PRESCRIBING INFORMATION

ADVAIR DISKUS® 100/50

(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

ADVAIR DISKUS® 250/50

(fluticasone propionate 250 mcg and salmeterol* 50 mcg inhalation powder)

ADVAIR DISKUS® 500/50

(fluticasone propionate 500 mcg and salmeterol* 50 mcg inhalation powder)

***As salmeterol xinafoate salt 72.5 mcg, equivalent to salmeterol base 50 mcg**

For Oral Inhalation Only

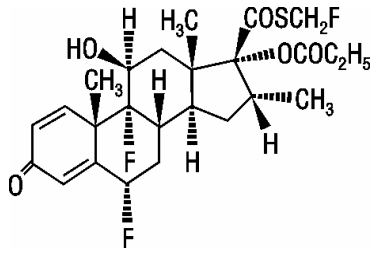
WARNING

Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS 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

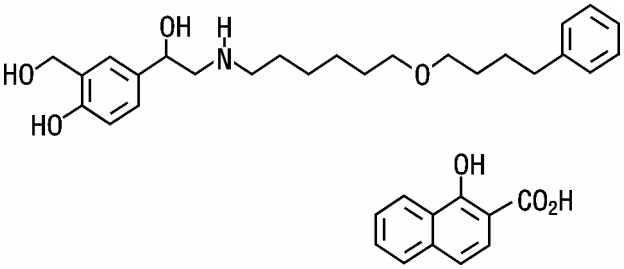
ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are combinations of fluticasone propionate and salmeterol xinafoate.

One active component of ADVAIR DISKUS 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 to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

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



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

ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are specially designed plastic devices containing a double-foil blister strip of a powder formulation of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 100, 250, or 500 mcg of microfine fluticasone propionate and 72.5 mcg of microfine salmeterol xinafoate salt, equivalent to 50 mcg of salmeterol base, in 12.5 mg of formulation containing lactose (which contains milk proteins). Each blister contains 1 complete dose of both medications. After a blister containing medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS 100/50, 250/50, and 500/50, respectively, 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 [FEV_1] 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS® inhalation device was 82.4 L/min (range, 46.1 to 115.3 L/min).

Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to 50 years) patients with asthma inhaling maximally through the DISKUS device show mean PIF of 122.2 L/min (range, 81.6 to 152.1 L/min). Inhalation profiles for pediatric patients with asthma inhaling maximally through the DISKUS device show a mean PIF of 75.5 L/min (range, 49.0 to 104.8 L/min) for the 4-year-old patient set (N = 20) and 107.3 L/min (range, 82.8 to 125.6 L/min) for the 8-year-old patient set (N = 20).

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

CLINICAL PHARMACOLOGY

Mechanism of Action: *ADVAIR DISKUS:* Since ADVAIR DISKUS contains both fluticasone propionate and salmeterol, the mechanisms of action described below for the individual components apply to ADVAIR DISKUS. These drugs represent 2 classes of medications (a synthetic corticosteroid and a selective, long-acting beta-adrenergic receptor agonist) that have different effects on clinical and physiological indices.

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.

Inflammation is also a component in the pathogenesis of chronic obstructive pulmonary disease (COPD). In contrast to asthma, however, the predominant inflammatory cells in COPD include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of corticosteroids in the treatment of COPD are not well defined and inhaled corticosteroids and fluticasone propionate when used apart from ADVAIR DISKUS are not indicated for the treatment of COPD.

Salmeterol Xinafoate: Salmeterol is a long-acting $beta_2$-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for $beta_2$-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on $beta_1$- and $beta_2$-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more selective for $beta_2$-adrenoceptors than albuterol. Although $beta_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-adrenoceptors are the predominant receptors in the heart, there are also $beta_2$-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic

AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

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

Pharmacokinetics: *ADVAIR DISKUS: Adult and Adolescent Patients 12 Years of Age and Older:* Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours and those of salmeterol were achieved in about 5 minutes.

In a single-dose crossover study, a higher than recommended dose of ADVAIR DISKUS was administered to 14 healthy adult subjects. Two (2) inhalations of the following treatments were administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, and fluticasone propionate powder 500 mcg alone. Mean peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL, respectively, and of salmeterol averaged 200 and 150 pg/mL, respectively, indicating no significant changes in systemic exposures of fluticasone propionate and salmeterol.

In a repeat-dose study, the highest recommended dose of ADVAIR DISKUS was administered to 45 adolescent and adult patients with asthma. One (1) inhalation twice daily of the following treatments was administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg alone. Mean peak steady-state plasma concentrations of fluticasone propionate averaged 57, 73, and 70 pg/mL, respectively, indicating no significant changes in systemic exposure of fluticasone propionate. No plasma concentrations of salmeterol were measured in this repeat-dose study.

No significant changes in excretion of fluticasone propionate or salmeterol were observed. The terminal half-life of fluticasone propionate averaged 5.33 to 7.65 hours when ADVAIR DISKUS was administered, which is similar to that reported when fluticasone propionate was given concurrently with salmeterol or when fluticasone propionate was given alone (average, 5.30 to 6.91 hours). No terminal half-life of salmeterol was reported upon administration of ADVAIR DISKUS or salmeterol given concurrently with fluticasone propionate.

Pediatric Patients: In a clinical study conducted in patients with asthma aged 4 to 11 years, fluticasone propionate concentrations were obtained in 61 patients at 20 and 40 minutes after dosing with 50 and 100 mcg of fluticasone propionate inhalation powder twice daily using the DISKUS. Plasma concentrations were low and ranged from undetectable (about 80% of the plasma samples) to 88 pg/mL. Mean peak fluticasone propionate plasma concentrations at the 50- and 100-mcg dose levels were 5 and 8 pg/mL, respectively.

Special Populations: Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted to examine gender differences or in special populations, such as elderly patients or patients with hepatic or renal impairment.

Drug Interactions: In the repeat- and single-dose studies, there was no evidence of significant drug interaction in systemic exposure between fluticasone propionate and salmeterol when given as ADVAIR DISKUS.

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. The systemic bioavailability of fluticasone propionate from the DISKUS device in healthy volunteers averages 18%.

Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone propionate inhalation powder using the DISKUS device. The mean fluticasone propionate plasma concentration was 110 pg/mL.

Peak steady-state fluticasone propionate plasma concentrations in subjects with COPD averaged 53 pg/mL (range, 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily (N = 30) via the DISKUS device.

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 91%. 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: Hepatic Impairment: Since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to

accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Gender: Full pharmacokinetic profiles were obtained from 9 female and 16 male patients with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using the DISKUS device and from 14 female and 43 male patients with COPD given 250 or 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Age: No relationship between fluticasone propionate systemic exposure and age was observed in 57 patients with COPD (aged 40 to 82 years) given 250 or 500 mcg twice daily.

Other: Formal pharmacokinetic studies using fluticasone propionate have not been conducted in other special populations.

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

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

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

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 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 was detected in either urine or feces.

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.

Special Populations: Hepatic Impairment: Since salmeterol is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Other: Formal pharmacokinetic studies using salmeterol base have not been conducted in other special populations.

Pharmacodynamics: *ADVAIR DISKUS: Adult and Adolescent Patients:* Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four (4) studies were conducted in healthy adult subjects: (1) a single-dose crossover study using 2 inhalations of ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg given alone, (2) a cumulative dose study using 50 to 400 mcg of salmeterol powder given alone or as ADVAIR DISKUS 500/50, (3) a repeat-dose study for 11 days using 2 inhalations twice daily of ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, or salmeterol powder 50 mcg, and (4) a single-dose study using 5 inhalations of ADVAIR DISKUS 100/50, fluticasone propionate powder 100 mcg alone, or placebo. In these studies no significant differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as ADVAIR DISKUS, concurrently with fluticasone propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic effects of salmeterol were not altered by the presence of fluticasone propionate in ADVAIR DISKUS. The potential effect of salmeterol on the effects of fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis was also evaluated in these studies. No significant differences across treatments were observed in 24-hour urinary cortisol excretion and, where measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone propionate were not altered by the presence of salmeterol in ADVAIR DISKUS in healthy subjects.

Asthma: In clinical studies with ADVAIR DISKUS in adult and adolescent patients 12 years of age and older with asthma, no significant differences were observed in the systemic pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adolescent and adult patients with asthma given either ADVAIR DISKUS 100/50 or ADVAIR DISKUS 250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

In a 28-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 500/50 twice daily was compared with the concurrent use of salmeterol powder 50 mcg plus fluticasone propionate powder 500 mcg from separate inhalers or fluticasone propionate powder 500 mcg alone. No significant differences across treatments were observed in plasma cortisol AUC after 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

In a 12-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 250/50 twice daily was compared with fluticasone propionate powder 250 mcg alone, salmeterol powder 50 mcg alone, and placebo. For most patients, the ability to increase cortisol production in response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with ADVAIR DISKUS. One patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who received placebo, 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients who received salmeterol.

Chronic Obstructive Pulmonary Disease: In clinical studies with ADVAIR DISKUS in patients with COPD associated with chronic bronchitis, no significant differences were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR DISKUS, the individual components of ADVAIR DISKUS, and placebo. In a study of ADVAIR DISKUS 250/50, 8 subjects (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in the fluticasone propionate 250 mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5) of these 8 subjects had a prolonged QTc interval at baseline.

In a 24-week study, 130 patients with COPD associated with chronic bronchitis received continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg, salmeterol powder 50 mcg, or placebo. No significant differences in ventricular or supraventricular arrhythmias and heart rate were observed among the groups treated with ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone propionate 500 mcg treatment groups).

Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in 101 patients with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate

powder 250 mcg, salmeterol powder 50 mcg, or placebo. For most patients, the ability to increase cortisol production in response to stress, as assessed by short cosyntropin stimulation, remained intact with ADVAIR DISKUS 250/50. One (1) patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by high-performance liquid chromatography) after dosing, compared with 2 patients (9%) who received fluticasone propionate 250 mcg, 2 patients (7%) who received salmeterol 50 mcg, and 1 patient (4%) who received placebo following 24 weeks of treatment or early discontinuation from study.

Pediatric Patients: In a 12-week study in patients with asthma aged 4 to 11 years who were receiving inhaled corticosteroids at study entry, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via the DISKUS. The values for 24-hour urinary cortisol excretion at study entry and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was also similar between the 2 groups.

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

Chronic Obstructive Pulmonary Disease: In a 24-week study, the steady-state fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of patients with COPD associated with chronic bronchitis (N = 86) randomized to twice-daily fluticasone propionate inhalation powder via the DISKUS 500 mcg, fluticasone propionate inhalation powder 250 mcg, or placebo. Serial serum cortisol concentrations were measured across a 12-hour dosing interval following at least 4 weeks of dosing. Serum cortisol concentrations following 250 and 500 mcg twice-daily dosing were 10% and 21% lower than placebo, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

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 (see PRECAUTIONS: General). 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.

Asthma: 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.

Chronic Obstructive Pulmonary Disease: In 24-week clinical studies in patients with COPD associated with chronic bronchitis, the incidence of clinically significant electrocardiogram (ECG) abnormalities (myocardial ischemia, ventricular hypertrophy, clinically significant conduction abnormalities, clinically significant arrhythmias) was lower for patients who received salmeterol (1%, 9 of 688 patients who received either salmeterol 50 mcg or ADVAIR DISKUS) compared with placebo (3%, 10 of 370 subjects).

No significant differences with salmeterol 50 mcg alone or in combination with fluticasone propionate as ADVAIR DISKUS 500/50 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 = 183) and after 12 weeks of therapy (N = 149). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar to those seen with placebo (see ADVERSE REACTIONS: Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis).

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

Asthma: *Adult and Adolescent Patients 12 Years of Age and Older:* In clinical trials comparing ADVAIR DISKUS with the individual components, improvements in most efficacy endpoints were greater with ADVAIR DISKUS than with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar results between ADVAIR DISKUS and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from separate inhalers.

Studies Comparing ADVAIR DISKUS to Fluticasone Propionate Alone or Salmeterol Alone: Three (3) double-blind, parallel-group clinical trials were conducted with ADVAIR DISKUS in 1,208 adolescent and adult patients (≥12 years, baseline FEV_1 63% to 72% of predicted normal) with asthma that was not optimally controlled on their current therapy. All treatments were inhalation powders, given as 1 inhalation from the DISKUS device twice daily, and other maintenance therapies were discontinued.

Study 1: Clinical Trial With ADVAIR DISKUS 100/50: This placebo-controlled, 12-week, US study compared ADVAIR DISKUS 100/50 with its individual components,

fluticasone propionate 100 mcg and salmeterol 50 mcg. The study was stratified according to baseline asthma maintenance therapy; patients were using either inhaled corticosteroids (N = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg) or salmeterol (N = 106). Baseline FEV_1 measurements were similar across treatments: ADVAIR DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and placebo, 2.15 L.

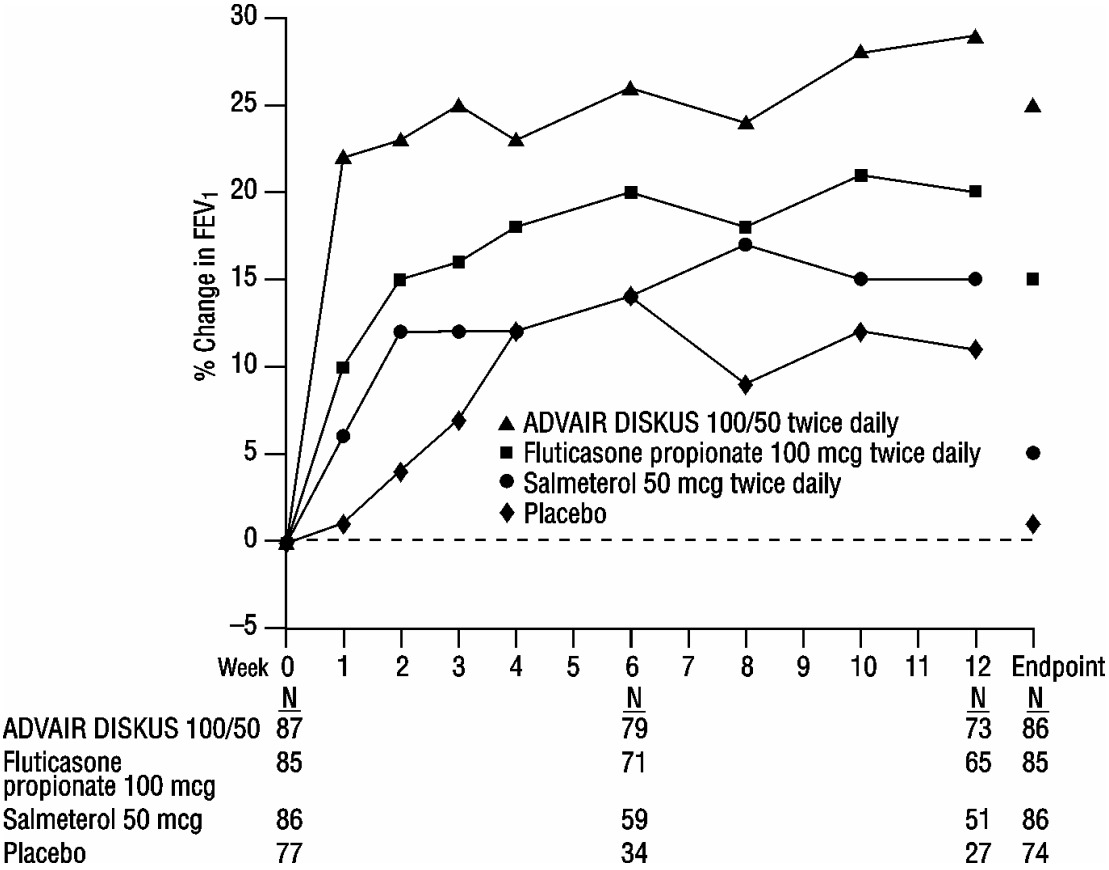
Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were utilized for this placebo-controlled study. Worsening asthma was defined as a clinically important decrease in FEV_1 or peak expiratory flow (PEF), increase in use of VENTOLIN® (albuterol, USP) Inhalation Aerosol, 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 DISKUS 100/50 were withdrawn due to worsening asthma compared with fluticasone propionate, salmeterol, and placebo.

Table 1. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)

ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
3%	11%	35%	49%

The FEV_1 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, FEV_1 results at Endpoint (last available FEV_1 result) are also provided. Patients receiving ADVAIR DISKUS 100/50 had significantly greater improvements in FEV_1 (0.51 L, 25%) compared with fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L, 1%). These improvements in FEV_1 with ADVAIR DISKUS were achieved regardless of baseline asthma maintenance therapy (inhaled corticosteroids or salmeterol).

Figure 1. Mean Percent Change From Baseline in FEV_1 in Patients With Asthma Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)



	N			N		N	N
ADVAIR DISKUS 100/50	87			79		73	86
Fluticasone propionate 100 mcg	85			71		65	85
Salmeterol 50 mcg	86			59		51	86
Placebo	77			34		27	74

The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in Table 2.

Table 2. Peak Expiratory Flow Results for Patients With Asthma Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)

Efficacy Variable*	ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
AM PEF (L/min)				
Baseline	393	374	369	382
Change from baseline	53	17	-2	-24
PM PEF (L/min)				
Baseline	418	390	396	398
Change from baseline	35	18	-7	-13

*Change from baseline = change from baseline at Endpoint (last available data).

The subjective impact of asthma on patients' perception 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 DISKUS 100/50 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 1.25 compared to placebo).

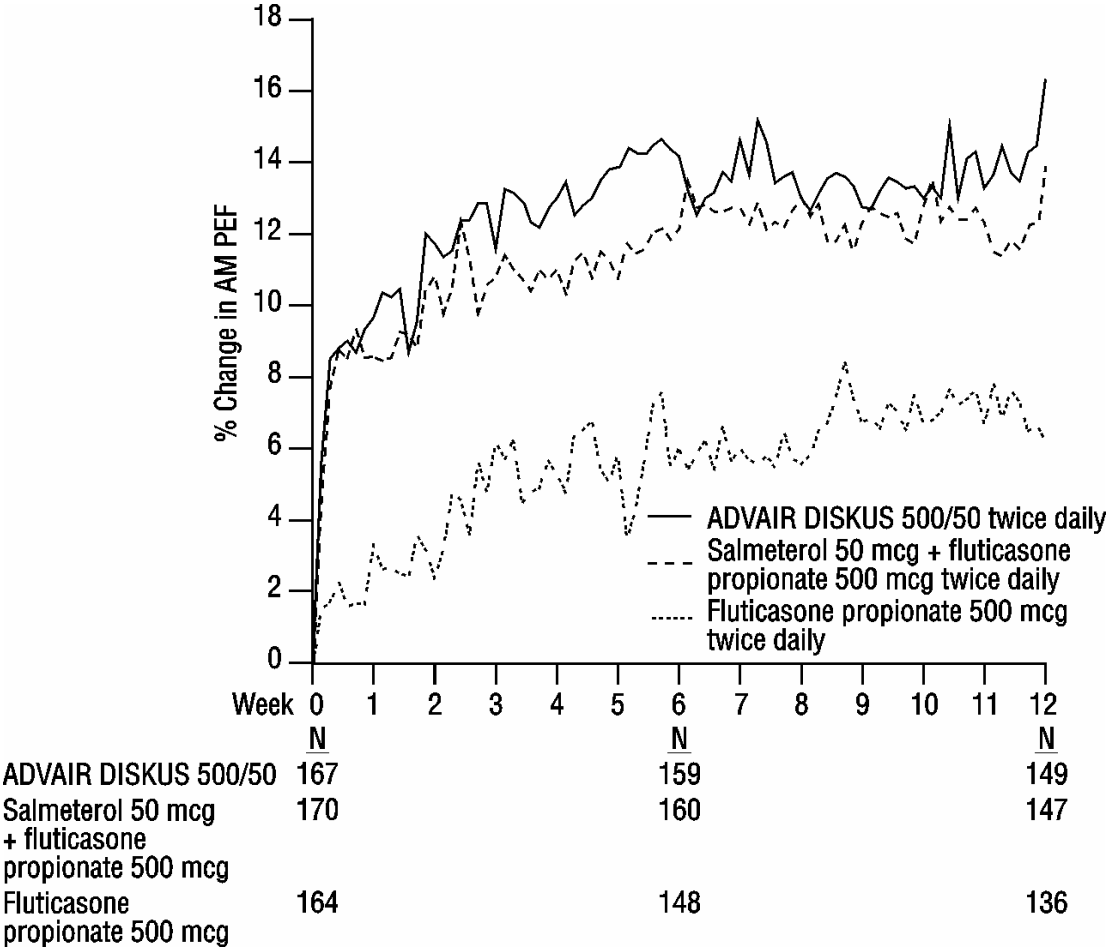
Study 2: Clinical Trial With ADVAIR DISKUS 250/50: This placebo-controlled, 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components, fluticasone propionate 250 mcg and salmeterol 50 mcg in 349 patients with asthma using inhaled corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100 to 1,600 mcg). Baseline FEV_1 measurements were similar across treatments: ADVAIR DISKUS 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

Efficacy results in this study were similar to those observed in Study 1. Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in FEV_1 (0.48 L, 23%) compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and placebo (decrease of 0.11 L, decrease of 5%). Statistically significantly fewer patients receiving ADVAIR DISKUS 250/50 were withdrawn from this study for worsening asthma (4%) compared with fluticasone propionate (22%), salmeterol (38%), and placebo (62%). In addition, ADVAIR DISKUS 250/50 was superior to fluticasone propionate, salmeterol, and placebo for improvements in morning and evening PEF. Patients receiving ADVAIR DISKUS 250/50 also had clinically meaningful improvements in overall asthma-specific quality of life as described in Study 1 (difference in AQLQ score of 1.29 compared to placebo).

Study 3: Clinical Trial With ADVAIR DISKUS 500/50: This 28-week, non-US study compared ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and concurrent therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from separate inhalers) twice daily in 503 patients with asthma using inhaled corticosteroids (daily doses of beclomethasone dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750 to 1,000 mcg inhalation powder]). The primary efficacy parameter, morning PEF, was collected daily for the first 12 weeks of the study. The primary purpose of weeks 13 to 28 was to collect safety data.

Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50, 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. As shown in Figure 2, morning PEF improved significantly with ADVAIR DISKUS 500/50 compared with fluticasone propionate 500 mcg over the 12-week treatment period. Improvements in morning PEF observed with ADVAIR DISKUS 500/50 were similar to improvements observed with concurrent therapy.

Figure 2. Mean Percent Change From Baseline in Morning Peak Expiratory Flow in Patients With Asthma Previously Treated With Inhaled Corticosteroids (Study 3)



Week	0	1	2	3	4	5	6	7	8	9	10	11	12
	N						N						N
ADVAIR DISKUS 500/50	167						159						149
Salmeterol 50 mcg + fluticasone propionate 500 mcg	170						160						147
Fluticasone propionate 500 mcg	164						148						136

Onset of Action and Progression of Improvement in Asthma Control: The onset of action and progression of improvement in asthma control were evaluated in the 2 placebo-controlled US trials. Following the first dose, the median time to onset of clinically significant bronchodilatation (≥15% improvement in FEV_1) in most patients was seen within 30 to 60 minutes. Maximum improvement in FEV_1 generally occurred within 3 hours, and clinically significant improvement was maintained for 12 hours (see Figure 3).

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

No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR DISKUS 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV_1 following 12 weeks of therapy.

Figure 3. Percent Change in Serial 12-hour FEV_1 in Patients With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)

First Treatment Day

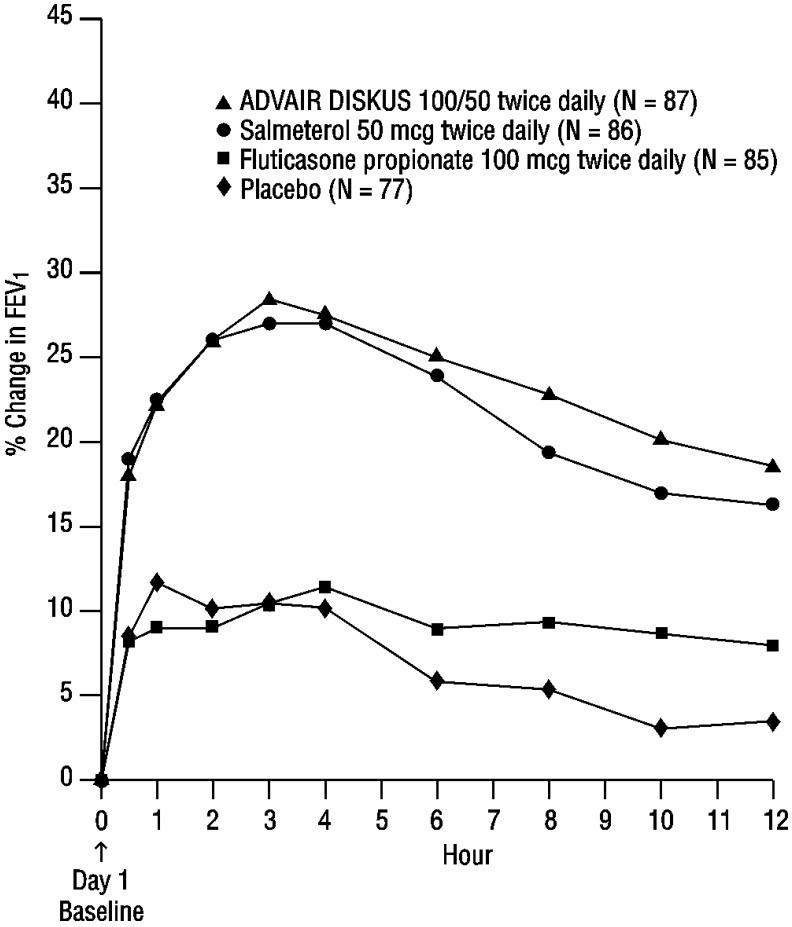
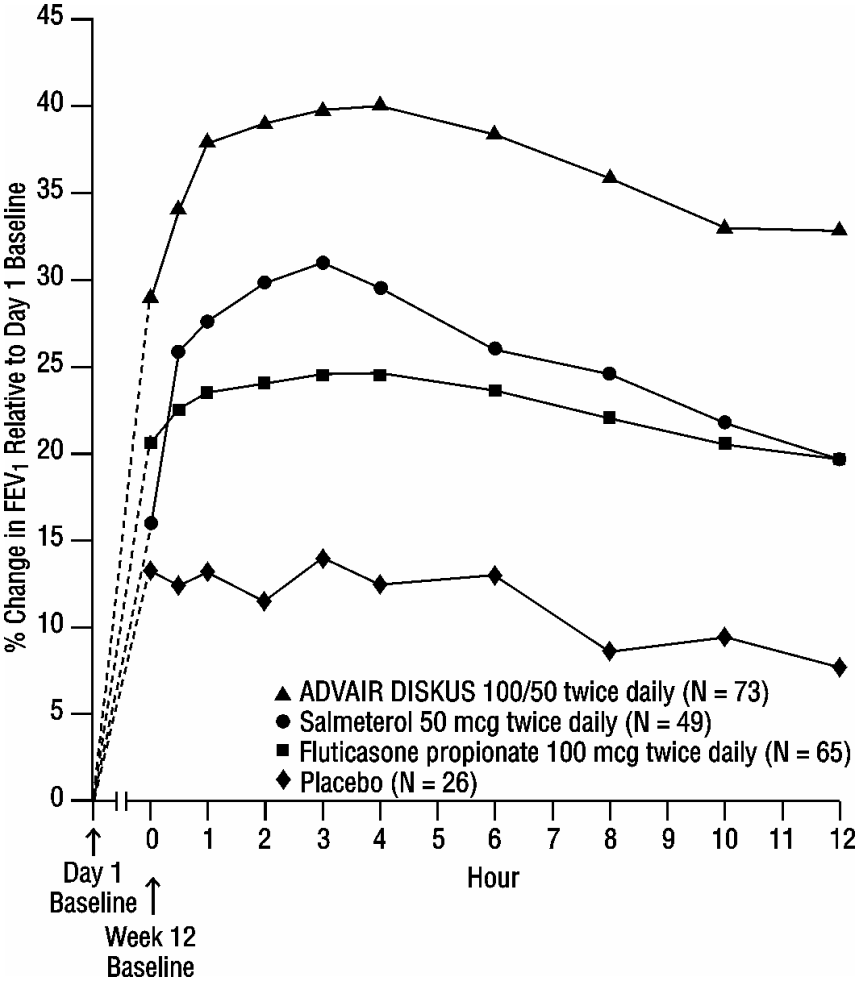


Figure 4. Percent Change in Serial 12-hour FEV_1 in Patients With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)

Last Treatment Day (Week 12)



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

Pediatric Patients: In a 12-week US study, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg twice daily in 203 children with asthma aged 4 to 11 years. At study entry, the children were symptomatic on low doses of inhaled corticosteroids (beclomethasone dipropionate 252 to 336 mcg/day; budesonide 200 to 400 mcg/day; flunisolide 1,000 mcg/day; triamcinolone acetonide 600 to 1,000 mcg/day; or fluticasone propionate 88 to 250 mcg/day). The primary objective of this study was to determine the safety of ADVAIR DISKUS 100/50 compared with fluticasone propionate inhalation powder

100 mcg in this age-group; however, the study also included secondary efficacy measures of pulmonary function. Morning predose FEV_1 was obtained at baseline and Endpoint (last available FEV_1 result) in children aged 6 to 11 years. In patients receiving ADVAIR DISKUS 100/50, FEV_1 increased from 1.70 L at baseline (N = 79) to 1.88 L at Endpoint (N = 69) compared with an increase from 1.65 L at baseline (N = 83) to 1.77 L at Endpoint (N = 75) in patients receiving fluticasone propionate 100 mcg.

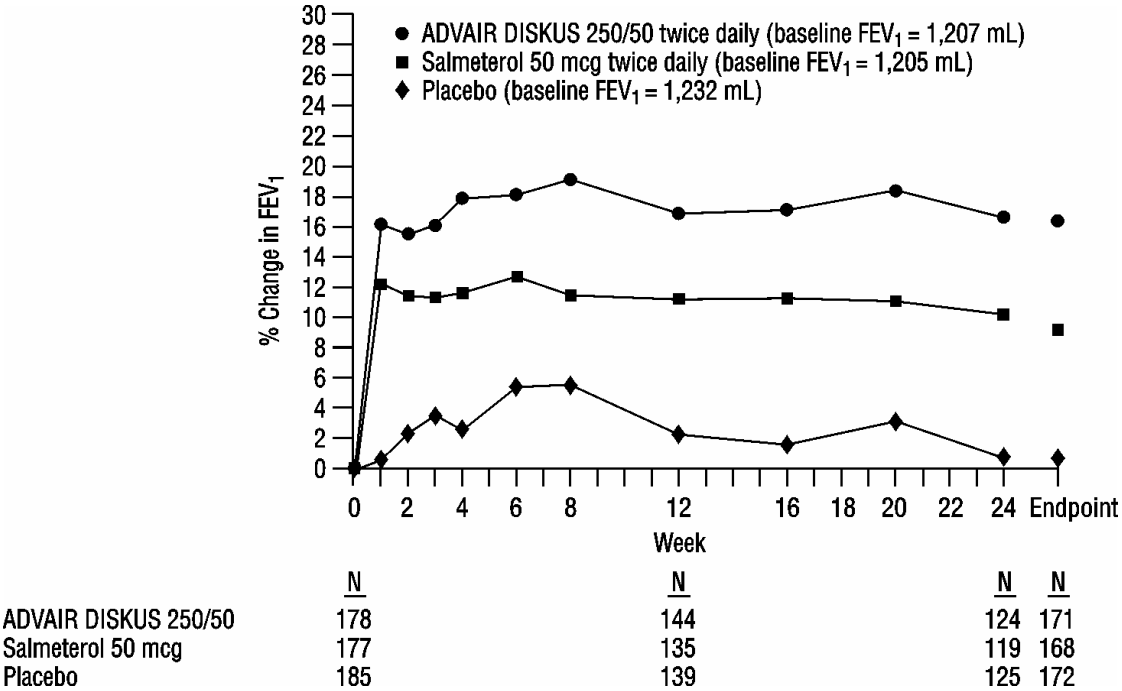
The findings of this study, along with extrapolation of efficacy data from patients 12 years of age and older, support the overall conclusion that ADVAIR DISKUS 100/50 is efficacious in the maintenance treatment of asthma in patients aged 4 to 11 years.

Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis: In a clinical trial evaluating twice-daily treatment with ADVAIR DISKUS 250/50 in patients with COPD associated with chronic bronchitis, improvements in lung function (as defined by predose and postdose FEV_1) were significantly greater with ADVAIR DISKUS than with fluticasone propionate 250 mcg, salmeterol 50 mcg, or placebo. The study was a randomized, double-blind, parallel-group, 24-week trial. All patients had a history of cough productive of sputum that was not attributable to another disease process on most days for at least 3 months of the year for at least 2 years. Study treatments were inhalation powders given as 1 inhalation from the DISKUS device twice daily. Maintenance COPD therapies were discontinued, with the exception of theophylline.

Figures 5 and 6 display predose and 2-hour postdose FEV_1 results. To account for patient withdrawals during the study, FEV_1 at Endpoint (last evaluable FEV_1) was evaluated. Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in predose FEV_1 at Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL, 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung function with ADVAIR DISKUS (Figure 5). Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in postdose FEV_1 at Endpoint (281 mL, 27%) compared with fluticasone propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the contribution of salmeterol to the improvement in lung function with ADVAIR DISKUS (Figure 6).

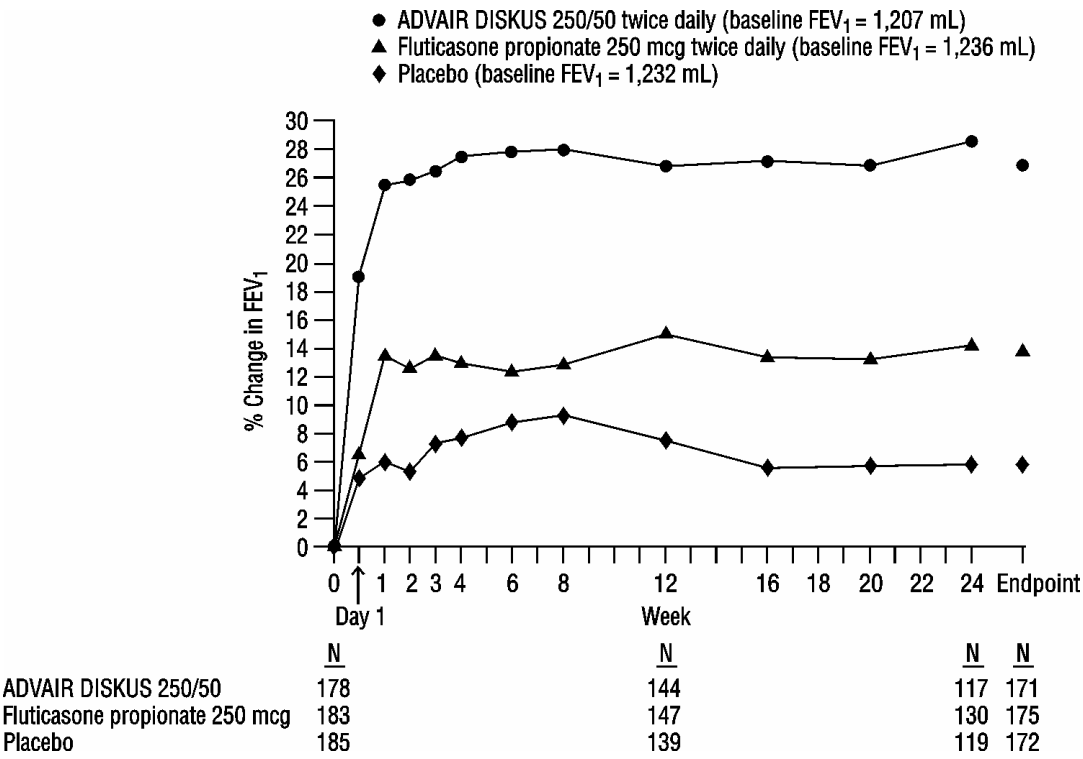
A similar degree of improvement in lung function was also observed with ADVAIR DISKUS 500/50 twice daily.

Figure 5. Predose FEV_1: Mean Percent Change From Baseline in Patients With COPD Associated With Chronic Bronchitis



	N	N	N	N
ADVAIR DISKUS 250/50	178	144	124	171
Salmeterol 50 mcg	177	135	119	168
Placebo	185	139	125	172

Figure 6. Two-Hour Postdose FEV_1: Mean Percent Changes From Baseline Over Time in Patients With COPD Associated With Chronic Bronchitis



Patients treated with ADVAIR DISKUS 250/50 or ADVAIR DISKUS 500/50 did not have a significant reduction in chronic bronchitis symptoms (as measured by the Chronic Bronchitis Symptom Questionnaire) or in COPD exacerbations compared to patients treated with placebo over the 24 weeks of therapy. The improvement in lung function with ADVAIR DISKUS 500/50 was similar to the improvement seen with ADVAIR DISKUS 250/50. Since there is evidence of more systemic exposure to fluticasone propionate from this higher dose and no documented advantage for efficacy, ADVAIR DISKUS 500/50 is not recommended for use in COPD.

The benefit of treatment of patients with COPD associated with chronic bronchitis with ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated.

INDICATIONS AND USAGE

Asthma: ADVAIR DISKUS is indicated for the long-term, twice-daily, maintenance treatment of asthma in patients 4 years of age and older.

Long-acting $beta_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS 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 DISKUS is not indicated in

patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta$_2$-agonists.

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

Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:

ADVAIR DISKUS 250/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis.

ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not recommended (see DOSAGE AND ADMINISTRATION: Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis).

The benefit of treating patients with COPD associated with chronic bronchitis with ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients who are treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis for periods longer than 6 months should be reevaluated periodically to assess the continuing benefits and potential risks of treatment.

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

CONTRAINDICATIONS

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

Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see DESCRIPTION and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site Specific*).

WARNINGS

Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS 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 beta$_2$-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 7). 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 $beta_2$-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 DISKUS, 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)

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

* 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.

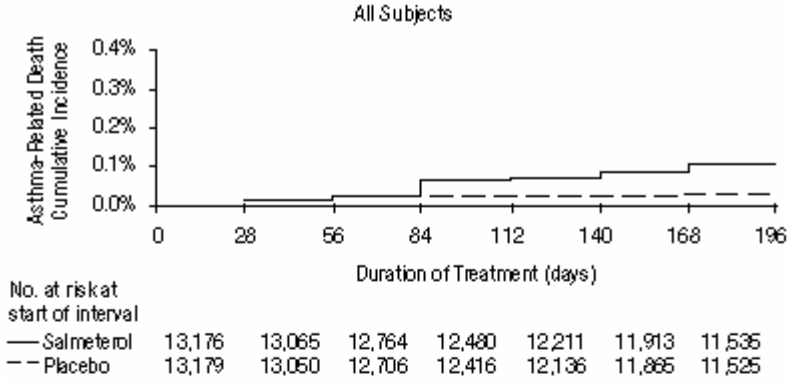
† Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week treatment period.

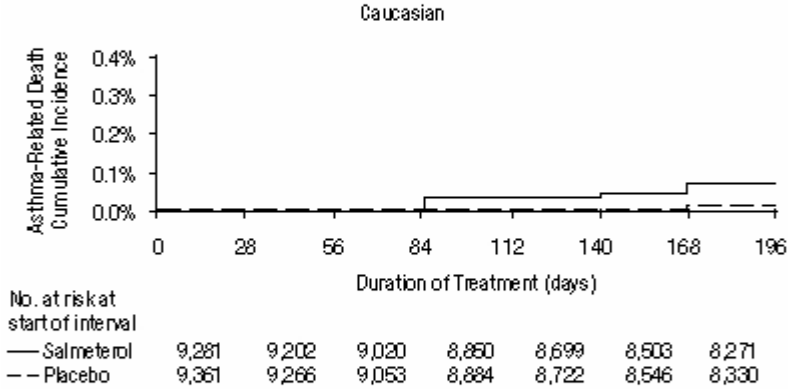
‡ Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period.

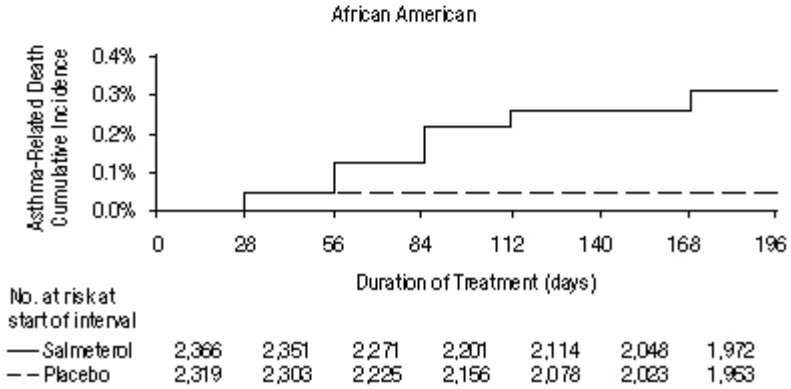
Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

§ 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 subjects 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 7. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART), by Duration of Treatment







A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate of asthma-related death was numerically, though not statistically significantly, greater in patients 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 beta$_2$ adrenergic agonists.

The following additional WARNINGS about ADVAIR DISKUS should be noted.

1. ADVAIR DISKUS 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 DISKUS, 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 beta$_2$-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 DISKUS Should Not Be Used to Treat Acute Symptoms. An inhaled, short-acting beta$_2$-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms of shortness of breath. When prescribing ADVAIR DISKUS, the physician must also provide the patient with an inhaled, short-acting beta$_2$-agonist (e.g., albuterol) for treatment of shortness of breath that occurs acutely, despite regular twice-daily (morning and evening) use of ADVAIR DISKUS.

When beginning treatment with ADVAIR DISKUS, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs. For patients taking ADVAIR DISKUS, inhaled, short-acting beta$_2$-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 Beta$_2$-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 beta$_2$-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 DISKUS with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation twice daily (morning and evening) of ADVAIR DISKUS.

4. ADVAIR DISKUS 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 physiological amounts of glucocorticoid 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 DISKUS Should Not Be Used in Conjunction With an Inhaled, Long-Acting $Beta_2$-Agonist. Patients who are receiving ADVAIR DISKUS twice daily should not use additional salmeterol or other inhaled, long-acting $beta_2$-agonists (e.g., formoterol) for prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma or the maintenance treatment of bronchospasm associated with COPD. Additional benefit would not be gained from using supplemental salmeterol or formoterol for prevention of EIB since ADVAIR DISKUS already contains an inhaled, long-acting $beta_2$-agonist.

6. The Recommended Dosage Should Not Be Exceeded. ADVAIR 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, ADVAIR DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ADVAIR DISKUS, it should be treated immediately with an inhaled, short-acting bronchodilator, ADVAIR DISKUS should be discontinued immediately, and alternative therapy should be instituted.

8. Immediate Hypersensitivity Reactions. Immediate hypersensitivity reactions may occur after administration of ADVAIR 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 fluticasone propionate and salmeterol, components of ADVAIR DISKUS.

10. Cardiovascular Disorders. ADVAIR DISKUS, 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 DISKUS, 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 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 DISKUS 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.

13. Drug Interaction With Ritonavir. A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, 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.

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 DISKUS, and may require

discontinuation of ADVAIR DISKUS. ADVAIR DISKUS, 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 electrocardiograms (ECGs) have been seen infrequently in individual patients in controlled clinical studies with ADVAIR DISKUS 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 DISKUS.

Metabolic and Other Effects: Long-term use of orally inhaled corticosteroids may affect normal bone metabolism, resulting in a loss of bone mineral density (BMD). A 2-year study of 160 patients (females 18 to 40 and males 18 to 50 years of age) with asthma receiving chlorofluorocarbon-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar region L1 through L4. Long-term treatment effects of fluticasone propionate on BMD in the COPD population have not been studied.

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 DISKUS may pose an additional risk. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended, including prior to instituting ADVAIR DISKUS 250/50 and periodically thereafter. If significant reductions in BMD are seen and ADVAIR DISKUS 250/50 is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered. ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of COPD associated with chronic bronchitis, and higher doses, including ADVAIR DISKUS 500/50, are not recommended.

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS; therefore, regular eye examinations should be considered.

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

Doses of the related $beta_2$-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 DISKUS 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 DISKUS, 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 DISKUS 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 DISKUS.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with ADVAIR DISKUS 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 DISKUS should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

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. The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known.

A 52-week, placebo-controlled study to assess the potential growth effects of fluticasone propionate inhalation powder (FLOVENT® ROTADISK®) at 50 and 100 mcg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (N = 76), 6.07 cm/year in the 50-mcg group (N = 98), and 5.66 cm/year in the 100-mcg group (N = 89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of

6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the 100-mcg group (n = 79). In children 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: boys – 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year.

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

The long-term effects of ADVAIR DISKUS in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or longer. In clinical studies in patients with asthma 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.

In clinical studies with ADVAIR DISKUS, 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 DISKUS, but at times therapy with ADVAIR DISKUS 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 DISKUS, 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*).

Chronic Obstructive Pulmonary Disease: ADVAIR DISKUS 250/50 twice daily is the only dosage recommended for the treatment of airflow obstruction in patients with COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not recommended, as no additional improvement in lung function (defined by predose and postdose

FEV_1) was observed in clinical trials and higher doses of corticosteroids increase the risk of systemic effects.

The benefit of treatment of patients with COPD associated with chronic bronchitis with ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients who are treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis for periods longer than 6 months should be reevaluated periodically to assess the continuing benefits and potential risks of treatment.

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 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 inhalation device appropriately and how it should be used 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, one of the active ingredients in ADVAIR DISKUS, 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 DISKUS, or other asthma-controller therapy modifies this risk.
2. ADVAIR DISKUS is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient in how it should be used). ADVAIR DISKUS is not meant to relieve acute asthma symptoms or exacerbations of COPD.
3. The physician should be notified immediately if any of the following signs of seriously worsening asthma occur:
   - decreasing effectiveness of inhaled, short-acting $beta_2$-agonists;
   - need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists;
   - significant decrease in lung function as outlined by the physician.
4. Patients should not stop therapy with ADVAIR DISKUS without physician/provider guidance since symptoms may recur after discontinuation.
5. Patients should be cautioned regarding common adverse effects associated with $beta_2$-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 DISKUS, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.

7. Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be told to monitor and, where appropriate, seek treatment for this condition.
8. When patients are prescribed ADVAIR DISKUS, other medications for asthma and COPD should be used only as directed by their physicians.
9. ADVAIR DISKUS should not be used with a spacer device.
10. Patients who are pregnant or nursing should contact their physicians about the use of ADVAIR DISKUS.
11. Patients should use ADVAIR DISKUS at regular intervals as directed. Results of clinical trials indicate 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.
12. The bronchodilation from a single dose of ADVAIR DISKUS may last up to 12 hours or longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not be exceeded. Patients who are receiving ADVAIR DISKUS twice daily should not use salmeterol or other inhaled, long-acting beta$_2$-agonists (e.g., formoterol) for prevention of EIB or maintenance treatment of asthma or the maintenance treatment of bronchospasm in COPD.
13. Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult their physicians without delay.
14. Effective and safe use of ADVAIR 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.
    - After inhalation, rinse the mouth with water without swallowing.
    - Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
    - Always keep the DISKUS in a dry place.
    - Discard **1 month** 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.
15. For the proper use of ADVAIR DISKUS and to attain maximum improvement, the patient should read and carefully follow the Instructions for Using ADVAIR DISKUS in the Medication Guide accompanying the product.
16. Most patients are able to taste or feel a dose delivered from ADVAIR DISKUS. However, whether or not patients are able to sense delivery of a dose, you should instruct them not to exceed the recommended dose of 1 inhalation each morning and evening, approximately 12 hours apart. You should instruct them to contact you or the pharmacist if they have questions.

Drug Interactions: ADVAIR DISKUS has been used concomitantly with other drugs, including short-acting beta$_2$-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma or COPD, without adverse drug reactions. No formal drug interaction studies have been performed with ADVAIR DISKUS.

Short-Acting Beta$_2$-Agonists: In clinical trials with patients with asthma, the mean daily need for albuterol by 166 adult and adolescent patients 12 years of age and older using ADVAIR DISKUS was approximately 1.3 inhalations/day, and ranged from 0 to 9 inhalations/day. Five percent (5%) of patients using ADVAIR DISKUS in these trials averaged 6 or more inhalations per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations per day.

In a COPD clinical trial, the mean daily need for albuterol for patients using ADVAIR DISKUS 250/50 was 4.1 inhalations/day. Twenty-six percent (26%) of patients using ADVAIR DISKUS 250/50 averaged 6 or more inhalations per day over the course of the 24-week trial. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations of albuterol per day.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent patients 12 years of age and older receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials with patients with asthma, 39 patients receiving ADVAIR DISKUS 100/50, 250/50, or 500/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 304 patients receiving ADVAIR DISKUS without theophylline. Similar results were observed in patients receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily concurrently with a theophylline product (N = 39) or without theophylline (N = 132).

In a COPD clinical trial, 17 patients receiving ADVAIR DISKUS 250/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 161 patients receiving ADVAIR DISKUS without theophylline. Based on the available data, the concomitant administration of methylxanthines with ADVAIR DISKUS did not alter the observed adverse event profile.

Fluticasone Propionate Nasal Spray: In adult and adolescent patients 12 years of age and older taking ADVAIR DISKUS in clinical trials, no difference in the profile of adverse events or HPA axis effects was noted between patients taking FLONASE® (fluticasone propionate) Nasal Spray, 50 mcg concurrently (N = 46) and those who were not (N = 130).

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: ADVAIR DISKUS 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 DISKUS, 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 DISKUS, 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 is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *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 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 plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when ADVAIR DISKUS is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.

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 and 10 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to, respectively, the maximum recommended daily inhalation dose in adults and children 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 daily inhalation dose in adults on a mcg/m^2 basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

Salmeterol: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral 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 plasma area under the curves [AUCs]) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. 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 and 25 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis). No tumors were seen at 0.21 mg/kg (approximately 15 and 8 times, respectively, the maximum recommended daily inhalation dose in adults and children 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 160 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

Pregnancy: ***Teratogenic Effects: ADVAIR DISKUS:*** 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 daily inhalation dose in adults on a mcg/m^2 basis) with 10 mg/kg orally of salmeterol (approximately 410 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) was teratogenic. Cleft palate, fetal death, increased implantation loss and delayed ossification were 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 daily inhalation dose in adults on a mcg/m^2 basis) and up to 1.4 mg/kg orally of salmeterol (approximately 55 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). In rats, no teratogenicity was observed at combination doses up to 30 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) and up to 1 mg/kg of salmeterol (approximately 80 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Combining 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) with 10 mg/kg orally of salmeterol (approximately 810 times the maximum recommended daily inhalation dose in adults on a

mg/m^2 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 DISKUS in pregnant women. ADVAIR DISKUS 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 (less than or equivalent to the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis), respectively, revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY).

Fluticasone propionate crossed the placenta following administration of a subcutaneous dose of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis), administration of a subcutaneous or an oral dose of 100 mcg/kg to rats (approximately equivalent to the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis), and administration of an oral dose of 300 mcg/kg to rabbits (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate 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 rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m^2 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/m^2 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 salmeterol in pregnant women. Salmeterol 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/m^2 basis).

Use in Labor and Delivery: There are no well-controlled human studies that have investigated effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of ADVAIR DISKUS 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 DISKUS, 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 DISKUS, 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 daily inhalation dose in adults on a mcg/m^2 basis) resulted in measurable radioactivity in milk.

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

Caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.

Pediatric Use: Use of ADVAIR DISKUS 100/50 in patients 4 to 11 years of age is supported by extrapolation of efficacy data from older patients and by safety and efficacy data from a study of ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years (see CLINICAL TRIALS: Asthma: *Pediatric Patients* and ADVERSE REACTIONS: Asthma: *Pediatric Patients*). The safety and effectiveness of ADVAIR DISKUS in children with asthma under 4 years of age have not been established.

Controlled clinical studies have shown that orally inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been 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.

Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS, may cause a reduction in growth velocity in children and adolescents (see PRECAUTIONS: General: *Metabolic and Other Effects*). The growth of pediatric patients receiving orally inhaled corticosteroids, including ADVAIR DISKUS, 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. To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, each patient should be titrated to the lowest strength that effectively controls his/her asthma (see DOSAGE AND ADMINISTRATION: Asthma).

Geriatric Use: Of the total number of patients in clinical studies of ADVAIR DISKUS for asthma, 44 were 65 years of age or older and 3 were 75 years of age or older. Of the total number of patients in a clinical study of ADVAIR DISKUS 250/50 for COPD, 85 were 65 years of age or older and 31 were 75 years of age or older. For both diseases, 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 $beta_2$-agonists, special caution should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by $beta_2$-agonists. Based on available data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR DISKUS in geriatric patients is warranted.

ADVERSE REACTIONS

Long-acting $beta_2$-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 DISKUS. 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 DISKUS, or other asthma controller therapy modifies the risk of asthma-related death.

Asthma: *Adult and Adolescent Patients 12 Years of Age and Older:* The incidence of common adverse events in Table 4 is based upon 2 placebo-controlled, 12-week, US clinical studies (Studies 1 and 2). A total of 705 adolescent and adult patients (349 females and 356 males) previously treated with salmeterol or inhaled corticosteroids were treated twice daily with ADVAIR DISKUS (100/50- or 250/50-mcg doses), fluticasone propionate inhalation powder (100- or 250-mcg doses), salmeterol inhalation powder 50 mcg, or placebo.

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

Adverse Event	ADVAIR DISKUS 100/50 (N = 92) %	ADVAIR DISKUS 250/50 (N = 84) %	Fluticasone Propionate 100 mcg (N = 90) %	Fluticasone Propionate 250 mcg (N = 84) %	Salmeterol 50 mcg (N = 180) %	Placebo (N = 175) %
Ear, nose, & throat						
Upper respiratory tract infection	27	21	29	25	19	14
Pharyngitis	13	10	7	12	8	6
Upper respiratory inflammation	7	6	7	8	8	5
Sinusitis	4	5	6	1	3	4
Hoarseness/dysphonia	5	2	2	4	<1	<1
Oral candidiasis	1	4	2	2	0	0
Lower respiratory						
Viral respiratory infections	4	4	4	10	6	3
Bronchitis	2	8	1	2	2	2
Cough	3	6	0	0	3	2
Neurology						
Headaches	12	13	14	8	10	7
Gastrointestinal						
Nausea & vomiting	4	6	3	4	1	1
Gastrointestinal discomfort & pain	4	1	0	2	1	1
Diarrhea	4	2	2	2	1	1
Viral gastrointestinal infections	3	0	3	1	2	2
Non-site specific						
Candidiasis unspecified site	3	0	1	4	0	1
Musculoskeletal						
Musculoskeletal pain	4	2	1	5	3	3
Average duration of exposure (days)	77.3	78.7	72.4	70.1	60.1	42.3

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 either of the groups receiving ADVAIR DISKUS and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account. Rare cases of

immediate and delayed hypersensitivity reactions, including rash and other rare events of angioedema and bronchospasm, have been reported.

These adverse reactions were mostly mild to moderate in severity.

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

Blood and Lymphatic: Lymphatic signs and symptoms.

Cardiovascular: Palpitations.

Drug Interaction, Overdose, and Trauma: Muscle injuries, fractures, wounds and lacerations, contusions and hematomas, burns.

Ear, Nose, and Throat: Rhinorrhea/postnasal drip; ear, nose, and throat infections; ear signs and symptoms; nasal signs and symptoms; nasal sinus disorders; rhinitis; sneezing; nasal irritation; blood in nasal mucosa.

Eye: Keratitis and conjunctivitis, viral eye infections, eye redness.

Gastrointestinal: Dental discomfort and pain, gastrointestinal signs and symptoms, gastrointestinal infections, gastroenteritis, gastrointestinal disorders, oral ulcerations, oral erythema and rashes, constipation, appendicitis, oral discomfort and pain.

Hepatobiliary Tract and Pancreas: Abnormal liver function tests.

Lower Respiratory: Lower respiratory signs and symptoms, pneumonia, lower respiratory infections.

Musculoskeletal: Arthralgia and articular rheumatism; muscle stiffness, tightness, and rigidity; bone and cartilage disorders.

Neurology: Sleep disorders, tremors, hypnagogic effects, compressed nerve syndromes.

Non-Site Specific: Allergies and allergic reactions, congestion, viral infections, pain, chest symptoms, fluid retention, bacterial infections, wheeze and hives, unusual taste.

Skin: Viral skin infections, urticaria, skin flakiness and acquired ichthyosis, disorders of sweat and sebum, sweating.

The incidence of common adverse events reported in Study 3, a 28-week, non-US clinical study of 503 patients previously treated with inhaled corticosteroids who were treated twice daily with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation powder 500 mcg was similar to the incidences reported in Table 4.

Pediatric Patients: Pediatric Study: ADVAIR DISKUS 100/50 was well tolerated in clinical trials conducted in children with asthma aged 4 to 11 years. The incidence of common adverse events in Table 5 is based upon a 12-week US study in 203 patients with asthma aged 4 to 11 years (74 females and 129 males) who were receiving inhaled corticosteroids at study entry and were randomized to either ADVAIR DISKUS 100/50 or fluticasone propionate inhalation powder 100 mcg twice daily.

Table 5. Overall Adverse Events With ≥3% Incidence With ADVAIR DISKUS 100/50 in Patients 4 to 11 Years of Age With Asthma

Adverse Event	ADVAIR DISKUS 100/50 (N = 101) %	Fluticasone Propionate 100 mcg (N = 102) %
Ear, nose, & throat		
Upper respiratory tract infection	10	17
Throat irritation	8	7
Ear, nose, & throat infections	4	<1
Epistaxis	4	<1
Pharyngitis/throat infection	3	2
Ear signs & symptoms	3	<1
Sinusitis	3	0
Neurology		
Headache	20	20
Gastrointestinal		
Gastrointestinal discomfort & pain	7	5
Nausea & vomiting	5	3
Candidiasis mouth/throat	4	<1
Non-site specific		
Fever	5	13
Chest symptoms	3	<1
Average duration of exposure (days)	74.8	78.8

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 ADVAIR DISKUS 100/50.

Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis: The incidence of common adverse events in Table 6 is based upon 1 placebo-controlled, 24-week, US clinical trial in patients with COPD associated with chronic bronchitis. A total of 723 adult patients (266 females and 457 males) were treated twice daily with ADVAIR DISKUS 250/50, fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder 50 mcg, or placebo.

Table 6. Overall Adverse Events With ≥3% Incidence With ADVAIR DISKUS 250/50 in Patients With Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis

Adverse Event	ADVAIR DISKUS 250/50 (N = 178) %	Fluticasone Propionate 250 mcg (N = 183) %	Salmeterol 50 mcg (N = 177) %	Placebo (N = 185) %
Ear, nose, & throat				
Candidiasis mouth/throat	10	6	3	1
Throat irritation	8	5	4	7
Hoarseness/dysphonia	5	3	<1	0
Sinusitis	3	8	5	3
Lower respiratory				
Viral respiratory infections	6	4	3	3
Neurology				
Headaches	16	11	10	12
Dizziness	4	<1	3	2
Non-site specific				
Fever	4	3	0	3
Malaise & fatigue	3	2	2	3
Musculoskeletal				
Musculoskeletal pain	9	8	12	9
Muscle cramps & spasms	3	3	1	1
Average duration of exposure (days)	141.3	138.5	136.1	131.6

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 ADVAIR DISKUS 250/50 and were more common than in the placebo group.

These adverse reactions were mostly mild to moderate in severity.

Other adverse events that occurred in the groups receiving ADVAIR DISKUS 250/50 with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

Cardiovascular: Syncope.

Drug Interaction, Overdose, and Trauma: Postoperative complications.

Ear, Nose, and Throat: Ear, nose, and throat infections; ear signs and symptoms; laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection.

Endocrine and Metabolic: Hypothyroidism.

Eye: Dry eyes, eye infections.

Gastrointestinal: Constipation, gastrointestinal signs and symptoms, oral lesions.

Hepatobiliary Tract and Pancreas: Abnormal liver function tests.

Lower Respiratory: Breathing disorders, lower respiratory signs and symptoms.

Non-Site Specific: Bacterial infections, candidiasis unspecified site, edema and swelling, nonspecific conditions, viral infections.

Psychiatry: Situational disorders.

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 DISKUS, fluticasone propionate, and/or salmeterol or a combination of these factors.

In extensive US and worldwide postmarketing experience with salmeterol, a component of ADVAIR DISKUS, 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), ventricular tachycardia.

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

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

Eye: Cataracts, glaucoma.

Gastrointestinal: Abdominal pain, dyspepsia, xerostomia.

Musculoskeletal: Back pain, cramps, muscle spasm, myositis.

Neurology: Paresthesia, restlessness.

Non-Site Specific: Immediate and delayed hypersensitivity reaction (including very rare anaphylactic reaction), pallor. Very rare anaphylactic reaction in patients with severe milk protein allergy.

Psychiatry: Agitation, aggression, depression.

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

Skin: Contact dermatitis, contusions, ecchymoses, photodermatitis.

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 DISKUS, 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 DISKUS 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 DISKUS: No deaths occurred in rats given an inhaled single-dose combination of salmeterol 3.6 mg/kg (approximately 290 and 140 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis) and 1.9 mg/kg of fluticasone propionate (approximately 15 and 35 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 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 inhalation aerosol was 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 (>4,100 and >9,600 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis). In rats the subcutaneous median lethal dose was >1,000 mg/kg (>8,100 and >19,200 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 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 240 and 110 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 and 90 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6,100 and 2,900 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis) and in rats at 1,000 mg/kg (approximately 81,000 and 38,000 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION

ADVAIR DISKUS should be administered by the orally inhaled route only (see Instructions for Using ADVAIR DISKUS in the Medication Guide accompanying the product). After inhalation, the patient should rinse the mouth with water without swallowing. ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid therapy.

Asthma: Long-acting $beta_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS 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 DISKUS is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting $beta_2$-agonists.

ADVAIR DISKUS is available in 3 strengths, ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50, containing 100, 250, and 500 mcg of fluticasone propionate, respectively, and 50 mcg of salmeterol per inhalation.

ADVAIR DISKUS should be administered twice daily every day. More frequent administration (more than twice daily) or a higher number of inhalations (more than 1 inhalation twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. The safety and efficacy of ADVAIR DISKUS when administered in excess of recommended doses have not been established.

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

Patients who are receiving ADVAIR DISKUS twice daily should not use additional salmeterol or other inhaled, long-acting beta$_2$-agonists (e.g., formoterol) for prevention of EIB, or for any other reason.

Adult and Adolescent Patients 12 Years of Age and Older: For patients 12 years of age and older, the dosage is 1 inhalation twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for ADVAIR DISKUS for patients 12 years of age and older are based upon patients' current asthma therapy.

- For patients not adequately controlled on an inhaled corticosteroid, Table 7 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 ADVAIR DISKUS 100/50 or 250/50 twice daily (see INDICATIONS AND USAGE).

The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

For all patients it is desirable to titrate to the lowest effective strength after adequate asthma stability is achieved.

Table 7. Recommended Dosages of ADVAIR DISKUS for Patients With Asthma Aged 12 Years and Older Not Adequately Controlled on Inhaled Corticosteroids

Current **Daily Dose** of Inhaled Corticosteroid		Recommended Strength and Dosing Schedule of ADVAIR DISKUS
Beclomethasone dipropionate HFA inhalation aerosol	≤160 mcg	100/50 twice daily
	320 mcg	250/50 twice daily
	640 mcg	500/50 twice daily
Budesonide inhalation aerosol	≤400 mcg	100/50 twice daily
	800-1,200 mcg	250/50 twice daily
	1,600 mcg*	500/50 twice daily
Flunisolide inhalation aerosol	≤1,000 mcg	100/50 twice daily
	1,250-2,000 mcg	250/50 twice daily
Flunisolide HFA inhalation aerosol	≤320 mcg	100/50 twice daily
	640 mcg	250/50 twice daily
Fluticasone propionate HFA inhalation aerosol	≤176 mcg	100/50 twice daily
	440 mcg	250/50 twice daily
	660-880 mcg*	500/50 twice daily
Fluticasone propionate inhalation powder	≤200 mcg	100/50 twice daily
	500 mcg	250/50 twice daily
	1,000 mcg*	500/50 twice daily
Mometasone furoate inhalation powder	220 mcg	100/50 twice daily
	440 mcg	250/50 twice daily
	880 mcg	500/50 twice daily
Triamcinolone acetonide inhalation aerosol	≤1,000 mcg	100/50 twice daily
	1,100-1,600 mcg	250/50 twice daily

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

Improvement in asthma control following inhaled administration of ADVAIR DISKUS 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 DISKUS with a higher strength may provide additional improvement in asthma control.

If a previously effective dosage regimen of ADVAIR DISKUS 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 DISKUS with a higher

strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be considered.

Pediatric Patients: For patients aged 4 to 11 years who are symptomatic on an inhaled corticosteroid the dosage is 1 inhalation of ADVAIR DISKUS 100/50 twice daily (morning and evening, approximately 12 hours apart).

Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis: The dosage for adults is 1 inhalation (250/50 mcg) twice daily (morning and evening, approximately 12 hours apart).

ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not recommended, as no additional improvement in lung function was observed in clinical trials and higher doses of corticosteroids increase the risk of systemic effects.

If shortness of breath occurs in the period between doses, an inhaled, short-acting $beta_2$-agonist should be taken for immediate relief.

Patients who are receiving ADVAIR DISKUS twice daily should not use additional salmeterol or other inhaled, long-acting $beta_2$-agonists (e.g., formoterol) for the maintenance treatment of COPD or for any other reason.

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

Directions for Use: Illustrated Patient's Instructions for Use accompany each package of ADVAIR DISKUS.

HOW SUPPLIED

ADVAIR DISKUS 100/50 is supplied as a disposable, purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0695-02).

ADVAIR DISKUS 250/50 is supplied as a disposable, purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0696-02).

ADVAIR DISKUS 500/50 is supplied as a disposable, purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional

pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0697-02).

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. The DISKUS inhalation device is not reusable. The device should be discarded 1 month 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. Do not attempt to take the device apart.

GlaxoSmithKline
Research Triangle Park, NC 27709

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MEDICATION GUIDE

ADVAIR [*ad′vair*] DISKUS®
(fluticasone propionate and salmeterol inhalation powder)

ADVAIR DISKUS
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

ADVAIR DISKUS
(fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder)

ADVAIR DISKUS
(fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder)

Read the Medication Guide that comes with ADVAIR 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 ADVAIR DISKUS?

- **ADVAIR DISKUS 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 beta$_2$-agonist medicine or LABA. LABA medicines are used in patients with asthma and chronic obstructive pulmonary disease (COPD). LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.

- **In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in ADVAIR DISKUS), 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 DISKUS, 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 DISKUS.

- **ADVAIR DISKUS does not relieve sudden symptoms. Always have a short-acting beta$_2$-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 DISKUS unless told to do so by your healthcare provider because your symptoms might get worse.**

- **ADVAIR DISKUS** 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 DISKUS. You may need different treatment.**

- **Get emergency medical care if:**
  - **breathing problems worsen quickly, and**
  - **you use your short-acting beta$_2$-agonist medicine, but it does not relieve your breathing problems.**

What is ADVAIR DISKUS?

ADVAIR DISKUS combines an inhaled corticosteroid medicine, fluticasone propionate (the same medicine found in FLOVENT) and a long-acting beta$_2$-agonist medicine, salmeterol (the same medicine found in SEREVENT). ADVAIR DISKUS is used for asthma and chronic obstructive pulmonary disease (COPD) as follows:

Asthma

ADVAIR 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.

ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). Because LABA medicines such as salmeterol may increase the chance of death from asthma problems, ADVAIR 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 beta$_2$-agonist medicines once in awhile

Chronic Obstructive Pulmonary Disease (COPD)

ADVAIR 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 ADVAIR 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**
- **have osteoporosis**
- **have an immune system problem**
- **are pregnant or planning to become pregnant.** It is not known if ADVAIR DISKUS may harm your unborn baby.
- **are breastfeeding.** It is not known if ADVAIR DISKUS passes into your milk and if it can harm your baby.
- **are allergic to ADVAIR DISKUS, any other medicines, or food products**
- **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 DISKUS 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 DISKUS?

See the step-by-step instructions for using the ADVAIR DISKUS at the end of this Medication Guide. Do not use the ADVAIR 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 ADVAIR DISKUS with an adult's help, as instructed by the child's healthcare provider.

- Use ADVAIR DISKUS exactly as prescribed. **Do not use ADVAIR DISKUS more often than prescribed.** ADVAIR DISKUS comes in 3 strengths. Your healthcare provider will prescribe the one that is best for your condition.

- The usual dose of ADVAIR DISKUS is 1 inhalation twice a day (morning and evening). The 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR DISKUS.

- If you miss a dose of ADVAIR DISKUS, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.

- Do not use a spacer device with ADVAIR DISKUS.

- Do not breathe into ADVAIR DISKUS.

- **While you are using ADVAIR DISKUS twice a day, you should not use other medicines that contain a long-acting beta$_2$-agonist or LABA for any reason. Other LABA medicines include SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder) or FORADIL® AEROLIZER™ (formoterol fumarate inhalation powder).**

- 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 beta$_2$-agonist medicine with you. Use your short-acting beta$_2$-agonist medicine if you have breathing problems between doses of ADVAIR DISKUS.

- **Call your healthcare provider or get medical care right away if:**
  - your breathing problems worsen with ADVAIR DISKUS
  - you need to use your short-acting beta$_2$-agonist medicine more often than usual
  - your short-acting beta$_2$-agonist medicine does not work as well for you at relieving symptoms
  - you need to use 4 or more inhalations of your short-acting beta$_2$-agonist medicine for 2 or more days in a row
  - you use 1 whole canister of your short-acting beta$_2$-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 DISKUS regularly for 1 week

What are the possible side effects with ADVAIR DISKUS?

- **ADVAIR DISKUS 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 DISKUS?"

Other possible side effects with ADVAIR 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**
- **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 DISKUS.
- **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 DISKUS. Ask your healthcare provider or pharmacist for more information.

How do I store ADVAIR DISKUS?

- Store ADVAIR 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 ADVAIR DISKUS 1 month after you remove it from the foil pouch, or after the dose indicator reads "0", whichever comes first.
- **Keep ADVAIR DISKUS and all medicines out of the reach of children.**

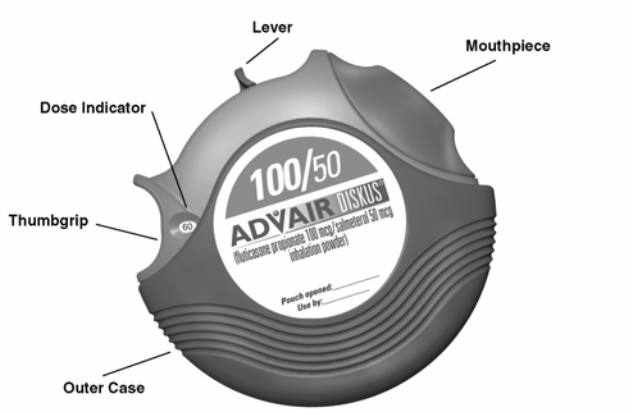
General Information about ADVAIR DISKUS

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

This Medication Guide summarizes the most important information about ADVAIR 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 ADVAIR DISKUS that was written for healthcare professionals. You can also contact the company that makes ADVAIR DISKUS (toll free) at 1-888-825-5249 or at www.advair.com.

Instructions for Using ADVAIR DISKUS

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



How to Use Your ADVAIR DISKUS

Take the ADVAIR DISKUS out of the box and foil overwrap pouch. Write the **"Pouch opened"** and **"Use by"** dates on the label on top of the DISKUS. **The "Use by" date is 1 month 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)*. If you are using a "sample" DISKUS, the numbers 5 to 0 will appear in red after 23 doses.

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

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

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.

Rinse your mouth with water after breathing-in the medicine. Spit the water out. Do not swallow.

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 the steps 1 to 4.)

Figure 6

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.
- After each dose, rinse your mouth with water and spit the water out. Do not swallow.
- 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

GlaxoSmithKline

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