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

*As salmeterol xinafoate salt 30.45 mcg, equivalent to salmeterol base 21 mcg

For Oral Inhalation Only

**WARNING**

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. 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) (see WARNINGS).

**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 \( C_{25}H_{31}F_{3}O_{5}S \). 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-\( \alpha \)-[\([6-(4-phenylbutoxy)hexyl]amino\)]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:

![Chemical Structure of Salmeterol Xinafoate](image)

Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is \( C_{25}H_{37}NO_{5} \cdot C_{11}H_{8}O_{3} \). It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

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 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 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 shaking well before each spray and releasing 2 test sprays into the air away from the face.

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

CLINICAL PHARMACOLOGY

Mechanism of Action: **ADVAIR HFA Inhalation Aerosol:** 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, long-acting beta2-adrenergic receptor agonist) 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, and neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

**Salmeterol Xinafoate:** Salmeterol is a long-acting beta2-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta2-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on beta1- and beta2-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more selective for beta2-adrenoceptors than albuterol. Although beta2-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1-adrenoceptors are the predominant receptors in the heart, there are also beta2-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 beta2-agonists may have cardiac effects.

The pharmacologic effects of beta2-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 D₂, 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.

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

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (i.e., 380 to 1,300 times the maximum human exposure based on comparisons of area under the plasma concentration versus time curve [AUC] values), primarily producing ataxia, tremors, dyspnea, or salivation. These events are similar to effects produced by the structurally related CFCs, which have been used extensively in metered-dose inhalers. 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 beta₂-agonists) when given in combination with high doses of fluticasone propionate. This effect was not observed in clinical studies.

**Pharmacokinetics:** **ADVAIR HFA Inhalation Aerosol:** 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 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder); 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. Peak plasma salmeterol concentrations ranged from 220 to 470 pg/mL.

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 vs. 120 pg/mL) and salmeterol (170 vs. 510 pg/mL) were significantly lower compared to individual inhalers.

In 15 healthy subjects, systemic exposure to fluticasone propionate from 4 inhalations of ADVAIR HFA 230/21 (920/84 mcg) and 2 inhalations of ADVAIR DISKUS 500/50
but approximately half the systemic exposure from 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg (880 mcg, AUC = 1,543 pg•h/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). Systemic exposure to salmeterol was higher (317 vs. 169 pg•h/mL) and peak salmeterol concentrations were lower (196 vs. 223 pg/mL) following ADVAIR HFA compared to ADVAIR DISKUS, although pharmacodynamic results were comparable.

Absolute bioavailability of fluticasone propionate from ADVAIR HFA in 15 healthy subjects was 5.3%. 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. No terminal half-life estimates were calculated for salmeterol.

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•h/mL [95% CI 150, 502]) and ADVAIR DISKUS (338 pg•h/mL [95% CI 197, 581]). Systemic exposure to salmeterol was also similar for ADVAIR HFA (53 pg•h/mL [95% CI 17, 164]) and ADVAIR DISKUS (70 pg•h/mL [95% CI 19, 254]).

**Special Populations: Hepatic and Renal Impairment:** Formal pharmacokinetic studies using ADVAIR HFA have not been conducted to examine gender differences or in special populations, such as elderly patients or 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 repeat- and single-dose studies, there was no evidence of significant drug interaction on systemic exposure to fluticasone propionate and salmeterol when given alone or in combination via the DISKUS. Similar definitive studies have not been performed with ADVAIR HFA.

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

**Distribution:** Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.
The percentage of fluticasone propionate bound to human plasma proteins averages 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

**Metabolism:** The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

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

**Special Populations: Gender:** In 19 male and 33 female patients with asthma, systemic exposure was similar from 2 inhalations of fluticasone propionate CFC inhalation aerosol 44, 110, and 220 mcg twice daily.

**Drug Interactions:** Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the strong cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable, peak levels (C<sub>max</sub>) averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and AUC<sub>(0-τ)</sub> averaged 8.43 pg•hr/mL (range, 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C<sub>max</sub> and AUC<sub>(0-τ)</sub> 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 systemic fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

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

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mcg 3 times daily) did not affect fluticasone propionate pharmacokinetics.
**Salmeterol Xinafoate:** 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 excreted independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

**Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (42 mcg of salmeterol inhalation aerosol twice daily). Following chronic administration of an inhaled dose of 42 mcg 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 and no accumulation with repeated doses.

**Distribution:** 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:** Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominately 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 cytochrome P450 3A4 (CYP3A4). Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of α-hydroxysalmeterol in vitro.

**Elimination:** 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.

**Drug Interactions:** Salmeterol is a substrate of CYP3A4.

**Inhibitors of Cytochrome P450 3A4: Ketoconazole:** 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 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. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended.

Erythromycin: In a repeat-dose study in 15 healthy subjects, concomitant administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol C\textsubscript{max} at steady state (ratio with and without erythromycin 1.4; 90% CI: 0.96, 2.03; p = 0.12). Coadministration of salmeterol and erythromycin did not result in a clinically significant effect on mean heart rate, QTc, or plasma potassium.

Pharmacodynamics: ADVAIR HFA Inhalation Aerosol: Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four 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 to 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. The potential effect of salmeterol on the effects of fluticasone propionate on the hypothalamic-pituitary-adrenal (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.

In clinical studies with ADVAIR HFA in patients 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 adolescent and adult 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.

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 (see CLINICAL TRIALS: Studies Comparing ADVAIR HFA to Fluticasone Propionate Alone or Salmeterol Alone: Study 3) in 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. 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 (see CLINICAL TRIALS: Studies Comparing ADVAIR HFA to Fluticasone Propionate Alone or Salmeterol Alone: Study 4) in 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). The geometric mean ratio of 24-hour urinary cortisol excretion at week 12 compared with baseline was 0.9 for all 3 treatment groups.

**Fluticasone Propionate:** In clinical trials with fluticasone propionate inhalation powder using doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL) 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 in 64 patients with mild, persistent asthma (mean FEV1 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.

**Salmeterol Xinafoate:** Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium in some patients (see PRECAUTIONS). 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 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.

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 significance of these findings is unknown.

CLINICAL TRIALS
ADVAIR HFA has been studied in patients with asthma 12 years of age and older. ADVAIR HFA has not been studied in patients under 12 years of age or in patients with COPD. In clinical trials comparing ADVAIR HFA Inhalation Aerosol with the 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.

Studies Comparing ADVAIR HFA to Fluticasone Propionate Alone or Salmeterol Alone: Four (4) double-blind, parallel-group clinical trials were conducted with ADVAIR HFA in 1,517 adolescent and adult patients (≥12 years, mean baseline forced expiratory volume in 1 second [FEV₁] 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.

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 FEV₁ 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 FEV₁ 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 FEV₁ or peak expiratory flow (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 1, 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 to fluticasone propionate 44 mcg; however, the difference was not statistically significant.

**Table 1. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously Treated With Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)**

<table>
<thead>
<tr>
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<th>Fluticasone Propionate CFC Inhalation Aerosol 44 mcg (n = 92)</th>
<th>Salmeterol CFC Inhalation Aerosol 21 mcg (n = 92)</th>
<th>Placebo HFA Inhalation Aerosol (n = 87)</th>
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<tr>
<td>ADVAIR HFA 45/21</td>
<td>2%</td>
<td>8%</td>
<td>25%</td>
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</table>

The FEV₁ results are displayed in Figure 1. Because this trial used predetermined criteria for worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV₁ results at Endpoint (last available FEV₁ result) are also provided. Patients receiving ADVAIR HFA 45/21 had significantly greater improvements in FEV₁ (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 FEV₁ with ADVAIR HFA 45/21 were achieved regardless of baseline asthma therapy (albuterol alone, salmeterol, or inhaled corticosteroids).
Figure 1. 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)

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 2.
Table 2. Secondary Efficacy Variable Results for Patients Previously Treated With Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)

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

*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 to 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 FEV₁. Baseline FEV₁ 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%).

**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 to salmeterol (24%) and placebo (54%). Fewer patients receiving ADVAIR HFA 115/21 were withdrawn due to worsening asthma (7%) compared to 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 2, 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.
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 beta2-agonists alone (n = 42), salmeterol (n = 91), or inhaled corticosteroids (n = 277). Patients treated with short-acting beta2-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 FEV1 measurements ranged from 2.3 to 2.6 L.

Improvements in FEV1 (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.

Onset of Action and Progression of Improvement in Asthma Control: 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 FEV₁) in most patients was seen within 30 to 60 minutes. Maximum improvement in FEV₁ occurred within 4 hours, and clinically significant improvement was maintained for 12 hours (see Figure 3).

Following the initial dose, predose FEV₁ 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 3 and 4) or ADVAIR HFA 230/21 as assessed by FEV₁ following 12 weeks of therapy.

**Figure 3. Percent Change in Serial 12-Hour FEV₁ in Patients Previously Using Either Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)**

![Graph showing percent change in serial 12-hour FEV₁ over time for different treatments.](image)

- ADVAIR HFA 45/21 2 inhalations twice daily (n = 92)
- Fluticasone propionate inhalation aerosol 44 mcg 2 inhalations twice daily (n = 89)
- Salmeterol inhalation aerosol 21 mcg 2 inhalations twice daily (n = 92)
- Placebo (n = 87)
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.

**INDICATIONS AND USAGE**

ADVAIR HFA is indicated for the long-term, twice-daily maintenance treatment of asthma in patients 12 years of age and older.

Long-acting beta2-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2
maintenance therapies. ADVAIR HFA is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta2-agonists.

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

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

Hypersensitivity to any of the ingredients of these preparations contraindicates their use.

WARNINGS
Long-acting beta2-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies.

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 long-acting beta2-agonist–naive patients with asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared to 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 patients treated with salmeterol than those treated with placebo (0.10% vs. 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% vs. 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% vs. 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 beta2-agonists, it is possible that the findings seen in the SMART study represent a class effect.
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 asthma-controller therapy modifies the risk of asthma-related death.

Table 3: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol (n, %)</th>
<th>Placebo (n, %)</th>
<th>Relative Risk† (95% Confidence Interval)</th>
<th>Excess Deaths Expressed per 10,000 Patients‡ (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Population§</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Salmeterol: N = 13,176</td>
<td>13 (0.10%)</td>
<td>3 (0.02%)</td>
<td>4.37 (1.25, 15.34)</td>
<td>8 (3, 13)</td>
</tr>
<tr>
<td>Placebo: N = 13,179</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Caucasian</strong></td>
<td></td>
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<tr>
<td>Salmeterol: N = 9,281</td>
<td>6 (0.07%)</td>
<td>1 (0.01%)</td>
<td>5.82 (0.70, 48.37)</td>
<td>6 (1, 10)</td>
</tr>
<tr>
<td>Placebo: N = 9,361</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>African American</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol: N = 2,366</td>
<td>7 (0.31%)</td>
<td>1 (0.04%)</td>
<td>7.26 (0.89, 58.94)</td>
<td>27 (8, 46)</td>
</tr>
<tr>
<td>Placebo: N = 2,319</td>
<td></td>
<td></td>
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</tbody>
</table>

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

The following additional WARNINGS about ADVAIR HFA should be noted.

1. ADVAIR HFA should not be initiated in patients during rapidly deteriorating or potentially
life-threatening episodes of asthma. Serious acute respiratory events, including fatalities, have
been reported both in the United States and worldwide 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, or previous life-threatening acute asthma
exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g.,
unresponsive to usual medications; increasing need for inhaled, short-acting beta2-agonists;
increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency
room visits; sudden or progressive deterioration in pulmonary function). However, they 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.

2. ADVAIR HFA should not be used to treat acute symptoms. An inhaled, short-acting
beta2-agonist, not ADVAIR HFA, should be used to relieve acute symptoms of shortness of
breath. When prescribing ADVAIR HFA, the physician must also provide the patient with an
inhaled, short-acting beta2-agonist (e.g., albuterol) for treatment of shortness of breath that
occurs acutely, 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 beta2-agonists on a regular basis (e.g., 4 times a day) should be instructed to
discontinue the regular use of these drugs. For patients taking ADVAIR HFA, inhaled,
short-acting beta2-agonists should only be used for symptomatic relief of acute symptoms of
shortness of breath (see PRECAUTIONS: Information for Patients).

3. Increasing use of inhaled, short-acting beta2-agonists is a marker of deteriorating asthma. The
physician and patient should be alert to such changes. The patient’s condition may deteriorate
acutely over a period of hours or chronically over several days or longer. If the patient’s inhaled,
short-acting beta2-agonist becomes less effective, the patient needs more inhalations than usual,
or the patient develops a significant decrease in lung function, this may be a marker of
destabilization of the disease. In this setting, 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.

4. ADVAIR HFA should not be used for transferring patients from systemic corticosteroid
therapy. Particular care is needed for patients who have been transferred from systemically active
corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have
occurred in patients with asthma during and after transfer from systemic corticosteroids to less
systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

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

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

5. **ADVAIR HFA should not be used in conjunction with an inhaled, long-acting beta2-agonist.** Patients who are receiving ADVAIR HFA twice daily should not use additional salmeterol or other long-acting beta2-agonists (e.g., formoterol) for prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma. Additional benefit would not be gained from using supplemental salmeterol or formoterol for prevention of EIB since ADVAIR HFA already contains an inhaled, long-acting beta2-agonist.

6. **The recommended dosage should not be exceeded.** ADVAIR HFA should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. 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.

7. **Paradoxical bronchospasm.** As with other inhaled asthma 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.

8. **Immediate hypersensitivity reactions.** Immediate hypersensitivity reactions may occur after administration of ADVAIR HFA, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

9. **Upper airway symptoms.** Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving fluticasone propionate and salmeterol, components of ADVAIR HFA.

10. **Cardiovascular disorders.** 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. 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.

11. Discontinuation of systemic corticosteroids. Transfer of patients from systemic corticosteroid therapy to ADVAIR HFA may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

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


Fluticasone Propionate: A drug interaction study in healthy subjects has shown that ritonavir (a strong cytochrome P450 3A4 inhibitor) can significantly increase systemic fluticasone propionate exposure (AUC), resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Fluticasone Propionate: Drug Interactions and PRECAUTIONS: Drug Interactions: Inhibitors of Cytochrome P450). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Salmeterol: Because of the potential for drug interactions and the potential for increased risk of cardiovascular adverse events, the concomitant use of ADVAIR HFA with strong CYP 3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Salmeterol Xinafoate: Drug Interactions).
PRECAUTIONS

General: Cardiovascular Effects: Cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of salmeterol, a component of ADVAIR HFA, and may require discontinuation of ADVAIR HFA. ADVAIR HFA, like all medications containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in ECGs have been seen infrequently in individual patients in controlled clinical studies with ADVAIR HFA and salmeterol. Clinically significant changes in systolic and/or diastolic blood pressure and pulse rate have been seen infrequently in individual patients in controlled clinical studies with salmeterol, a component of ADVAIR HFA.

Metabolic and Other Effects: Long-term use of orally inhaled corticosteroids may affect normal bone metabolism, resulting in a loss of bone mineral density. In patients with major risk factors for decreased bone mineral content, such as tobacco use, advanced age, sedentary lifestyle, poor nutrition, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), ADVAIR HFA may pose an additional risk.

Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. 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.

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

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 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.

A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from the therapeutic use of corticosteroids, including inhaled corticosteroids (see PRECAUTIONS: Pediatric Use). The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known. Patients should be maintained on the lowest strength of ADVAIR HFA that effectively controls their asthma.

The long-term effects of ADVAIR HFA in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients received inhaled fluticasone propionate on a continuous basis in a clinical study for up to 4 years. In clinical studies with patients treated for 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients following the long-term administration of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR HFA.

Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids, including fluticasone propionate, a component of ADVAIR HFA.

In clinical studies with ADVAIR HFA, the development of localized infections of the pharynx with Candida albicans has occurred. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on treatment with ADVAIR HFA, but at times therapy with ADVAIR HFA may need to be interrupted.

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.

**Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a component of ADVAIR HFA, may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not
always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see ADVERSE REACTIONS: Observed During Clinical Practice: Eosinophilic Conditions).

**Information for Patients:** Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document.

Patients being treated with ADVAIR HFA should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. It is important that patients understand how to use ADVAIR HFA in relation to other asthma medications they are taking.

1. **Patients should be informed that salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death.** They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other component of ADVAIR HFA, or other asthma-controller therapy modifies this risk.

2. 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 beta2-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient in how it should be used).

3. The physician should be notified immediately if any of the following signs of seriously worsening asthma occur:
   - decreasing effectiveness of inhaled, short-acting beta2-agonists;
   - need for more inhalations than usual of inhaled, short-acting beta2-agonists;
   - significant decrease in lung function as outlined by the physician.

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

5. Patients should be cautioned regarding common adverse effects associated with beta2-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

6. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR HFA, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.

7. When patients are prescribed ADVAIR HFA, other medications for asthma should be used only as directed by the physician.

8. Patients who are pregnant or nursing should contact the physician about the use of ADVAIR HFA.
9. Patients should use ADVAIR HFA at regular intervals as directed. Results of clinical trials indicated significant improvement may occur within the first 30 minutes of taking the first dose; however, the full benefit may not be achieved until treatment has been administered for 1 week or longer. The patient should not use more than the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

10. The bronchodilation from a single dose of ADVAIR HFA may last up to 12 hours or longer. The recommended dosage (2 inhalations twice daily, morning and evening) should not be exceeded. Patients who are receiving ADVAIR HFA twice daily should not use salmeterol or other inhaled, long-acting beta2-agonists (e.g., formoterol) for prevention of EIB or maintenance treatment of asthma.

11. Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult the physician without delay.

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

13. After inhalation, rinse the mouth with water and spit out. Do not swallow.

14. Clean the inhaler at least once a week after the evening dose. Keeping the canister and plastic actuator clean is important to prevent medicine buildup. (See Instructions for Using ADVAIR HFA in the Medication Guide accompanying the product.)

15. Use ADVAIR HFA only with the actuator supplied with the product. Discard the inhaler after 120 sprays have been used.

16. Patients should never immerse the canister into water to determine the amount remaining in the canister (“float test”).

17. For the proper use of ADVAIR HFA and to attain maximum improvement, the patient should read and carefully follow the Instructions for Using ADVAIR HFA in the Medication Guide accompanying the product.

**Drug Interactions:** ADVAIR HFA has been used concomitantly with other drugs, including short-acting beta2-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma, without adverse drug reactions. No formal drug interaction studies have been performed with ADVAIR HFA.

**Short-Acting Beta2-Agonists:** In three 12-week US clinical trials, the mean daily need for additional beta2-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 events 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 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).

**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.

**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 asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

**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, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

**Inhibitors of Cytochrome P450:** Fluticasone propionate and salmeterol are substrates of cytochrome P450 3A4.

**Fluticasone propionate:** A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Fluticasone Propionate: Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing’s syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased systemic fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.
**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 beta2-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. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Salmeterol Xinafoate: Drug Interactions).

**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 4 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis) for 104 weeks. Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

**Salmeterol:** In an 18-month oral carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 10 times the maximum recommended human daily inhalation dose based on comparison of the AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (approximately 2 times the maximum recommended human daily inhalation dose in 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 65 times the maximum recommended human daily inhalation dose on a mg/m^2 basis). No tumors were seen at 0.21 mg/kg (approximately 20 times the maximum recommended human daily inhalation dose 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 male and female rats treated...
with salmeterol at oral doses up to 2 mg/kg (approximately 190 times the maximum recommended human daily inhalation dose on a mg/m² basis).

**Pregnancy: Teratogenic Effects: ADVAIR HFA Inhalation Aerosol:** Pregnancy Category C. From the reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using combinations of fluticasone propionate and salmeterol compared to toxicity data from the components administered separately. In mice combining 150 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 480 times the maximum recommended human daily inhalation dose on a mcg/m² basis) were teratogenic. Cleft palate, fetal death, increased implantation loss and delayed ossification was seen. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) and up to 1.4 mg/kg orally of salmeterol (approximately 70 times the maximum recommended human daily inhalation dose on a mg/m² basis). In rats, no teratogenicity was observed at combination doses up to 30 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) and up to 1 mg/kg of salmeterol (approximately 95 times the maximum recommended human daily inhalation dose on a mg/m² basis). Combining 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum recommended human daily inhalation dose on a mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 970 times the maximum recommended human daily inhalation dose on a mg/m² basis) produced maternal toxicity, decreased placental weight, decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone.

There are no adequate and well-controlled studies with ADVAIR HFA in pregnant women. ADVAIR HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Fluticasone Propionate:** Pregnancy Category C. Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively (less than and equivalent to, respectively, the maximum recommended human daily inhalation dose on a mcg/m² basis), revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification. No teratogenicity was seen in the rat at inhalation doses up to 68.7 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis).

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 5 times the maximum recommended human daily inhalation dose on mcg/m² basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Fluticasone Propionate: Absorption).
Fluticasone propionate crossed the placenta following administration of a subcutaneous dose of 100 mcg/kg to mice (less than the maximum recommended human daily inhalation dose on a mcg/m² basis), a subcutaneous or an oral dose of 100 mcg/kg to rats (equivalent to the maximum recommended human daily inhalation dose on a mcg/m² basis), and an oral dose of 300 mcg/kg to rabbits (approximately 5 times the maximum recommended human daily inhalation dose on a mcg/m² basis).

There are no adequate and well-controlled studies in pregnant women. ADVAIR HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

**Salmeterol:** Pregnancy Category C. No teratogenic effects occurred in the rat at oral doses up to 2 mg/kg (approximately 190 times the maximum recommended human daily inhalation dose on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 25 times the maximum recommended human daily inhalation dose based on the comparison of the AUCs), 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 significant effects occurred at an oral dose of 0.6 mg/kg (approximately 10 times the maximum recommended human daily inhalation dose based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at an oral dose of 10 mg/kg (approximately 1,900 times the maximum recommended human daily inhalation dose on a mg/m² basis). 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 of 10 mg/kg to mice and rats (approximately 480 and 970 times, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis).

There are no adequate and well-controlled studies with salmeterol in pregnant women.

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

**Use in 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 for management of asthma during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

**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, a component of ADVAIR HFA, is excreted in human breast milk.
However, other corticosteroids have been detected in human milk. Subcutaneous administration
to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the maximum
recommended human daily inhalation dose on a mcg/m² basis) resulted in measurable
radioactivity in milk.
Since there are no data from controlled trials on the use of ADVAIR HFA by nursing mothers,
a decision should be made whether to discontinue nursing or to discontinue ADVAIR HFA,
taking into account the importance of ADVAIR HFA to the mother.
Caution should be exercised when ADVAIR HFA is administered to a nursing woman.

**Pediatric Use:** Thirty-eight (38) patients 12 to 17 years of age were treated with ADVAIR
HFA in US pivotal clinical trials. Patients in this age-group demonstrated efficacy results similar
to those observed in patients 18 years of age and older. There were no obvious differences in the
type or frequency of adverse events reported in this age-group compared with patients 18 years
of age and older.
The safety and effectiveness of ADVAIR HFA in children under 12 years have not been
established.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in
growth in pediatric patients. In these studies, the mean reduction in growth velocity was
approximately 1 cm/year (range, 0.3 to 1.8 cm/year) and appears to depend upon dose and
duration of exposure. This effect was observed in the absence of laboratory evidence of HPA
axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic
corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis
function. The long-term effects of this reduction in growth velocity associated with orally
inhaled corticosteroids, including the impact on final adult height, are unknown. The potential
for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids
has not been adequately studied. The effects on growth velocity of treatment with orally inhaled
corticosteroids for over 1 year, including the impact on final adult height, are unknown. The
growth of children and adolescents receiving orally inhaled corticosteroids, including ADVAIR
HFA, should be monitored. 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 and the risks associated with alternative therapies. 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 (see
DOSAGE AND ADMINISTRATION).

**Geriatric Use:** Of the total number of patients in clinical studies treated with ADVAIR HFA,
41 were 65 years of age or older and 21 were 75 years of age or older. No overall differences in
safety were observed between these patients and younger patients, and other reported clinical
experience, including studies of the individual components, has not identified differences in
responses between the elderly and younger patients, but greater sensitivity of some older
individuals cannot be ruled out. As with other products containing beta2-agonists, special caution
should be observed when using ADVAIR HFA in geriatric patients who have concomitant
cardiovascular disease that could be adversely affected by beta2-agonists. Based on available
data for ADVAIR HFA or its active components, no adjustment of dosage of ADVAIR HFA in
geriatric patients is warranted.

ADVERSE REACTIONS

Long-acting beta2-adrenergic agonists, such as salmeterol, may 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). Salmeterol is a component of ADVAIR HFA. However, the data from this
study are not adequate to determine whether concurrent use of inhaled corticosteroids,
such as fluticasone propionate, the other component of ADVAIR HFA, or other asthma
controller therapy modifies the risk of asthma-related death.

The incidence of common adverse events in Table 4 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 adolescent and adult 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 CFC inhalation aerosol (44- or 110-mcg doses), salmeterol CFC inhalation aerosol
21 mcg, or placebo HFA inhalation aerosol.

Table 4. Overall Adverse Events With ≥3% Incidence in US Controlled Clinical Trials
With ADVAIR HFA Inhalation Aerosol in Patients With Asthma

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>ADVAIR HFA 45/21 (n = 187)</th>
<th>ADVAIR HFA 115/21 (n = 94)</th>
<th>Fluticasone Propionate CFC Inhalation Aerosol 44 mcg (n = 186)</th>
<th>Fluticasone Propionate CFC Inhalation Aerosol 110 mcg (n = 91)</th>
<th>Salmeterol CFC Inhalation Aerosol 21 mcg (n = 274)</th>
<th>Placebo HFA Inhalation Aerosol (n = 176)</th>
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<tbody>
<tr>
<td>Ear, nose, &amp; throat</td>
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<td>12</td>
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<td>Medical Condition</td>
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<td>Lower respiratory</td>
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<td>Intoxication &amp; hangover</td>
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<td>Average duration of exposure (days)</td>
<td>81.3</td>
<td>78.6</td>
<td>79.9</td>
<td>74.6</td>
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</table>

Table 4 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in any of the groups receiving ADVAIR HFA and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account. These adverse reactions were mostly mild to moderate in severity.

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

**Cardiovascular:** Tachycardia, arrhythmias, myocardial infarction.

**Drug Interaction, Overdose, and Trauma:** Postoperative complications, wounds and lacerations, soft tissue injuries, poisoning and toxicity, pressure-induced disorder.
**Ear, Nose, and Throat:** Ear, nose, and throat infection; ear signs and symptoms; rhinorrhea/postnasal drip; epistaxis; nasal congestion/blockage; laryngitis; unspecified oropharyngeal plaques; dryness of nose.

**Endocrine and Metabolic:** Weight gain.

**Eye:** Allergic eye disorders, eye edema and swelling.

**Gastrointestinal:** Gastrointestinal discomfort and pain, dental discomfort and pain, candidiasis mouth/throat, hyposalivation, gastrointestinal infections, disorders of hard tissue of teeth, hemorrhoids, gastrointestinal gaseous symptoms, abdominal discomfort and pain, constipation, oral abnormalities.

**Musculoskeletal:** Arthralgia and articular rheumatism, muscle cramps and spasms, musculoskeletal inflammation, bone and skeletal pain.

**Neurology:** Sleep disorders, migraines.

**Non-Site Specific:** Allergies and allergic reactions, viral infections, bacterial infections, candidiasis unspecified site, congestion, inflammation.

**Reproduction:** Bacterial reproductive infections.

**Respiratory:** Lower respiratory signs and symptoms, lower respiratory infections, lower respiratory hemorrhage.

**Skin:** Eczema, dermatitis and dermatosis.

**Urology:** Urinary infections.

**Observed During Clinical Practice:** In addition to adverse events reported from clinical trials, the following events have been identified during worldwide use of any formulation of ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to ADVAIR, fluticasone propionate, and/or salmeterol or a combination of these factors.

In extensive US and worldwide postmarketing experience with salmeterol, a component of ADVAIR HFA, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also occurred in a few patients with less severe asthma. It was not possible from these reports to determine whether salmeterol contributed to these events.
**Cardiovascular:** Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular tachycardia), hypertension, ventricular tachycardia.

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

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

**Eye:** Cataracts, glaucoma.

**Gastrointestinal:** Dyspepsia, xerostomia.

**Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

**Musculoskeletal:** Back pain, myositis.

**Neurology:** Paresthesia, restlessness.

**Non-Site Specific:** Fever, immediate and delayed hypersensitivity reaction, 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; stridor; choking.

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

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

**Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a component of ADVAIR HFA, may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. While ADVAIR HFA should not be used for transferring patients from systemic corticosteroid therapy, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see PRECAUTIONS: General: *Eosinophilic Conditions*).

**OVERDOSAGE**

**ADVAIR HFA Inhalation Aerosol:** No deaths occurred in rats given a single-dose combination of salmeterol 3.6 mg/kg and fluticasone propionate 1.9 mg/kg given as the inhalation powder (approximately 290 and 15 times, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis).
**Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in signs/symptoms of hypercorticism (see PRECAUTIONS: General: Metabolic and Other Effects). 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 were well tolerated. Fluticasone propionate given by inhalation aerosol at doses 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. In mice the oral median lethal dose was >1,000 mg/kg (>4,400 times the maximum recommended human daily inhalation dose on a mg/m² basis). In rats the subcutaneous median lethal dose was >1,000 mg/kg (>8,800 times the maximum recommended human daily inhalation dose on a mg/m² basis).

**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 signs and symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. 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 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. No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg (approximately 280 times the maximum recommended human daily inhalation dose on a mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 230 times the maximum recommended human daily inhalation dose on a mg/m² basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 7,200 times the maximum recommended human daily inhalation dose on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 97,000 times the maximum recommended human daily inhalation dose on a mg/m² basis).
DOSAGE AND ADMINISTRATION

ADVAIR HFA should be administered by the orally inhaled route only in patients 12 years of age and older. ADVAIR HFA should not be used for transferring patients from systemic corticosteroid therapy. ADVAIR HFA has not been studied in patients under 12 years of age or in patients with COPD.

Long-acting beta-2-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR HFA, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. ADVAIR HFA is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta2-agonists.

ADVAIR HFA is available in 3 strengths, ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR HFA 115/21 Inhalation Aerosol, and ADVAIR HFA 230/21 Inhalation Aerosol, containing 45, 115, and 230 mcg of fluticasone propionate, respectively, and 21 mcg of salmeterol per inhalation.

ADVAIR HFA should be administered as 2 inhalations twice daily every day. More frequent administration (more than twice daily) 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. The safety and efficacy of ADVAIR HFA when administered in excess of recommended doses have not been established.

If symptoms arise in the period between doses, an inhaled, short-acting beta2-agonist should be taken for immediate relief.

Patients who are receiving ADVAIR HFA twice daily should not use additional salmeterol or other inhaled, long-acting beta2-agonists (e.g., formoterol) for prevention of EIB or for any other reason.

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

The recommended starting dosages for ADVAIR HFA are based upon patients’ current asthma therapy.

- For patients not adequately controlled on an inhaled corticosteroid, Table 5 provides the recommended starting dosage.
- For patients not currently on inhaled corticosteroids, whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, the recommended starting dosage is 2 inhalations of ADVAIR HFA 45/21 or ADVAIR HFA 115/21 twice daily (see INDICATIONS AND USAGE).

The maximum recommended dosage is 2 inhalations of ADVAIR HFA 230/21 twice daily.
For all patients it is desirable to titrate to the lowest effective strength after adequate asthma stability is achieved.

### Table 5. Recommended Dosages of ADVAIR HFA Inhalation Aerosol for Patients Not Adequately Controlled on Inhaled Corticosteroids

<table>
<thead>
<tr>
<th>Current Daily Dose of Inhaled Corticosteroid</th>
<th>Recommended Strength of ADVAIR HFA (2 inhalations twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate HFA inhalation aerosol</td>
<td></td>
</tr>
<tr>
<td>≤160 mcg</td>
<td>45/21</td>
</tr>
<tr>
<td>320 mcg</td>
<td>115/21</td>
</tr>
<tr>
<td>640 mcg</td>
<td>230/21</td>
</tr>
<tr>
<td>Budesonide inhalation powder</td>
<td>≤400 mcg</td>
</tr>
<tr>
<td>800-1,200 mcg</td>
<td>45/21</td>
</tr>
<tr>
<td>1,600 mcg *</td>
<td>115/21</td>
</tr>
<tr>
<td>230/21</td>
<td></td>
</tr>
<tr>
<td>Flunisolide CFC inhalation aerosol</td>
<td>≤1,000 mcg</td>
</tr>
<tr>
<td>1,250-2,000 mcg</td>
<td>45/21</td>
</tr>
<tr>
<td>Flunisolide HFA inhalation aerosol</td>
<td>≤320 mcg</td>
</tr>
<tr>
<td>640 mcg</td>
<td>45/21</td>
</tr>
<tr>
<td>Fluticasone propionate HFA inhalation aerosol</td>
<td>≤176 mcg</td>
</tr>
<tr>
<td>440 mcg</td>
<td>45/21</td>
</tr>
<tr>
<td>660-880 mcg *</td>
<td>115/21</td>
</tr>
<tr>
<td>Fluticasone propionate inhalation powder</td>
<td>≤200 mcg</td>
</tr>
<tr>
<td>500 mcg</td>
<td>45/21</td>
</tr>
<tr>
<td>1,000 mcg *</td>
<td>115/21</td>
</tr>
<tr>
<td>Mometasone furoate inhalation powder</td>
<td>220 mcg</td>
</tr>
<tr>
<td>440 mcg</td>
<td>45/21</td>
</tr>
<tr>
<td>880 mcg</td>
<td>115/21</td>
</tr>
<tr>
<td>Triamcinolone acetonide inhalation aerosol</td>
<td>≤1,000 mcg</td>
</tr>
<tr>
<td>1,100-1,600 mcg</td>
<td>45/21</td>
</tr>
</tbody>
</table>

* ADVAIR HFA should not be used for transferring patients from systemic corticosteroid therapy.

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, or 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 shaking well before each spray and releasing 2 test sprays into the air, away from the face.

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

**HOW SUPPLIED**

Each strength of ADVAIR HFA Inhalation Aerosol is supplied in a 12-g pressurized aluminum canister containing 120 metered inhalations in a box of 1.* Each canister is supplied with a purple actuator with a light purple strapcap and is 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.

*NDC 0173-0715-00  ADVAIR HFA 45/21 Inhalation Aerosol
*NDC 0173-0716-00  ADVAIR HFA 115/21 Inhalation Aerosol
*NDC 0173-0717-00  ADVAIR HFA 230/21 Inhalation Aerosol

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 inhalation cannot be assured after 120 inhalations, even though the canister is not completely empty and will continue to operate. The inhaler should be discarded when 120 actuations have been used. Never immerse the canister into water to determine the amount remaining in the canister ("float test").

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.

ADVAIR HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.
MEDICATION GUIDE

ADVAIR® HFA \textit{[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 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 contains 2 medicines:
  - fluticasone propionate (the same medicine found in FLOVENT®), an inhaled
corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the
lungs. Inflammation in the lungs can lead to asthma symptoms.
  - salmeterol (the same medicine found in SEREVENT®), a long-acting beta₂-agonist
medicine or LABA. LABA medicines are used in patients with asthma. 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.
• In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in ADVAIR HFA), may increase the chance of death from asthma problems. In a large asthma study, more patients who used salmeterol died from asthma problems compared with patients who did not use salmeterol. It is not known whether fluticasone propionate, the other medicine in ADVAIR HFA, changes your chance of death from asthma problems seen with salmeterol. Talk with your healthcare provider about this risk and the benefits of treating your asthma with ADVAIR HFA.

• ADVAIR HFA does not relieve sudden symptoms. Always have a short-acting beta2-agonist medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.

• Do not stop using ADVAIR HFA unless told to do so by your healthcare provider because your symptoms might get worse.

• ADVAIR HFA should be used only if your healthcare provider decides that another asthma-controller medicine alone does not control your asthma or that you need 2 asthma-controller medicines.

• 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 short-acting beta2-agonist medicine, but it does not relieve your breathing problems.

What is ADVAIR HFA?
ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate (the same medicine found in FLOVENT) and a long-acting beta2-agonist medicine, salmeterol (the same medicine found in SEREVENT). ADVAIR HFA is used for asthma as follows:

ADVAIR HFA is used long term, twice a day to control symptoms of asthma, and prevent symptoms such as wheezing in adolescents and adults 12 years of age and older.

ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). Because LABA medicines, such as salmeterol, may increase the chance of death from asthma problems, ADVAIR HFA is not for adults and children with asthma who:
• are well controlled with another asthma-controller medicine, such as a low to medium
dose of an inhaled corticosteroid medicine
• only need short-acting beta₂-agonist medicines once in awhile

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
• 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.

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 the 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 will prescribe the
one that is best for your condition.
• The usual dosage of ADVAIR HFA is 2 inhalations twice a day (morning and evening). The 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR HFA.

• 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 twice a day, do not use other medicines that contain a long-acting beta2-agonist or LABA for any reason. Other LABA-containing medicines include ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder), SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder), FORADIL® AEROLIZER® (formoterol fumarate inhalation powder), SYMBICORT® (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol, PERFOROMIST™ (formoterol fumarate) Inhalation Solution, and BROVANA™ (arformoterol tartrate) Inhalation Solution.

• Do not change or stop any of your medicines used to control or treat your breathing problems. Your healthcare provider will adjust your medicines as needed.

• Make sure you always have a short-acting beta2-agonist medicine with you. Use your short-acting beta2-agonist medicine if you have breathing problems between doses of ADVAIR HFA.

• Call your healthcare provider or get medical care right away if:
  • your breathing problems worsen with ADVAIR HFA
  • you need to use your short-acting beta2-agonist medicine more often than usual
  • your short-acting beta2-agonist medicine does not work as well for you at relieving symptoms
  • you need to use 4 or more inhalations of your short-acting beta2-agonist medicine for 2 or more days in a row
  • you use 1 whole canister of your short-acting beta2-agonist medicine in 8 weeks’ time
  • your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  • you have asthma and your symptoms do not improve after using ADVAIR HFA regularly for 1 week

What are the possible side effects with ADVAIR HFA?
• ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). In patients with asthma, LABA medicines, such as salmeterol, may increase the chance of
death from asthma problems. See “What is the most important information I should know about ADVAIR HFA?”

Other possible side effects with ADVAIR HFA include:

- serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue; and breathing problems. Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.
- increased blood pressure
- a fast and irregular heartbeat
- chest pain
- headache
- tremor
- nervousness
- immune system effects and a higher chance for infections
- lower bone mineral density. This may be a problem for people who already have a higher chance for 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 irritation

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 with the mouthpiece down.
- Do not puncture the canister. Do not use or store ADVAIR HFA near heat or an open flame. Never throw it into a fire or 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. It may harm them.
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.

Instructions for Using Your ADVAIR HFA

Follow the instructions below for using your ADVAIR HFA.

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

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

The purple actuator that comes with ADVAIR HFA should not be used with any other product canisters. Actuators that come with other products should not be used with an ADVAIR HFA canister.

Prime the inhaler before using it for the first time. To prime the inhaler, shake it well for 5 seconds. Then spray it 1 time into the air away from your face. Shake and spray the inhaler like this 3 more times to finish priming it. Avoid spraying in eyes.

If you have not used your inhaler in more than 4 weeks or if you have dropped it, shake it well for 5 seconds and spray it 2 times into the air away from your face.

Shake the inhaler well for 5 seconds just before each use.

1. Take the cap off the mouthpiece (see Figure 1). The strap on the cap will stay attached to the actuator.

   Look for foreign objects inside the inhaler before each use, especially if the strap is no longer attached to the actuator or if the cap is not being used to cover the mouthpiece.

   Make sure the canister is fully and firmly inserted into the actuator.

Shake the inhaler well for 5 seconds right before each use.
2. **Breathe out fully through your mouth**, pushing as much air out of your lungs as you can.

   Put the mouthpiece all the way into your mouth. Hold the inhaler with the mouthpiece down (see Figure 1). Close your lips around it.

3. It is important to get the medicine in the spray into your lungs where it works. To do this, you need to **inhale the spray at the same time you take in a slow, deep breath**.

   So, just after starting to take in a slow, deep breath through your mouth, press down firmly on the top of the metal canister (see Figure 2) and keep breathing in through your mouth.

   Take your finger off the canister after the spray comes out of the canister. Take the mouthpiece out of your mouth after you have finished breathing in.

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 again. Repeat steps 2 through 4.

6. **Put the cap back on the mouthpiece after each time you use the inhaler**.

7. After you finish taking this medicine, rinse your mouth with water. Spit out the water. Do not swallow it.
8. Never put the canister in water to find out how much medicine is left in the canister ("float test").

9. You should keep track of the number of inhalations used from your inhaler. **Then throw away the inhaler after you have used 120 inhalations.** Even though the canister might not be empty and will keep spraying, you might not get the right amount of medicine in each inhalation.

Before you get to 120 inhalations, ask your doctor if you need to refill your prescription. **Do not** use after the expiration date, which is shown as “EXP” on the product label and box.

**Cleaning your ADVAIR HFA Inhalation Aerosol:**

Clean the inhaler at least once a week after your evening dose. Keeping the canister and plastic actuator clean is important to prevent medicine buildup.

Step 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.

Step 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 3). Then wipe the inside of the mouthpiece with a clean tissue dampened with water. Let the actuator air-dry overnight.

![Figure 3](image)

Step 3. Put the mouthpiece cover back on after the actuator has dried.

Rx only

GlaxoSmithKline

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Research Triangle Park, NC 27709

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Month Year

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

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 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 contains 2 medicines:
  • fluticasone propionate (the same medicine found in FLOVENT®), an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
  • salmeterol (the same medicine found in SEREVENT®), a long-acting beta2-agonist medicine or LABA. LABA medicines are used in patients with asthma. 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.

- In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in ADVAIR HFA), may increase the chance of death from asthma problems. In a large asthma study, more patients who used salmeterol died from asthma problems compared with patients who did not use salmeterol. It is not known whether fluticasone propionate, the other medicine in ADVAIR HFA, changes your chance of death from asthma problems seen with salmeterol. Talk with your healthcare provider about this risk and the benefits of treating your asthma with ADVAIR HFA.

- ADVAIR HFA does not relieve sudden symptoms. Always have a short-acting beta<sub>2</sub>-agonist medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.

- Do not stop using ADVAIR HFA unless told to do so by your healthcare provider because your symptoms might get worse.

- ADVAIR HFA should be used only if your healthcare provider decides that another asthma-controller medicine alone does not control your asthma or that you need 2 asthma-controller medicines.

- 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 short-acting beta<sub>2</sub>-agonist medicine, but it does not relieve your breathing problems.

What is ADVAIR HFA?

ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate (the same medicine found in FLOVENT) and a long-acting beta<sub>2</sub>-agonist medicine, salmeterol (the same medicine found in SEREVENT). ADVAIR HFA is used for asthma as follows:

ADVAIR HFA is used long term, twice a day to control symptoms of asthma, and prevent symptoms such as wheezing in adolescents and adults 12 years of age and older.
ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). Because LABA medicines, such as salmeterol, may increase the chance of death from asthma problems, ADVAIR HFA is not for adults and children with asthma who:

- are well controlled with another asthma-controller medicine, such as a low to medium dose of an inhaled corticosteroid medicine
- only need short-acting beta₂-agonist medicines once in awhile

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
- 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.

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 the 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 will prescribe the one that is best for your condition.

• The usual dosage of ADVAIR HFA is 2 inhalations twice a day (morning and evening). The 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR HFA.

• 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 twice a day, do not use other medicines that contain a long-acting beta2-agonist or LABA for any reason.** Other LABA-containing medicines include ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder), SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder), FORADIL® AEROLIZER® (formoterol fumarate inhalation powder), SYMBICORT® (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol, PERFOROMIST™ (formoterol fumarate) Inhalation Solution, and BROVANA™ (arformoterol tartrate) Inhalation Solution.

• Do not change or stop any of your medicines used to control or treat your breathing problems. Your healthcare provider will adjust your medicines as needed.

• Make sure you always have a short-acting beta2-agonist medicine with you. Use your short-acting beta2-agonist medicine if you have breathing problems between doses of ADVAIR HFA.

• **Call your healthcare provider or get medical care right away if:**
  • your breathing problems worsen with ADVAIR HFA
  • you need to use your short-acting beta2-agonist medicine more often than usual
  • your short-acting beta2-agonist medicine does not work as well for you at relieving symptoms
  • you need to use 4 or more inhalations of your short-acting beta2-agonist medicine for 2 or more days in a row
  • you use 1 whole canister of your short-acting beta2-agonist medicine in 8 weeks’ time
  • your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  • you have asthma and your symptoms do not improve after using ADVAIR HFA regularly for 1 week
What are the possible side effects with ADVAIR HFA?

- ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). In patients with asthma, LABA medicines, such as salmeterol, may increase the chance of death from asthma problems. See “What is the most important information I should know about ADVAIR HFA?”

Other possible side effects with ADVAIR HFA include:

- serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue; and breathing problems. Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.
- increased blood pressure
- a fast and irregular heartbeat
- chest pain
- headache
- tremor
- nervousness
- immune system effects and a higher chance for infections
- lower bone mineral density. This may be a problem for people who already have a higher chance for 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 irritation

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 with the mouthpiece down.
- Do not puncture the canister. Do not use or store ADVAIR HFA near heat or an open flame. Never throw it into a fire or 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. It may harm them.

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.

### Instructions for Using Your ADVAIR HFA

Follow the instructions below for using your ADVAIR HFA.

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

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

3. **The purple actuator that comes with ADVAIR HFA should not be used with any other product canisters. Actuators that come with other products should not be used with an ADVAIR HFA canister.**

4. **Prime the inhaler** before using it for the first time. To prime the inhaler, shake it well for 5 seconds. Then spray it 1 time into the air away from your face. Shake and spray the inhaler like this 3 more times to finish priming it. **Avoid spraying in eyes.**

5. If you have not used your inhaler in more than 4 weeks or if you have dropped it, shake it well for 5 seconds and spray it 2 times into the air away from your face.

6. **Shake the inhaler well** for 5 seconds just before each use.

7. **1. Take the cap off the mouthpiece (see Figure 1). The strap on the cap will stay attached to the actuator.**

8. Look for foreign objects inside the inhaler before each use, especially if the strap is no longer attached to the actuator or if the cap is not being used to cover the mouthpiece.

9. **Make sure the canister is fully and firmly inserted into the actuator.**

10. **Shake the inhaler well** for 5 seconds right before each use.
2. **Breathe out fully through your mouth**, pushing as much air out of your lungs as you can.

   Put the mouthpiece all the way into your mouth. Hold the inhaler with the mouthpiece down (see Figure 1). Close your lips around it.

3. It is important to get the medicine in the spray into your lungs where it works. To do this, you need to **inhale the spray at the same time you take in a slow, deep breath**.

   So, just after starting to take in a slow, deep breath through your mouth, press down firmly on the top of the metal canister (see Figure 2) and keep breathing in through your mouth.

   Take your finger off the canister after the spray comes out of the canister. Take the mouthpiece out of your mouth after you have finished breathing in.

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 again. Repeat steps 2 through 4.

6. **Put the cap back on the mouthpiece after each time you use the inhaler**.

7. After you finish taking this medicine, rinse your mouth with water. Spit out the water. Do not swallow it.
8. Never put the canister in water to find out how much medicine is left in the canister (“float test”).

9. You should keep track of the number of inhalations used from your inhaler. **Then throw away the inhaler after you have used 120 inhalations.** Even though the canister might not be empty and will keep spraying, you might not get the right amount of medicine in each inhalation.

   Before you get to 120 inhalations, ask your doctor if you need to refill your prescription.

   **Do not** use after the expiration date, which is shown as “EXP” on the product label and box.

**Cleaning your ADVAIR HFA Inhalation Aerosol:**

Clean the inhaler at least once a week after your evening dose. Keeping the canister and plastic actuator clean is important to prevent medicine buildup.

**Step 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.

**Step 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 3). Then wipe the inside of the mouthpiece with a clean tissue dampened with water. Let the actuator air-dry overnight.

**Step 3.** Put the mouthpiece cover back on after the actuator has dried.

**Rx only**

GlaxoSmithKline

Research Triangle Park, NC 27709
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This Medication Guide has been approved by the U.S. Food and Drug Administration.
SEREVENT® DISKUS®
(salmeterol xinafoate inhalation powder)

For Oral Inhalation Only

**WARNING**

Long-acting beta₂-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. 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) (see WARNINGS and CLINICAL TRIALS: Asthma: Salmeterol Multi-center Asthma Research Trial).

**DESCRIPTION**

SEREVENT DISKUS (salmeterol xinafoate inhalation powder) contains salmeterol xinafoate as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The active component of the formulation is salmeterol base, a highly selective beta₂-adrenergic bronchodilator. The chemical name of salmeterol xinafoate is 4-hydroxy-α₁-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalene-carboxylate. Salmeterol xinafoate has the following chemical structure:

![Chemical Structure of Salmeterol Xinafoate](image)

Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is C₂₅H₃₇NO₄•C₁₁H₂O₃. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

SEREVENT DISKUS is a specially designed plastic inhalation delivery system containing a double-foil blister strip of a powder formulation of salmeterol xinafoate intended for oral inhalation only. The DISKUS®, which is the delivery component, is an integral part of the drug
product. Each blister on the double-foil strip within the unit contains 50 mcg of salmeterol administered as the salmeterol xinafoate salt in 12.5 mg of formulation containing lactose (which contains milk proteins). After a blister containing medication is opened by activating the DISKUS, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, SEREVENT DISKUS delivers 47 mcg when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in 1 second [FEV1] 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS was 82.4 L/min (range, 46.1 to 115.3 L/min).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action:** Salmeterol is a long-acting beta2-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta2-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on beta1- and beta2-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more selective for beta2-adrenoceptors than albuterol. Although beta2-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1-adrenoceptors are the predominant receptors in the heart, there are also beta2-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 they raise the possibility that even highly selective beta2-agonists may have cardiac effects.

The pharmacologic effects of beta2-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 D2, 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.

**Pharmacokinetics:** 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.

**Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low or
undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder
twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol
inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in
7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of
167 pg/mL at 20 minutes and no accumulation with repeated doses.

**Distribution:** 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:** Salmeterol base is extensively metabolized by hydroxylation, with subsequent
elimination predominantly in the feces. No significant amount of unchanged salmeterol base has
been 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 cytochrome P450 3A4 (CYP3A4).
Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of
α-hydroxysalmeterol in vitro.

**Elimination:** In 2 healthy 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.

**Special Populations:** The pharmacokinetics of salmeterol base has not been studied in
elderly patients nor in patients with hepatic or renal impairment. Since salmeterol is
predominantly cleared by hepatic metabolism, liver function impairment may lead to
accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely
monitored.

**Drug Interactions:** Salmeterol is a substrate of CYP3A4.

**Inhibitors of Cytochrome P450 3A4: Ketoconazole:** 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 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
Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended.

**Erythromycin:** 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\text{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.

**Pharmacodynamics:** Inhaled salmeterol, like other beta-adrenergic agonist drugs, can in some patients produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium (see PRECAUTIONS: General). The cardiovascular effects (heart rate, blood pressure) associated with salmeterol inhalation aerosol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising 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). Adolescent and adult patients receiving 50-mcg doses of salmeterol inhalation powder (\(N = 60\)) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted. Also, pediatric patients receiving 50-mcg doses of salmeterol inhalation powder (\(N = 67\)) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 3 months of therapy, and no clinically significant dysrhythmias were noted.

In 24-week clinical studies in patients with chronic obstructive pulmonary disease (COPD), the incidence of clinically significant abnormalities on the predose electrocardiograms (ECGs) at Weeks 12 and 24 in patients who received salmeterol 50 mcg was not different compared with placebo.

No effect of treatment with salmeterol 50 mcg was observed on pulse rate and systolic and diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign measurements after the first dose (\(N = 91\)) and after 12 weeks of therapy (\(N = 74\)). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar for patients receiving either salmeterol or placebo (see ADVERSE REACTIONS).

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 significance of these findings is unknown.
Asthma: During the initial treatment day in several multiple-dose clinical trials with SEREVENT DISKUS in patients with asthma, the median time to onset of clinically significant bronchodilatation (≥15% improvement in FEV₁) ranged from 30 to 48 minutes after a 50-mcg dose.

One hour after a single dose of 50 mcg of SEREVENT DISKUS, the majority of patients had ≥15% improvement in FEV₁. Maximum improvement in FEV₁ generally occurred within 180 minutes, and clinically significant improvement continued for 12 hours in most patients.

In 2 randomized, double-blind studies, SEREVENT DISKUS was compared with albuterol inhalation aerosol and placebo in adolescent and adult patients with mild-to-moderate asthma (protocol defined as 50% to 80% predicted FEV₁, actual mean of 67.7% at baseline), including patients who did and who did not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was demonstrated over the 12-week period with no change in effectiveness over this time period (see Figure 1). There were no gender- or age-related differences in safety or efficacy. No development of tachyphylaxis to the bronchodilator effect was noted in these studies. FEV₁ measurements (mean change from baseline) from these two 12-week studies are shown in Figure 1 for both the first and last treatment days.
Table 1 shows the treatment effects seen during daily treatment with SEREVENT DISKUS for 12 weeks in adolescent and adult patients with mild-to-moderate asthma.
Table 1. Daily Efficacy Measurements in Two 12-Week Clinical Trials (Combined Data)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time</th>
<th>Placebo</th>
<th>SEREVENT DISKUS</th>
<th>Albuterol Inhalation Aerosol</th>
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<tr>
<td>No. of randomized subjects</td>
<td></td>
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<td>149</td>
<td>148</td>
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<tr>
<td>Mean AM peak expiratory flow (L/min)</td>
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<td>395</td>
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<td></td>
<td>12 weeks</td>
<td>396</td>
<td>427*</td>
<td>394</td>
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<td>Mean % days with no asthma symptoms</td>
<td>baseline</td>
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<td>13</td>
<td>12</td>
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<tr>
<td></td>
<td>12 weeks</td>
<td>20</td>
<td>33</td>
<td>21</td>
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<td>Mean % nights with no awakenings</td>
<td>baseline</td>
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<td>68</td>
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<td></td>
<td>12 weeks</td>
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<td>85*</td>
<td>71</td>
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<td>Rescue medications (mean no. of inhalations per day)</td>
<td>baseline</td>
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<td>4.3</td>
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<tr>
<td></td>
<td>12 weeks</td>
<td>3.3</td>
<td>1.6†</td>
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<tr>
<td>Asthma exacerbations</td>
<td></td>
<td>14%</td>
<td>15%</td>
<td>16%</td>
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</table>

*Statistically superior to placebo and albuterol (p<0.001).
†Statistically superior to placebo (p<0.001).

Maintenance of efficacy for periods up to 1 year has been documented.

SEREVENT DISKUS and SEREVENT® (salmeterol xinafoate) Inhalation Aerosol were compared to placebo in 2 additional randomized, double-blind clinical trials in adolescent and adult patients with mild-to-moderate asthma. SEREVENT DISKUS 50 mcg and SEREVENT Inhalation Aerosol 42 mcg, both administered twice daily, produced significant improvements in pulmonary function compared with placebo over the 12-week period. While no statistically significant differences were observed between the active treatments for any of the efficacy assessments or safety evaluations performed, there were some efficacy measures on which the metered-dose inhaler appeared to provide better results. Similar findings were noted in 2 randomized, single-dose, crossover comparisons of SEREVENT DISKUS and SEREVENT Inhalation Aerosol for the prevention of exercise-induced bronchospasm (EIB). Therefore, while SEREVENT DISKUS was comparable to SEREVENT Inhalation Aerosol in clinical trials in mild-to-moderate patients with asthma, it should not be assumed that they will produce clinically equivalent outcomes in all patients.

In a randomized, double-blind, controlled study (N = 449), 50 mcg of SEREVENT DISKUS was administered twice daily to pediatric patients with asthma who did and who did not receive concurrent inhaled corticosteroids. The efficacy of salmeterol inhalation powder was demonstrated over the 12-week treatment period with respect to periodic serial peak expiratory flow (PEF) (36% to 39% postdose increase from baseline) and FEV₁ (32% to 33% postdose increase from baseline). Salmeterol was effective in demographic subgroup analyses (gender and age) and was effective when coadministered with other inhaled asthma medications such as short-acting bronchodilators and inhaled corticosteroids. A second randomized, double-blind,
placebo-controlled study (N = 207) with 50 mcg of salmeterol inhalation powder via an alternate device supported the findings of the trial with the DISKUS.

**Effects in Patients With Asthma on Concomitant Inhaled Corticosteroids:** In 4 clinical trials in adult and adolescent patients with asthma (N = 1,922), the effect of adding salmeterol to inhaled corticosteroid therapy was evaluated. The studies utilized the inhalation aerosol formulation of salmeterol xinafoate for a treatment period of 6 months. They compared the addition of salmeterol therapy to an increase (at least doubling) of the inhaled corticosteroid dose.

Two randomized, double-blind, controlled, parallel-group clinical trials (N = 997) enrolled patients (ages 18 to 82 years) with persistent asthma who were previously maintained but not adequately controlled on inhaled corticosteroid therapy. During the 2-week run-in period, all patients were switched to beclomethasone dipropionate 168 mcg twice daily. Patients still not adequately controlled were randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg twice daily or an increase of beclomethasone dipropionate to 336 mcg twice daily. As compared to the doubled dose of beclomethasone dipropionate, the addition of SEREVENT Inhalation Aerosol resulted in statistically significantly greater improvements in pulmonary function and asthma symptoms, and statistically significantly greater reduction in supplemental albuterol use. The percent of patients who experienced asthma exacerbations overall was not different between groups (i.e., 16.2% in the group receiving SEREVENT Inhalation Aerosol versus 17.9% in the higher-dose beclomethasone dipropionate group).

Two randomized, double-blind, parallel-group clinical trials (N = 925) enrolled patients (ages 12 to 78 years) with persistent asthma who were previously maintained but not adequately controlled on prior therapy. During the 2- to 4-week run-in period, all patients were switched to fluticasone propionate 88 mcg twice daily. Patients still not adequately controlled were randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg twice daily or an increase of fluticasone propionate to 220 mcg twice daily. As compared to the increased (2.5 times) dose of fluticasone propionate, the addition of SEREVENT Inhalation Aerosol resulted in statistically significantly greater improvements in pulmonary function and asthma symptoms, and statistically significantly greater reductions in supplemental albuterol use. Fewer patients receiving SEREVENT Inhalation Aerosol experienced asthma exacerbations than those receiving the higher dose of fluticasone propionate (8.8% versus 13.8%).

**Exercise-Induced Bronchospasm:** In 2 randomized, single-dose, crossover studies in adolescents and adults with EIB (N = 53), 50 mcg of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise. For many patients, this protective effect against EIB was still apparent up to 8.5 hours following a single dose.
Table 2. Results of 2 Exercise-Induced Bronchospasm Studies in Adolescents and Adults

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th></th>
<th>SEREVENT DISKUS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 52)</td>
<td>% Total</td>
<td>(N = 52)</td>
<td>% Total</td>
</tr>
<tr>
<td>0.5-Hour postdose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>exercise challenge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Fall in FEV1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>15</td>
<td>29</td>
<td>31</td>
<td>60</td>
</tr>
<tr>
<td>≥10%, &lt;20%</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>≥20%</td>
<td>34</td>
<td>65</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Mean maximal % fall in FEV1 (SE)</td>
<td>-25% (1.8)</td>
<td></td>
<td>-11% (1.9)</td>
<td></td>
</tr>
<tr>
<td>8.5-Hour postdose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>exercise challenge</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>% Fall in FEV1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>12</td>
<td>23</td>
<td>26</td>
<td>50</td>
</tr>
<tr>
<td>≥10%, &lt;20%</td>
<td>7</td>
<td>13</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>≥20%</td>
<td>33</td>
<td>63</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>Mean maximal % fall in FEV1 (SE)</td>
<td>-27% (1.5)</td>
<td></td>
<td>-16% (2.0)</td>
<td></td>
</tr>
</tbody>
</table>

In 2 randomized studies in children 4 to 11 years old with asthma and EIB (N = 50), a single 50-mcg dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise, with protection lasting up to 11.5 hours in repeat testing following this single dose in many patients.

**Salmeterol Multi-center Asthma Research Trial:** The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta2-agonist–naive patients with asthma (average age of 39 years, 71% Caucasian, 18% African American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared to 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 2). In the total population, a higher rate of asthma-related death occurred in patients treated with salmeterol than those treated with placebo (0.10% vs. 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% vs. 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% vs. 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...
The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids or other asthma-controller therapy modifies the risk of asthma-related death.

**Table 3: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)**

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol n (%&lt;sup&gt;*&lt;/sup&gt;)</th>
<th>Placebo n (%&lt;sup&gt;*&lt;/sup&gt;)</th>
<th>Relative Risk&lt;sup&gt;†&lt;/sup&gt; (95% Confidence Interval)</th>
<th>Excess Deaths Expressed per 10,000 Patients&lt;sup&gt;‡&lt;/sup&gt; (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Population§</strong></td>
<td>Salmeterol: N = 1,3176</td>
<td>13 (0.10%)</td>
<td>4.37 (1.25, 15.34)</td>
<td>8 (3, 13)</td>
</tr>
<tr>
<td></td>
<td>Placebo: N = 1,3179</td>
<td>3 (0.02%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Caucasian</strong></td>
<td>Salmeterol: N = 9,281</td>
<td>6 (0.07%)</td>
<td>5.82 (0.70, 48.37)</td>
<td>6 (1, 10)</td>
</tr>
<tr>
<td></td>
<td>Placebo: N = 9,361</td>
<td>1 (0.01%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>African American</strong></td>
<td>Salmeterol: N = 2,366</td>
<td>7 (0.31%)</td>
<td>7.26 (0.89, 58.94)</td>
<td>27 (8, 46)</td>
</tr>
<tr>
<td></td>
<td>Placebo: N = 2,319</td>
<td>1 (0.04%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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.

† 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.

‡ 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.

§ 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).
Figure 2. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART), by Duration of Treatment

**Chronic Obstructive Pulmonary Disease:** In 2 clinical trials evaluating twice-daily
treatment with SEREVENT DISKUS 50 mcg (N = 336) compared to placebo (N = 366) in patients with chronic bronchitis with airflow limitation, with or without emphysema, improvements in pulmonary function endpoints were greater with salmeterol 50 mcg than with placebo. Treatment with SEREVENT DISKUS did not result in significant improvements in secondary endpoints assessing COPD symptoms in either clinical trial. Both trials were randomized, double-blind, parallel-group studies of 24 weeks’ duration and were identical in design, patient entrance criteria, and overall conduct.

Figure 3 displays the integrated 2-hour postdose FEV₁ results from the 2 clinical trials. The percent change in FEV₁ refers to the change from baseline, defined as the predose value on Treatment Day 1. To account for patient withdrawals during the study, Endpoint (last evaluable FEV₁) data are provided. Patients receiving SEREVENT DISKUS 50 mcg had significantly greater improvements in 2-hour postdose FEV₁ at Endpoint (216 mL, 20%) compared to placebo (43 mL, 5%). Improvement was apparent on the first day of treatment and maintained throughout the 24 weeks of treatment.

Figure 3. Mean Percent Change From Baseline in Postdose FEV₁ Integrated Data From 2 Trials of Patients With Chronic Bronchitis and Airflow Limitation

Onset of Action and Duration of Effect: The onset of action and duration of effect of
SEREVENT DISKUS were evaluated in a subset of patients (n = 87) from 1 of the 2 clinical trials discussed above. Following the first 50-mcg dose, significant improvement in pulmonary function (mean FEV\textsubscript{1} increase of 12% or more and at least 200 mL) occurred at 2 hours. The mean time to peak bronchodilator effect was 4.75 hours. As seen in Figure 4, evidence of bronchodilatation was seen throughout the 12-hour period. Figure 4 also demonstrates that the bronchodilating effect after 12 weeks of treatment was similar to that observed after the first dose. The mean time to peak bronchodilator effect after 12 weeks of treatment was 3.27 hours.

**Figure 4. Serial 12-Hour FEV\textsubscript{1} on the First Day and at Week 12 of Treatment**

### INDICATIONS AND USAGE

**Asthma:** SEREVENT DISKUS is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma.

Long-acting beta\textsubscript{2}-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications.
(e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants
initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. It is not
indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting
beta2-agonists or for patients whose asthma can be successfully managed by inhaled
corticosteroids or other controller medications along with occasional use of inhaled, short-acting
beta2-agonists.

SEREVENT DISKUS is also indicated for prevention of exercise-induced bronchospasm in
patients 4 years of age and older.

Chronic Obstructive Pulmonary Disease: SEREVENT DISKUS is indicated for the long-
term, twice-daily (morning and evening) administration in the maintenance treatment of
bronchospasm associated with COPD (including emphysema and chronic bronchitis).

CONTRAINDICATIONS
SEREVENT DISKUS is contraindicated in patients with a history of hypersensitivity to
salmeterol or any other component of the drug product (see DESCRIPTION and ADVERSE
REACTIONS: Observed During Clinical Practice: Non-Site Specific).

WARNINGS
• Long-acting beta2-adrenergic agonists, such as salmeterol, the active ingredient in
SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when
treating patients with asthma, SEREVENT DISKUS should only be used as additional
therapy for patients not adequately controlled on other asthma-controller medications
(e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly
warrants initiation of treatment with 2 maintenance therapies, including SEREVENT
DISKUS.
• A large 28-week, placebo-controlled US study comparing the safety of salmeterol
(SEREVENT Inhalation Aerosol) with placebo, each added to usual asthma therapy,
showed an increase in asthma-related deaths in patients receiving salmeterol (see
CLINICAL TRIALS: Asthma: Salmeterol Multi-center Asthma Research Trial). Given
the similar basic mechanisms of action of beta2-agonists, it is possible that the findings
seen in the SMART study represent a class effect.
• 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 with asthma treated with salmeterol (42 mcg twice daily) than those
treated with albuterol (180 mcg 4 times daily) added to usual asthma therapy.
• The SNS and SMART studies enrolled patients with asthma. No studies have been
conducted that were adequate to determine whether the rate of death in patients with
COPD is increased by long-acting beta2-adrenergic agonists.
• It is important to watch for signs of worsening asthma, such as increasing use of
inhaled, short-acting beta2-agonists or a significant decrease in PEF or lung function.
Such findings require immediate evaluation. Patients should be advised to seek immediate medical attention should their condition deteriorate.

- **SEREVENT DISKUS should not be used to treat acute symptoms.** It is crucial to inform patients of this and prescribe an inhaled, short-acting beta₂-agonist for this purpose and to warn them that increasing inhaled beta₂-agonist use is a signal of deteriorating asthma that requires prompt consultation with a physician.

- **SEREVENT DISKUS should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition.** Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide when SEREVENT has been initiated in this situation. Although it is not possible from these reports to determine whether SEREVENT contributed to these adverse events or simply failed to relieve the deteriorating asthma, the use of SEREVENT DISKUS in this setting is inappropriate.

- **SEREVENT DISKUS is not a substitute for inhaled or oral corticosteroids.** Corticosteroids should not be stopped or reduced when SEREVENT DISKUS is initiated.

See PRECAUTIONS: Information for Patients and the Medication Guide accompanying the product.

The following additional WARNINGS about SEREVENT DISKUS should be noted.

1. **SEREVENT DISKUS should not be used as a treatment for acutely deteriorating asthma.** SEREVENT DISKUS is intended for the maintenance treatment of asthma (see INDICATIONS AND USAGE) and should not be introduced in acutely deteriorating asthma, which is a potentially life-threatening condition. There are no data demonstrating that SEREVENT DISKUS provides greater efficacy than or additional efficacy to inhaled, short-acting beta₂-agonists in patients with worsening asthma. Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide in patients receiving SEREVENT. 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, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled, short-acting beta₂-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT contributed to these events.

2. **SEREVENT DISKUS should not be used to treat acute symptoms.** An inhaled, short-acting beta₂-agonist, not SEREVENT DISKUS, should be used to relieve acute asthma or COPD symptoms. When prescribing SEREVENT DISKUS, the physician must also provide the patient with an inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of SEREVENT DISKUS.

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When beginning treatment with SEREVENT DISKUS, patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute asthma or COPD symptoms (see PRECAUTIONS: Information for Patients).

3. Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma or COPD. The physician and patient should be alert to such changes. The patient’s condition may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient’s inhaled, short-acting beta₂-agonist becomes less effective, the patient needs more inhalations than usual, or the patient develops a significant decrease in PEF or lung function, these may be markers of destabilization of their disease. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for corticosteroids. If the patient uses 4 or more inhalations per day of an inhaled, short-acting beta₂-agonist for 2 or more consecutive days, or if more than 1 canister (200 inhalations per canister) of inhaled, short-acting beta₂-agonist is used in an 8-week period in conjunction with SEREVENT DISKUS, then the patient should consult the physician for reevaluation. **Increasing the daily dosage of SEREVENT DISKUS in this situation is not appropriate. SEREVENT DISKUS should not be used more frequently than twice daily (morning and evening) at the recommended dose of 1 inhalation.**

4. SEREVENT DISKUS should not be used in conjunction with an inhaled, long-acting beta₂-agonist. SEREVENT DISKUS should not be used with other medications containing long-acting beta₂-agonists.

5. SEREVENT DISKUS is not a substitute for oral or inhaled corticosteroids. There are no data demonstrating that SEREVENT DISKUS has a clinical anti-inflammatory effect and could be expected to take the place of corticosteroids. When initiating SEREVENT DISKUS in patients receiving oral or inhaled corticosteroids for treatment of asthma, patients should be continued on a suitable dose of corticosteroids to maintain clinical stability even if they feel better as a result of initiating SEREVENT DISKUS. Any change in corticosteroid dosage should be made ONLY after clinical evaluation (see PRECAUTIONS: Information for Patients).

6. The recommended dosage should not be exceeded. As with other inhaled beta₂-adrenergic drugs, SEREVENT DISKUS should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. 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.

7. **Paradoxical bronchospasm.** As with other inhaled asthma and COPD medications, SEREVENT DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SEREVENT DISKUS, it should be treated immediately with a short-acting, inhaled bronchodilator; SEREVENT DISKUS should be discontinued immediately; and alternative therapy should be instituted.

8. **Immediate hypersensitivity reactions.** Immediate hypersensitivity reactions may occur after
administration of SEREVENT DISKUS, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

9. **Upper airway symptoms.** Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving SEREVENT DISKUS.

10. **Cardiovascular disorders.** SEREVENT DISKUS, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. SEREVENT DISKUS, like all other beta-adrenergic agonists, 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 SEREVENT DISKUS at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce 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.

11. **Potential drug interactions.** Because of the potential for drug interactions and the potential for increased risk of cardiovascular adverse events, the concomitant use of SEREVENT DISKUS with strong CYP 3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Drug Interactions).

**PRECAUTIONS**

**General: Cardiovascular Effects:** No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol at recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of salmeterol and may require discontinuation of SEREVENT DISKUS. SEREVENT DISKUS, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and ECGs have been seen infrequently in individual patients in controlled clinical studies with salmeterol.

**Metabolic Effects:** Doses of the related beta2-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of SEREVENT DISKUS at recommended
Information for Patients: Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document.

Patients being treated with SEREVENT DISKUS should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

It is important that patients understand how to use the DISKUS appropriately and how to use SEREVENT DISKUS in relation to other asthma or COPD medications they are taking. Patients should be given the following information:

1. Patients should be informed that salmeterol may increase the risk of asthma-related death.
2. SEREVENT DISKUS is not meant to relieve acute asthma or COPD symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting bronchodilator (the physician should provide the patient with such medication and instruct the patient in how it should be used).
3. The physician should be notified immediately if any of the following signs of seriously worsening asthma or COPD occur:
   - decreasing effectiveness of inhaled, short-acting beta2-agonists;
   - need for more inhalations than usual of inhaled, short-acting beta2-agonists;
   - significant decrease in PEF or lung function as outlined by the physician;
   - use of 4 or more inhalations per day of a short-acting beta2-agonist for 2 or more days consecutively;
   - use of more than 1 canister (200 inhalations per canister) of an inhaled, short-acting beta2-agonist in an 8-week period.
4. Patients should not stop therapy with SEREVENT DISKUS for asthma or COPD without physician/provider guidance since symptoms may worsen after discontinuation.
5. SEREVENT DISKUS should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with SEREVENT DISKUS.
6. Patients should be cautioned regarding adverse effects associated with beta2-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
7. When patients are prescribed SEREVENT DISKUS, other medications for asthma and COPD should be used only as directed by the physician.
8. SEREVENT DISKUS should not be used with a spacer device.
9. Patients who are pregnant or nursing should contact the physician about the use of SEREVENT DISKUS.
10. The action of SEREVENT DISKUS may last up to 12 hours or longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not be exceeded.
11. When used for the treatment of EIB, 1 inhalation of SEREVENT DISKUS should be taken 30 minutes before exercise.
   - Additional doses of SEREVENT should not be used for 12 hours.
   - Patients who are receiving SEREVENT DISKUS twice daily should not use additional SEREVENT for prevention of EIB.

12. Effective and safe use of SEREVENT DISKUS includes an understanding of the way that it should be used:
   - Never exhale into the DISKUS.
   - Never attempt to take the DISKUS apart.
   - Always activate and use the DISKUS in a level, horizontal position.
   - Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
   - Always keep the DISKUS in a dry place.
   - Discard **6 weeks** after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads “0”), whichever comes first.

13. For the proper use of SEREVENT DISKUS and to attain maximum benefit, the patient should read and follow carefully the Instructions for Using SEREVENT DISKUS in the Medication Guide accompanying the product.

14. Most patients are able to taste or feel a dose delivered from SEREVENT DISKUS. However, whether or not patients are able to sense delivery of a dose, they should not exceed the recommended dose of 1 inhalation twice daily, morning and evening. Patients should contact a physician or pharmacist if they have questions.

**Drug Interactions:**

**Inhibitors of Cytochrome P450 3A4:** In a drug interaction study in 20 healthy subjects, coadministration of salmeterol (50 mcg twice daily) and ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and $C_{\text{max}}$ increased 1.4-fold). Three (3) subjects were withdrawn due to beta2-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. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended.

**Short-Acting Beta2-Agonists:** In two 12-week, repetitive-dose adolescent and adult clinical trials in patients with asthma (N = 149), the mean daily need for additional beta2-agonist in patients using SEREVENT DISKUS was approximately 1½ inhalations/day. Twenty-six percent (26%) of the patients in these trials used between 8 and 24 inhalations of short-acting beta-agonist per day on 1 or more occasions. Nine percent (9%) of the patients in these trials averaged over 4 inhalations/day over the course of the 12-week trials. No increase in frequency of cardiovascular events was observed among the 3 patients who averaged 8 to 11 inhalations/day; however, the safety of concomitant use of more than 8 inhalations/day of
short-acting beta2-agonist with SEREVENT DISKUS has not been established. In 29 patients who experienced worsening of asthma while receiving SEREVENT DISKUS during these trials, albuterol therapy administered via either nebulizer or inhalation aerosol (1 dose in most cases) led to improvement in FEV1 and no increase in occurrence of cardiovascular adverse events.

In 2 clinical trials in patients with COPD, the mean daily need for additional beta2-agonist for patients using SEREVENT DISKUS was approximately 4 inhalations/day. Twenty-four percent (24%) of the patients using SEREVENT DISKUS in these trials averaged 6 or more inhalations of albuterol per day over the course of the 24-week trials. No increase in frequency of cardiovascular events was observed among patients who averaged 6 or more inhalations per day.

**Monoamine Oxidase Inhibitors and Tricyclic Antidepressants:** Salmeterol 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 on the vascular system may be potentiated by these agents.

**Corticosteroids and Cromoglycate:** In clinical trials, inhaled corticosteroids and/or inhaled cromolyn sodium did not alter the safety profile of salmeterol when administered concurrently.

**Methylxanthines:** The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving salmeterol has not been completely evaluated. In 1 clinical asthma trial, 87 patients receiving SEREVENT Inhalation Aerosol 42 mcg twice daily concurrently with a theophylline product had adverse event rates similar to those in 71 patients receiving SEREVENT Inhalation Aerosol without theophylline. Resting heart rates were slightly higher in the patients on theophylline but were little affected by therapy with SEREVENT Inhalation Aerosol.

In 2 clinical trials in patients with COPD, 39 subjects receiving SEREVENT DISKUS concurrently with a theophylline product had adverse event rates similar to those in 302 patients receiving SEREVENT DISKUS without theophylline. Based on the available data, the concomitant administration of methylxanthines with SEREVENT DISKUS did not alter the observed adverse event profile.

**Beta-Adrenergic Receptor Blocking Agents:** Beta-blockers not only block the pulmonary effect of beta-agonists, such as SEREVENT DISKUS, but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma or COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

**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, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.
**Carcinogenesis, Mutagenesis, Impairment of Fertility:** In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts at doses of 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose in adults and children based on comparison of the area under the plasma concentration versus time curves [AUCs]). The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (approximately 3 times the maximum recommended daily inhalation doses in adults and children 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 55 times the maximum recommended daily inhalation dose in adults and approximately 25 times the maximum recommended daily inhalation dose in children on a mg/m² basis). No tumors were seen at 0.21 mg/kg (approximately 15 times the maximum recommended daily inhalation dose in adults and approximately 8 times the maximum recommended daily inhalation dose in children on a mg/m² 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 male and female rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m² basis).

**Pregnancy: Teratogenic Effects:** Pregnancy Category C. No teratogenic effects occurred in rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs), 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 significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans. There are no adequate and well-controlled studies with SEREVENT DISKUS in pregnant women. SEREVENT DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice and rats (approximately 410 and 810 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m² basis).

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

**Nursing Mothers:** Plasma levels of salmeterol after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. However, since there are no data from controlled trials on the use of salmeterol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue SEREVENT DISKUS, taking into account the importance of SEREVENT DISKUS to the mother. Caution should be exercised when SEREVENT DISKUS is administered to a nursing woman.

**Pediatric Use:** The safety and efficacy of SEREVENT DISKUS has been evaluated in over 2,500 patients aged 4 to 11 years with asthma, 346 of whom were administered SEREVENT DISKUS for 1 year. Based on available data, no adjustment of dosage of SEREVENT DISKUS in pediatric patients is warranted for either asthma or EIB (see DOSAGE AND ADMINISTRATION).

In 2 randomized, double-blind, controlled clinical trials of 12 weeks’ duration, SEREVENT DISKUS 50 mcg was administered to 211 pediatric patients with asthma who did and who did not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was demonstrated over the 12-week treatment period with respect to PEF and FEV₁. SEREVENT DISKUS was effective in demographic subgroups (gender and age) of the population.

SEREVENT DISKUS was effective when coadministered with other inhaled asthma medications, such as short-acting bronchodilators and inhaled corticosteroids. SEREVENT DISKUS was well tolerated in the pediatric population, and there were no safety issues identified specific to the administration of SEREVENT DISKUS to pediatric patients.

In 2 randomized studies in children 4 to 11 years old with asthma and EIB, a single 50-mcg dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise, with protection lasting up to 11.5 hours in repeat testing following this single dose in many patients.

**Geriatric Use:** Of the total number of adolescent and adult patients with asthma who received SEREVENT DISKUS in chronic dosing clinical trials, 209 were 65 years of age and older. Of the total number of patients with COPD who received SEREVENT DISKUS in chronic dosing clinical trials, 167 were 65 years of age or older and 45 were 75 years of age or older. No apparent differences in the safety of SEREVENT DISKUS were observed when geriatric patients were compared with younger patients in clinical trials. As with other beta₂-agonists, however, special caution should be observed when using SEREVENT DISKUS in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug.

Data from the trials in patients with COPD suggested a greater effect on FEV₁ of SEREVENT DISKUS in the <65 years age-group, as compared with the ≥65 years age-group. However,
based on available data, no adjustment of dosage of SEREVENT DISKUS in geriatric patients is warranted.

**ADVERSE REACTIONS**

Data from a large, 28-week, 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 CLINICAL TRIALS: Asthma: Salmeterol Multi-center Asthma Research Trial).

**Asthma:** Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT DISKUS in patients 12 years of age and older with asthma. Table 4 reports the incidence of adverse events in these 2 studies.

Table 4. Adverse Event Incidence in Two 12-Week Adolescent and Adult Clinical Trials in Patients With Asthma

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N = 152)</th>
<th>SEREVENT DISKUS 50 mcg Twice Daily (N = 149)</th>
<th>Albuterol Inhalation Aerosol 180 mcg 4 Times Daily (N = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear, nose, and throat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal/sinus congestion, pallor</td>
<td>6</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>1</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Tracheitis/bronchitis</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Influenza</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 4 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common than in the placebo group.

Pharyngitis, sinusitis, upper respiratory tract infection, and cough occurred at ≥3% but were more common in the placebo group. However, throat irritation has been described at rates exceeding that of placebo in other controlled clinical trials.

Other adverse events that occurred in the group receiving SEREVENT DISKUS in these studies with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:
**Ear, Nose, and Throat:** Sinus headache.

**Gastrointestinal:** Nausea.

**Mouth and Teeth:** Oral mucosal abnormality.

**Musculoskeletal:** Pain in joint.

**Neurological:** Sleep disturbance, paresthesia.

**Skin:** Contact dermatitis, eczema.

**Miscellaneous:** Localized aches and pains, pyrexia of unknown origin.

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT DISKUS in patients aged 4 to 11 years with asthma. Table 5 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common than in the placebo group.

**Table 5. Adverse Event Incidence in Two 12-Week Pediatric Clinical Trials in Patients With Asthma**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N = 215)</th>
<th>SEREVENT DISKUS 50 mcg Twice Daily (N = 211)</th>
<th>Albuterol Inhalation Powder 200 mcg 4 Times Daily (N = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear, nose, and throat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear signs and symptoms</td>
<td>3</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>2</td>
<td>4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rashes</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

The following events were reported at an incidence of 1% to 2% (3 to 4 patients) in the salmeterol group and with a higher incidence than in the albuterol and placebo groups: gastrointestinal signs and symptoms, lower respiratory signs and symptoms, photodermatitis, and arthralgia and articular rheumatism.

In clinical trials evaluating concurrent therapy of salmeterol with inhaled corticosteroids, adverse events were consistent with those previously reported for salmeterol, or with events that would be expected with the use of inhaled corticosteroids.

**Chronic Obstructive Pulmonary Disease:** Two multicenter, 24-week, controlled studies
have evaluated twice-daily doses of SEREVENT DISKUS in patients with COPD. For presentation (Table 6), the placebo data from a third trial, identical in design, patient entrance criteria, and overall conduct but comparing fluticasone propionate with placebo, were integrated with the placebo data from these 2 studies (total N = 341 for salmeterol and 576 for placebo).

Table 6. Adverse Events With \( \geq 3\% \) Incidence in US Controlled Clinical Trials With SEREVENT DISKUS in Patients With Chronic Obstructive Pulmonary Disease*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 576)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Ear, nose, and throat</td>
<td></td>
</tr>
<tr>
<td>Throat irritation</td>
<td>6</td>
</tr>
<tr>
<td>Nasal congestion/blockage</td>
<td>3</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2</td>
</tr>
<tr>
<td>Ear signs and symptoms</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Lower respiratory</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>4</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2</td>
</tr>
<tr>
<td>Viral respiratory infection</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>10</td>
</tr>
<tr>
<td>Muscle cramps and spasms</td>
<td>1</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
</tr>
<tr>
<td>Average duration of exposure</td>
<td>128.9</td>
</tr>
<tr>
<td>(days)</td>
<td></td>
</tr>
</tbody>
</table>

* Table 6 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common in the group receiving SEREVENT DISKUS than in the placebo group.

Other events occurring in the group receiving SEREVENT DISKUS that occurred at a frequency of 1% to <3% and were more common than in the placebo group were as follows:

**Endocrine and Metabolic:** Hyperglycemia.
**Eye:** Keratitis and conjunctivitis.

**Gastrointestinal:** Candidiasis mouth/throat, dyspeptic symptoms, hyposalivation, dental discomfort and pain, gastrointestinal infections.

**Lower Respiratory:** Lower respiratory signs and symptoms.

**Musculoskeletal:** Arthralgia and articular rheumatism; muscle pain; bone and skeletal pain; musculoskeletal inflammation; muscle stiffness, tightness, and rigidity.

**Neurology:** Migraines.

**Non-Site Specific:** Pain, edema and swelling.

**Psychiatry:** Anxiety.

**Skin:** Skin rashes.

Adverse reactions to salmeterol are similar in nature to those seen with other selective beta₂-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor; nervousness; and paradoxical bronchospasm (see WARNINGS).

**Observed During Clinical Practice:** In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of salmeterol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to salmeterol or a combination of these factors.

In extensive US and worldwide postmarketing experience with salmeterol, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also occurred in a few patients with less severe asthma. It was not possible from these reports to determine whether salmeterol contributed to these events.

**Respiratory:** Reports of upper airway symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking; oropharyngeal irritation.

**Cardiovascular:** Arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), and anaphylaxis.

**Non-Site Specific:** Very rare anaphylactic reaction in patients with severe milk protein allergy.

**OVERDOSAGE**

The expected signs and symptoms with overdosage of SEREVENT DISKUS are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Overdosage with SEREVENT DISKUS may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia.
and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with SEREVENT DISKUS 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 SEREVENT DISKUS.

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

No deaths were seen in rats at an inhalation dose of 2.9 mg/kg (approximately 240 times the maximum recommended daily inhalation dose in adults and approximately 110 times the maximum recommended daily inhalation dose in children on a mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 times the maximum recommended daily inhalation dose in adults and approximately 90 times the maximum recommended daily inhalation dose in children on a mg/m² basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6,100 times the maximum recommended daily inhalation dose in adults and approximately 2,900 times the maximum recommended daily inhalation dose in children on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 81,000 times the maximum recommended daily inhalation dose in adults and approximately 38,000 times the maximum recommended daily inhalation dose in children on a mg/m² basis).

**DOSAGE AND ADMINISTRATION**

SEREVENT DISKUS should be administered by the orally inhaled route only (see Instructions for Using SEREVENT DISKUS in the Medication Guide accompanying the product). The patient must not exhale into the DISKUS and the DISKUS should only be activated and used in a level, horizontal position.

**Asthma:** Long-acting beta2-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting beta2-agonists or for patients whose asthma can be successfully managed by inhaled corticosteroids or other controller medications along with occasional use of inhaled, short-acting beta2-agonists.

For maintenance of bronchodilatation and prevention of symptoms of asthma, including the symptoms of nocturnal asthma, the usual dosage for adults and children 4 years of age and older
is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be reevaluated. If symptoms arise in the period between doses, an inhaled, short-acting beta2-agonist should be taken for immediate relief.

**Chronic Obstructive Pulmonary Disease:** For maintenance treatment of bronchospasm associated with COPD (including chronic bronchitis and emphysema), the usual dosage for adults is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). For both asthma and COPD, adverse effects are more likely to occur with higher doses of salmeterol, and more frequent administration or administration of a larger number of inhalations is not recommended.

To gain full therapeutic benefit, SEREVENT DISKUS should be administered twice daily (morning and evening) in the treatment of reversible airway obstruction.

**Geriatric Use:** Based on available data for SEREVENT DISKUS, no dosage adjustment is recommended.

**Prevention of Exercise-Induced Bronchospasm:** One inhalation of SEREVENT DISKUS at least 30 minutes before exercise has been shown to protect patients against EIB. When used intermittently as needed for prevention of EIB, this protection may last up to 9 hours in adolescents and adults and up to 12 hours in patients 4 to 11 years of age. Additional doses of SEREVENT should not be used for 12 hours after the administration of this drug. Patients who are receiving SEREVENT DISKUS twice daily should not use additional SEREVENT for prevention of EIB. If regular, twice-daily dosing is not effective in preventing EIB, other appropriate therapy for EIB should be considered.

**HOW SUPPLIED**

SEREVENT DISKUS is supplied as a disposable teal green unit containing 60 blisters. The drug product is packaged within a teal green, plastic-coated, moisture-protective foil pouch (NDC 0173-0521-00).

SEREVENT DISKUS is also supplied in an institutional pack of 1 disposable teal green unit containing 28 blisters. The drug product is packaged within a teal green, plastic-coated, moisture-protective foil pouch (NDC 0173-0520-00).

*Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place away from direct heat or sunlight. Keep out of reach of children. SEREVENT DISKUS should be discarded 6 weeks after removal from the moisture-protective foil pouch or after all blisters have been used (when the dose indicator reads “0”), whichever comes first. The DISKUS is not reusable. Do not attempt to take the DISKUS apart.*

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MEDICATION GUIDE

SEREVENT® [ser' uh-vent] DISKUS®
(salmeterol xinafoate inhalation powder)

Read the Medication Guide that comes with SEREVENT DISKUS 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 SEREVENT DISKUS?

SEREVENT DISKUS is a medicine called a long-acting beta2-agonist or LABA. LABA medicines are used in patients with asthma, exercise-induced bronchospasm (EIB), 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.

• In patients with asthma, LABA medicines, such as SEREVENT DISKUS, may increase the chance of death from asthma problems. In a large asthma study, more patients who used salmeterol (SEREVENT) died from asthma problems compared with patients who did not use salmeterol (SEREVENT). Talk with your healthcare provider about this risk and the benefits of treating your asthma with SEREVENT DISKUS.

• SEREVENT DISKUS does not relieve sudden symptoms. Always have a short-acting beta2-agonist medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.

• Do not stop using SEREVENT DISKUS unless told to do so by your healthcare provider because your symptoms might get worse.
• SEREVENT DISKUS:
  • should not be the only medicine prescribed for your asthma
  • should be used only if your healthcare provider decides that another
    asthma-controller medicine alone does not control your asthma or that you need 2
    asthma-controller medicines
  • Call your healthcare provider if breathing problems worsen over time while using
    SEREVENT DISKUS. You may need different treatment.
  • Get emergency medical care if:
    • breathing problems worsen quickly, and
    • you use your short-acting beta2-agonist medicine, but it does not relieve your
      breathing problems

What is SEREVENT DISKUS?
SEREVENT DISKUS is a long-acting beta2-agonist medicine (LABA). SEREVENT DISKUS is
used for asthma, exercise-induced bronchospasm (EIB), and chronic obstructive pulmonary
disease (COPD) as follows:

Asthma
SEREVENT DISKUS is used long term, twice a day, to control symptoms of asthma, and
prevent symptoms such as wheezing in adults and children ages 4 and older.

Because LABA medicines, such as SEREVENT DISKUS, may increase the chance of death
from asthma problems, SEREVENT DISKUS is not for adults and children with asthma
who:
• are well controlled with another asthma-controller medicine, such as a low to medium
dose of an inhaled corticosteroid medicine
• only need short-acting beta2-agonist medicines once in awhile

Exercise-Induced Bronchospasm (EIB)
SEREVENT DISKUS is used for the prevention of wheezing caused by exercise in adults and
children 4 years of age and older.

Chronic Obstructive Pulmonary Disease (COPD)
SEREVENT DISKUS is used long term, twice a day in controlling symptoms of COPD and
preventing wheezing in adults with COPD.

What should I tell my healthcare provider before using SEREVENT DISKUS?
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
- are pregnant or planning to become pregnant. It is not known if SEREVENT DISKUS may harm your unborn baby.
- are breastfeeding. It is not known if SEREVENT DISKUS passes into your milk and if it can harm your baby.
- are allergic to SEREVENT DISKUS, any other medicines, or food products

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. SEREVENT DISKUS and certain other medicines may interact with each other. This may cause serious side effects.

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

How do I use SEREVENT DISKUS?

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

- Children should use SEREVENT DISKUS with an adult’s help, as instructed by the child’s healthcare provider.
- Use SEREVENT DISKUS exactly as prescribed. Do not use SEREVENT DISKUS more often than prescribed.
- For asthma and COPD, the usual dose is 1 inhalation twice a day (morning and evening). The 2 doses should be about 12 hours apart.
- For preventing exercise-induced bronchospasm, take 1 inhalation at least 30 minutes before exercise. Do not use SEREVENT DISKUS more often than every 12 hours. Do not use extra SEREVENT DISKUS before exercise if you already use it twice a day.
- If you miss a dose of SEREVENT DISKUS, just skip that dose. Take your next dose at your

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usual time. Do not take 2 doses at one time.

- Do not use a spacer device with SEREVENT DISKUS.
- Do not breathe into SEREVENT DISKUS.
- While you are using SEREVENT DISKUS twice a day, do not use other medicines that contain a long-acting beta2-agonist or LABA for any reason. Other LABA medicines include ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder), ADVAIR® HFA (fluticasone propionate and salmeterol) Inhalation Aerosol, FORADIL® AEROLIZER® (formoterol fumarate inhalation powder), SYMBICORT® (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol, PERFOROMIST™ (formoterol fumarate) Inhalation Solution, and BROVANA™ (arformoterol tartrate) Inhalation Solution.
- Do not change or stop any of your medicines used to control or treat your breathing problems. Your healthcare provider will adjust your medicines as needed.
- Make sure you always have a short-acting beta2-agonist medicine with you. Use your short-acting beta2-agonist medicine if you have breathing problems between doses of SEREVENT DISKUS.
- Call your healthcare provider or get medical care right away if:
  - your breathing problems worsen with SEREVENT DISKUS
  - you need to use your short-acting beta2-agonist medicine more often than usual
  - your short-acting beta2-agonist medicine does not work as well for you at relieving symptoms
  - you need to use 4 or more inhalations of your short-acting beta2-agonist medicine for 2 or more days in a row
  - you use 1 whole canister of your short-acting beta2-agonist medicine in 8 weeks’ time
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  - you have asthma and your symptoms do not improve after using SEREVENT DISKUS regularly for 1 week.

What are the possible side effects with SEREVENT DISKUS?
- In patients with asthma, LABA medicines, such as SEREVENT, may increase the chance of death from asthma problems. See “What is the most important information I should know about SEREVENT DISKUS?”
Other possible side effects with SEREVENT DISKUS include:

- serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue; and breathing problems. Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.
- increased blood pressure
- a fast and irregular heartbeat
- chest pain
- headache
- tremor
- nervousness
- throat irritation

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 SEREVENT DISKUS. 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 SEREVENT DISKUS?

- Store SEREVENT DISKUS at room temperature between 68° to 77° F (20° to 25° C). Keep in a dry place away from heat and sunlight.
- Safely discard SEREVENT DISKUS 6 weeks after you remove it from the foil pouch, or after the dose indicator reads “0”, whichever comes first.
- Keep SEREVENT DISKUS and all medicines out of the reach of children.

General Information about SEREVENT DISKUS

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

This Medication Guide summarizes the most important information about SEREVENT DISKUS. If you would like more information, talk with your healthcare provider or pharmacist.

You can ask your healthcare provider or pharmacist for information about SEREVENT DISKUS that was written for healthcare professionals. You can also contact the company that makes SEREVENT DISKUS (toll free) at 1-888-825-5249 or at www.serevent.com.

Instructions for Using SEREVENT DISKUS

Follow the instructions below for using your SEREVENT DISKUS. You will breathe in
(inhale) the medicine from the DISKUS. If you have any questions, ask your healthcare provider or pharmacist.

Take the SEREVENT DISKUS out of the box and foil pouch. Write the “Pouch opened” and “Use by” dates on the label on top of the DISKUS. The “Use by” date is 6 weeks from date of opening the pouch.

- The DISKUS will be in the closed position when the pouch is opened.
- The dose indicator on the top of the DISKUS tells you how many doses are left. The dose indicator number will decrease each time you use the DISKUS. After you have used 55 doses from the DISKUS, the numbers 5 to 0 will appear in red to warn you that there are only a few doses left (see Figure 1).

Figure 1

Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.
1. **OPEN**

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

![Figure 2](image)

2. **CLICK**

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

![Figure 3](image)

Every time the lever is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter. To avoid releasing or wasting doses once the DISKUS is ready:
• Do not close the DISKUS.
• Do not tilt the DISKUS.
• Do not play with the lever.
• Do not move the lever more than once.

3. INHALE

Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the DISKUS level and away from your mouth (see Figure 4). Remember, never breathe out into the DISKUS mouthpiece.

Figure 4

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

Figure 5

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

The DISKUS delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the DISKUS if you do not feel or taste the medicine.

4. **Close the DISKUS when you are finished taking a dose so that the DISKUS will be ready for you to take your next dose.** Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go *(see Figure 6)*. The DISKUS will click shut. The lever will automatically return to its original position. The DISKUS is now ready for you to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4.)

![Figure 6](image)

**Remember:**
- Never breathe into the DISKUS.
- Never take the DISKUS apart.
- Always ready and use the DISKUS in a level, flat position.
- Do not use the DISKUS with a spacer device.
- Never wash the mouthpiece or any part of the DISKUS. **Keep it dry.**
- Always keep the DISKUS in a dry place.
- Never take an extra dose, even if you did not taste or feel the medicine.

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