medicine**
- **effects on heart**
  - increased blood pressure
  - a fast and irregular heartbeat
  - chest pain
- **effects on nervous system**
  - tremor
  - nervousness
- **reduced adrenal function (may result in loss of energy)**
- **changes in blood (sugar, potassium, certain types of white blood cells)**
- **weakened immune system and a higher chance of infections**
- **lower bone mineral density.** This may be a problem for people who already have a higher chance of low bone density (osteoporosis).
- **eye problems including glaucoma and cataracts.** You should have regular eye exams while using ADVAIR HFA.
- **slowed growth in children.** A child's growth should be checked often.
- **throat tightness**
- **pneumonia.** ADVAIR HFA contains the same medicine found in ADVAIR DISKUS®. ADVAIR DISKUS is used to treat people with asthma and people with chronic obstructive pulmonary disease (COPD). People with COPD have a higher chance of getting pneumonia. ADVAIR DISKUS may increase the chance of

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getting pneumonia. ADVAIR HFA has not been studied in people with COPD. Call your healthcare provider if you notice any of the following symptoms:

- increase in mucus (sputum) production
- change in mucus color
- fever
- chills
- increased cough
- increased breathing problems

Common side effects of ADVAIR HFA include:

- upper respiratory tract infection
- throat irritation
- hoarseness and voice changes
- headache
- dizziness
- nausea and vomiting

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

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

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

How do I store ADVAIR HFA?

- Store ADVAIR HFA at room temperature between 59°F to 86°F (15°C to 30°C), with the mouthpiece down.
- **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.
- Do not throw into fire or an incinerator.
- Keep ADVAIR HFA and all medicines out of the reach of children.

General Information about ADVAIR HFA

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

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For current labeling information, please visit https://www.fda.gov/drugsatfda

This Medication Guide summarizes the most important information about ADVAIR HFA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ADVAIR HFA that was written for healthcare professionals. You can also contact the company that makes ADVAIR HFA (toll free) at 1-888-825-5249 or at www.advair.com.

What are the ingredients in ADVAIR HFA?

Active ingredients: fluticasone propionate, salmeterol xinafoate
Inactive ingredient: propellant HFA-134a

Instructions for using your ADVAIR HFA

The parts of your ADVAIR HFA

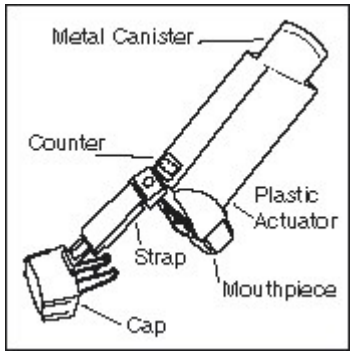

Figure 1

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

The canister has a counter to show how many sprays of medicine you have left. The number shows through a window in the back of the actuator. The counter starts at 124, or at 064 if you have a sample or institutional canister. The number will count down by 1 each time you spray the inhaler. The counter will stop counting at 000.

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

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

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

Using your ADVAIR HFA

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

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- Take your ADVAIR HFA inhaler out of the moisture-protective pouch just before you use it for the first time. Safely throw away the foil pouch and the drying packet that comes inside the pouch.

Priming your ADVAIR HFA

Before you use ADVAIR HFA for the first time, you must prime the inhaler so that you will get the right amount of medicine when you use it. To prime the inhaler, take the cap off the mouthpiece and shake the inhaler well for 5 seconds. Then spray the inhaler 1 time into the air away from your face. **Avoid spraying in eyes.** Shake and spray the inhaler like this 3 more times to finish priming it. The counter should now read 120, or 060 if you have a sample or institutional canister.

You must prime your inhaler again if you have not used it in more than 4 weeks or if you drop it. Take the cap off the mouthpiece, shake the inhaler well for 5 seconds. Then spray it into the air away from your face. Shake and spray the inhaler like this 1 more time to finish priming it.

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

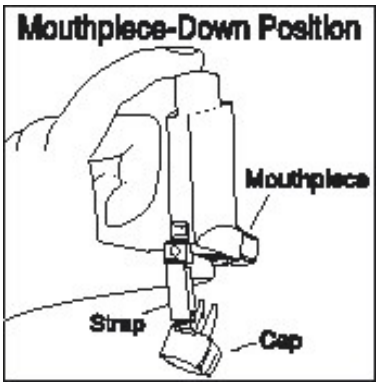

Figure 2

1. **Take the cap off the mouthpiece of the actuator** (see Figure 2).

   Look inside the mouthpiece for foreign objects, and take out any you see.

   Make sure the canister fits firmly in the actuator.

   Shake the inhaler well for 5 seconds.

2. Hold the inhaler with the mouthpiece down (see Figure 2).

   Breathe out through your mouth and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it.

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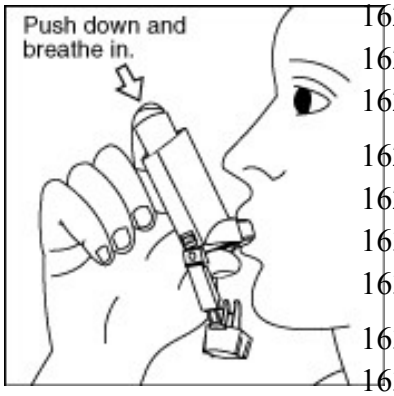

Figure 3

3. **Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth** (see Figure 3).

   Right after the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.

4. **Hold your breath as long as you can**, up to 10 seconds, then breathe normally.

5. **Wait about 30 seconds and shake the inhaler** well for 5 seconds. Repeat steps 2 through 4.

6. After you finish taking this medicine, rinse your mouth with water. Spit out the water. Do not swallow it.

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

Cleaning your ADVAIR HFA

Clean your inhaler at least 1 time each week after your evening dose. It is important to keep the canister and plastic actuator clean so the medicine will not build-up and block the spray.

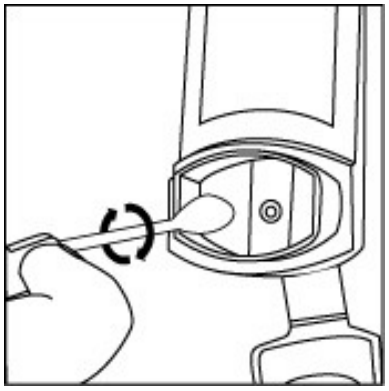

Figure 4

1. Take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator. Do not take the canister out of the plastic actuator.

2. Use a dry cotton swab to clean the small circular opening where the medicine sprays out of the canister. Carefully twist the swab in a circular motion to take off any medicine (see Figure 4).

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

4. Put the cap back on the mouthpiece after the actuator has dried.

Replacing your ADVAIR HFA

- **When the counter reads 020**, you should refill your prescription or ask your doctor if you need another prescription for ADVAIR HFA.

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- **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.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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