CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-077 /S019

Trade Name: Advair Diskus

Generic Name: fluticasone propionate/salmeterol powder

Sponsor: GlaxoSmithKline

Approval Date: August 11, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-077 /S019

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-077 /S019

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-077/S-019

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Attention: C. Elaine Jones, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Jones:

Please refer to your supplemental new drug application dated August 6, 2003, received August 7, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advair Diskus (fluticasone propionate/salmeterol inhalation powder).

This supplemental new drug application provides for revision to the package insert to incorporate results of the Serevent Multicenter Asthma Research Trial (SMART) including a boxed warning and revisions to the WARNINGS section and the Information for Patients subsection of the PRECAUTIONS section.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert submitted August 6, 2003).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-077/S-019." Approval of this submission by FDA is not required before the labeling is used.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Division Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Marianne Mann
8/11/03 05:46:27 PM
Signing for Dr. Chowdhury in his absence in my role as Acting Director

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-077/S019

LABELING

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**

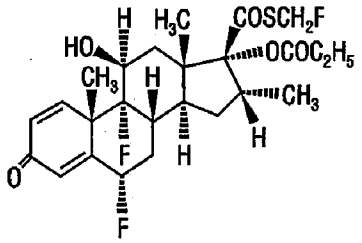
For Oral Inhalation Only

WARNING: 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 a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,174 patients treated for 28 weeks) versus those on placebo (4 of 13,179). Subgroup analyses suggest the risk may be greater in African-American patients compared to Caucasians (see WARNINGS).

DESCRIPTION

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

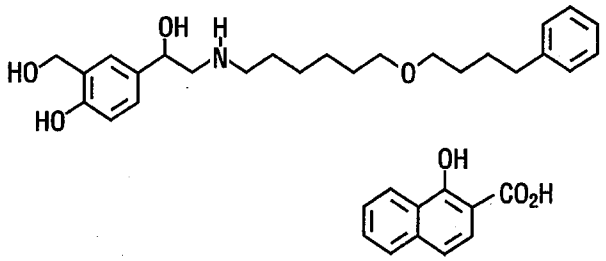
One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having the chemical name *S*-(fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



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 highly selective 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 $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. 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 (N = 9) 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® device was 80.0 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).

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:* ADVAIR DISKUS is designed to produce a greater improvement in pulmonary function and symptom control than either fluticasone propionate or salmeterol used alone at their recommended dosages. 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 long-acting beta-adrenergic receptor agonist) that have different effects on clinical, physiological, and inflammatory indices of asthma.

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

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

Salmeterol Xinafoate: Salmeterol is a long-acting $beta_2$-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:*** Following administration of ADVAIR DISKUS to healthy 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 subjects. Two 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 patients with asthma. One 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.

Special Populations: Formal pharmacokinetic studies using ADVAIR DISKUS were not 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 (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.

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 given fluticasone propionate inhalation powder 500 mcg twice daily using the DISKUS. No overall differences in fluticasone propionate pharmacokinetics were observed.

Other: Formal pharmacokinetic studies using fluticasone propionate were not carried out in other special populations.

Drug Interactions: In a multiple-dose drug interaction study, coadministration of fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics. In another drug interaction study, coadministration of fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased fluticasone propionate concentrations and reduced plasma cortisol area under the plasma concentration versus time curve (AUC), but had no effect on urinary excretion of cortisol. Since fluticasone propionate is a substrate of cytochrome P450 3A4, caution should be exercised when cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole) are coadministered with fluticasone propionate as this could result in increased plasma concentrations of fluticasone propionate.

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: Binding of salmeterol 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 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: Formal pharmacokinetic studies of salmeterol base have not been conducted in special populations. 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.

Pharmacodynamics: ***ADVAIR DISKUS:*** Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four studies were conducted in healthy 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.

In clinical studies with ADVAIR DISKUS in patients 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 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 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.

Fluticasone Propionate: In clinical trials with fluticasone propionate inhalation powder using doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL) were noted both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out in 64 patients with mild, persistent asthma (mean 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.

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

The effects of rising 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.

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

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 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.

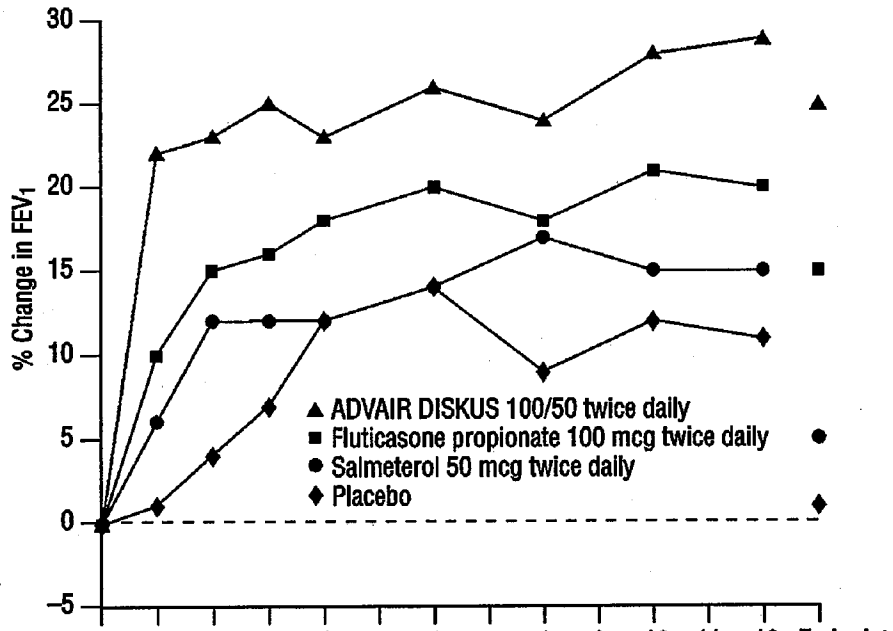
Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were utilized for this placebo-controlled study. Worsening asthma was defined as a clinically important decrease in FEV_1 or peak expiratory flow (PEF), increase in use of VENTOLIN® (albuterol, USP) Inhalation Aerosol, 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 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 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).

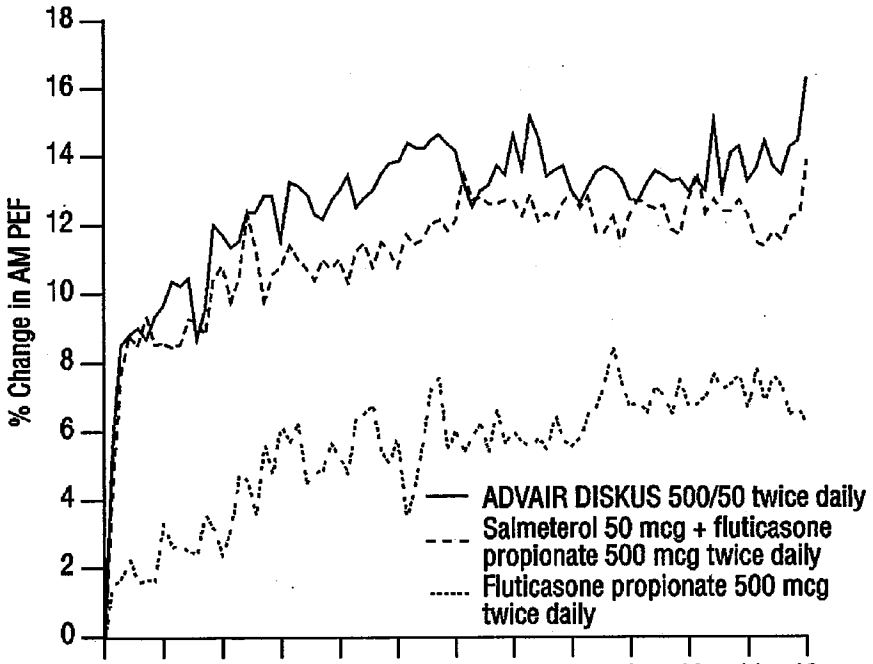
Study 2: Clinical Trial With ADVAIR DISKUS 250/50: This placebo-controlled, 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components, fluticasone propionate 250 mcg and salmeterol 50 mcg in 349 patients using inhaled corticosteroids (daily doses of beclomethasone dipropionate 462 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 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 Previously Treated With Inhaled Corticosteroids (Study 3)



	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 Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)

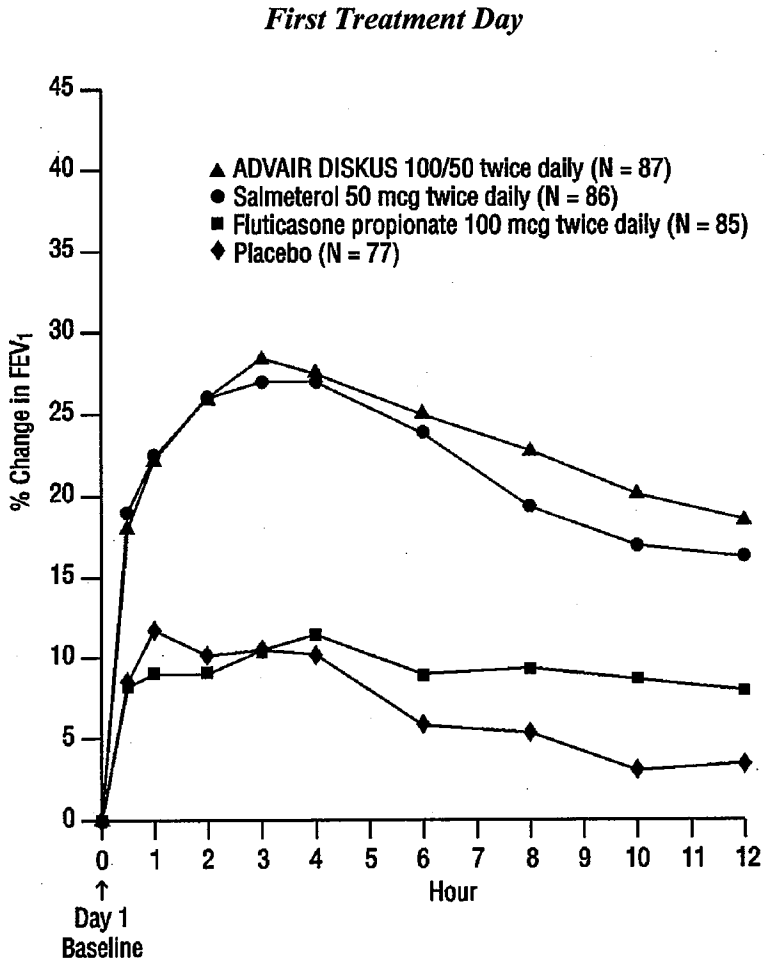
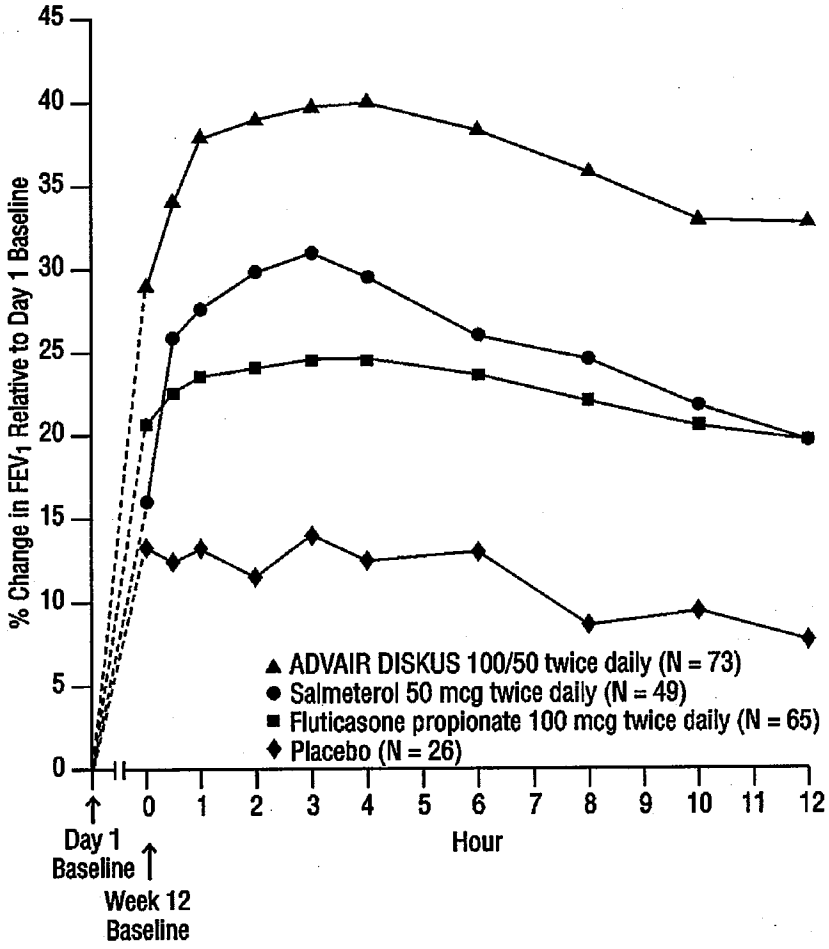


Figure 4. Percent Change in Serial 12-hour FEV_1 in Patients Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)

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.

INDICATIONS AND USAGE

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

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 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

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL, A COMPONENT OF ADVAIR DISKUS, MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. The Salmeterol Multi-center Asthma Research Trial (SMART) 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. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). Other endpoints included combined asthma-related deaths or life-threatening experiences and asthma-related deaths.

A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,353). The analysis showed no significant difference for the primary endpoint for the total population. However, a higher number of asthma-related deaths or life-threatening experiences (36 vs. 23) and a higher number of asthma-related deaths (13 vs. 4) occurred in the patients treated with SEREVENT Inhalation Aerosol. Post hoc subgroup analyses revealed no significant increase in respiratory- or asthma-related episodes, including deaths, in Caucasian patients. In African-Americans, the study showed a small, though statistically significantly greater, number of primary events (20 vs. 7), asthma-related deaths or life-threatening experiences (19 vs. 4), and asthma-related deaths (8 vs. 1) in patients taking SEREVENT Inhalation Aerosol compared to those taking placebo. Even though SMART did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African-American patients and difficulties in enrollment. The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, a component of ADVAIR DISKUS, provides protection from this risk. Therefore, it is not known whether the findings seen with SEREVENT Inhalation Aerosol would apply to ADVAIR DISKUS.

Findings similar to the SMART study findings were reported in a prior 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma-related death was numerically, though not statistically, greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol (180 mcg 4 times daily) added to usual asthma therapy.

Given the similar basic mechanisms of action of $beta_2$-agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect.

1. **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.

2. **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 or simply failed to relieve the deteriorating asthma.

3. <u>Do Not Use ADVAIR DISKUS to Treat Acute Symptoms:</u> An inhaled, short-acting $beta_2$-agonist, not ADVAIR DISKUS, should be used to relieve acute asthma symptoms. 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 symptoms that occur 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 asthma symptoms (see PRECAUTIONS: Information for Patients).

4. Watch for Increasing Use of Inhaled, Short-Acting Beta$_2$-Agonists, Which Is a Marker of Deteriorating Asthma: Asthma 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 PEF, these may be a marker of destabilization of asthma. 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.

5. Do Not Use an Inhaled, Long-Acting Beta$_2$-Agonist in Conjunction With ADVAIR DISKUS: Patients who are receiving ADVAIR DISKUS twice daily should not use salmeterol or other inhaled, long-acting beta$_2$-agonists for prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma. Additional benefit would not be gained from using supplemental salmeterol for prevention of EIB since ADVAIR DISKUS already contains salmeterol.

6. Do Not Exceed Recommended Dosage: 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 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 electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown.

11. Discontinuation of Systemic Corticosteroids: Transfer of patients from systemic corticosteroid therapy to ADVAIR DISKUS may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, and arthritis.

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.

PRECAUTIONS

General: 1. Cardiovascular Effects: No effect on the cardiovascular system is usually seen after the administration of inhaled ADVAIR DISKUS at recommended doses. The cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of salmeterol, 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.

2. Metabolic and Other Effects: 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 rarely 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 permit control of 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 these drugs 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.

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS: Pediatric Use). Patients should be maintained on the lowest strength of ADVAIR DISKUS 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 with patients treated for 2 years with inhaled fluticasone propionate, no

apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS.

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.

3. 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).

Information for Patients: 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 medications they are taking. Patients should be given the following information:

1. 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 exceed the prescribed dosage and should contact the physician if symptoms do not improve or if the condition worsens.
2. Patients should not stop therapy with ADVAIR DISKUS without physician/provider guidance since symptoms may recur after discontinuation.
3. 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.

4. 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 for prevention of EIB or maintenance treatment of asthma.
5. 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).
6. The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma:
   - 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 peak flow as outlined by the physician.
7. Patients should be cautioned regarding common adverse cardiovascular effects, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
8. When patients are prescribed ADVAIR DISKUS, other inhaled drugs and asthma medications should be used only as directed by the physician.
9. ADVAIR DISKUS should not be used with a spacer device.
10. Patients who are pregnant or nursing should contact the physician about the use of ADVAIR DISKUS.
11. 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 every blister has been used (when the dose indicator reads "0"), whichever comes first.
12. Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult their physicians without delay.
13. For the proper use of ADVAIR DISKUS and to attain maximum improvement, the patient should read and follow carefully the Patient's Instructions for Use accompanying the product.

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, without adverse drug reactions. No formal drug interaction studies have been performed with ADVAIR DISKUS.

Short-Acting Beta$_2$-Agonists: In clinical trials, the mean daily need for additional beta$_2$-agonist use in 166 patients using ADVAIR DISKUS was approximately 1.3 inhalations/day, and ranged from 0 to 9 inhalations/day. Five percent (5%) of the patients using ADVAIR DISKUS in these trials averaged 6 or more inhalations per day over the course of the 12-week trials. No observed increase in frequency of cardiovascular events was noted among patients who averaged 6 or more inhalations per day.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials, 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).

Fluticasone Propionate Nasal Spray: In patients 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.

Ketoconazole and Other Inhibitors of Cytochrome P450: In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single dose of fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in

increased mean fluticasone propionate concentrations, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. This interaction may be due to an inhibition of cytochrome P450 3A4 by ketoconazole, which is also the route of metabolism of fluticasone propionate. Care should be exercised when ADVAIR DISKUS is coadministered with long-term ketoconazole and other known 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 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than the maximum recommended daily inhalation dose in adults 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 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 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 60 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). No tumors were seen at 0.21 mg/kg (approximately 20 times the maximum recommended daily inhalation dose in adults 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 180 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 450 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 65 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 90 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Combining 100 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 900 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 an oral dose of 300 mcg/kg administered 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 180 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 1,800 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 450 and 900 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 for management of asthma during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers: Plasma levels of salmeterol, a component of ADVAIR 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: The safety and effectiveness of ADVAIR DISKUS in children under 12 years of age have not been established. In one 12-week study, 257 patients 4 to 11 years inadequately controlled using inhaled corticosteroids were randomized to ADVAIR DISKUS 100/50 or concurrent therapy with fluticasone propionate inhalation powder 100 mcg plus salmeterol inhalation powder 50 mcg twice daily. The pattern of adverse events reported in patients 4 to 11 years of age was similar to that seen in patients 12 years of age and older treated with ADVAIR DISKUS.

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). 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).

Geriatric Use: Of the total number of patients in clinical studies of ADVAIR DISKUS, 44 were 65 years of age or older and 3 were 75 years of age or older. No overall differences in safety were observed between these patients and younger patients, and other reported clinical experience, including studies of the individual components, has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other products containing $beta_2$-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

The incidence of common adverse events in Table 3 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.

888 **Table 3. Overall Adverse Events With ≥3% Incidence With ADVAIR DISKUS**

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, and 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

889

890 Table 3 includes all events (whether considered drug-related or nondrug-related by the
891 investigator) that occurred at a rate of 3% or greater in either of the groups receiving ADVAIR
892 DISKUS and were more common than in the placebo group. In considering these data,
893 differences in average duration of exposure should be taken into account.

These adverse reactions were mostly mild to moderate in severity. Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare events of angioedema and bronchospasm, have been reported.

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/post nasal 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 3.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of ADVAIR DISKUS, fluticasone propionate, and/or salmeterol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to 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 or simply failed to relieve the deteriorating asthma.

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 and irritation.

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

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: Eosinophilic Conditions).

OVERDOSAGE

ADVAIR DISKUS: No deaths occurred in rats given combinations of salmeterol and fluticasone propionate at acute inhalation doses of 3.6 and 1.9 mg/kg, respectively

(approximately 320 and 15 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

Fluticasone Propionate: Chronic overdosage with fluticasone propionate may result in signs/symptoms of hypercorticism (see PRECAUTIONS). 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. The oral and subcutaneous median lethal doses in mice and rats were >1,000 mg/kg (>4,300 and >8,700 times, respectively, the maximum recommended daily inhalation dose in adults 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 250 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 200 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6,500 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) and in rats at 1,000 mg/kg (approximately 86,000 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION

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 by the orally inhaled route only (see Patient's Instructions for Use).

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 are based upon patients' current asthma therapy.

- For patients who are not currently on an inhaled corticosteroid, whose disease severity warrants treatment with 2 maintenance therapies, including patients on non-corticosteroid maintenance therapy, the recommended starting dosage is ADVAIR DISKUS 100/50 twice daily.
- For patients on an inhaled corticosteroid, Table 4 provides the recommended starting dosage. 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 4. Recommended Dosages of ADVAIR DISKUS for Patients Taking Inhaled Corticosteroids

Current **Daily Dose** of Inhaled Corticosteroid		Recommended Strength and Dosing Schedule of ADVAIR DISKUS
Beclomethasone dipropionate	≤420 mcg	100/50 twice daily
	462-840 mcg	250/50 twice daily
Budesonide	≤400 mcg	100/50 twice daily
	800-1,200 mcg	250/50 twice daily
	1,600 mcg*	500/50 twice daily
Flunisolide	≤1,000 mcg	100/50 twice daily
	1,250-2,000 mcg	250/50 twice daily
Fluticasone propionate 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
Triamcinolone acetonide	≤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.

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 salmeterol for prevention of EIB, or for any other reason.

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 asthma control.

If a previously effective dosage regimen of ADVAIR DISKUS fails to provide adequate control of asthma, 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.

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 every blister has 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

August 2003 RL-2031

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-077/S019

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDAs 20-236, 20-692, and 21-077
INDs 30,905 and 50,703

GlaxoSmithKline
Five Moore Drive
P.O. Box 13398
Research Triangle Park, No 27709-3398

Attention: C. Elaine Jones, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Jones:

Please refer to your new drug application (NDA) for Serevent (salmeterol) Inhalation Aerosol, Serevent (salmeterol) Diskus, and Advair (salmeterol and fluticasone dipropionate) Diskus.

Reference is also made to our supplemental request letter dated June 27, 2003, and to the various telephone conversations between representatives from your company and the FDA in which you requested revision to the labeling requested in the June 27, 2003, letter.

We have considered your request for revisions and are requesting that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drugs:

Modify the existing labels for SEREVENT Inhalation Aerosol and SEREVENT DISKUS (NDAs 20-236 and 20-692) as follows.

1. Add the following text as a boxed warning preceding the Description section of the labels.

   WARNING: 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 a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,174 patients treated for / weeks) versus those on placebo (4 of 13,179). Subgroup analyses suggest the risk may be greater in African-American patients compared to Caucasians (see WARNINGS Clinical Trials:).

2. Add the following text to the CLNICAL PHARMACOLOGY: Clinical Trials section:

Salmeterol Multi-center Asthma Research Trial: The Salmeterol Multi-center Asthma Research Trial (SMART) enrolled long-acting beta$_2$-agonist-naive patients with asthma (average age of 39 years, 71% Caucasian, 18% African-American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol, 42 mcg twice daily over 28 weeks) compared to placebo when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related death ~ respiratory-related life-threatening experiences (intubation and mechanical ventilation). Other endpoints included combined asthma-related deaths and life-threatening experiences. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N=2[illegible]

Due to the low rate of primary events in the study, the findings of the planned interim analysis were not conclusive. The analysis showed no significant difference for the primary endpoint for the total population. However, a higher number of asthma-related deaths or life-threatening experiences ([illegible]), and a higher number of asthma-related deaths (13 vs. 4) occurred in the patients treated with salmeterol. Post hoc subgroup analyses revealed no significant increase in respiratory or asthma-related episodes in [illegible] In African-Americans, the study showed a small, though statistically significantly greater number of primary events (20 vs. 7), asthma-related deaths and life-threatening experiences (19 vs. 4), and asthma-related deaths (8 vs. 1) in patients taking salmeterol compared to those taking placebo. The numbers of patients from other ethnic groups were too small to draw any conclusions in these populations. Even though SMART did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African-American patients and difficulties in enrollment.

3. Add the following text to the WARNINGS section.

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. Data from this study, called the Salmeterol Multi-center Asthma Research Trial (SMART), further suggest that the risk might be greater in African-American patients, in whom the increased risk was statistically significant at the time of the interim analysis. These results led to stopping the study prematurely (see [illegible] Clinical Trials[illegible]). The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids provides protection from this risk. Given the similar basic mechanisms of action of beta$_2$-agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect. Findings similar to the SMART study findings were reported in a prior 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma-related death was numerically, though not statistically greater in [illegible]

treated with salmeterol (42mcg twice daily) versus albuterol (180mcg four times a day) added to usual asthma therapy.

4. Add the words "asthma or" to the following sentence in the Information for Patients subsection of the WARNINGS section:

   Patients should not stop SEREVENT for *asthma or* COPD without physician/provider guidance since symptoms may recur after discontinuation.

Modify the existing labels for ADVAIR DISKUS products as follows.

5. Add the following text as a boxed warning preceding the Description section of the labels.

   WARNING: 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 a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,174 patients treated for X weeks) versus those on placebo (4 of 13,179). Subgroup analyses suggest the risk may be greater in African-American patients compared to Caucasians (see WARNINGS)

6. Add the following text to the WARNINGS section.

   DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL, A COMPONENT OF ADVAIR DISKUS, MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. The Salmeterol Multi-center Asthma Research Trial (SMART) enrolled long-acting $beta_2$-agonist-naive patients with asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42mcg twice daily over 28 weeks compared to placebo, when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths and respiratory-related life-threatening experiences (intubation and mechanical ventilation). Other endpoints included combined asthma-related deaths

   A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N=2). The analysis showed no significant difference for the primary endpoint for the total population. However, a higher number of asthma-related deaths and life-threatening experiences , and a higher number of asthma-related deaths (13 vs. 4), occurred in the patients treated with SEREVENT Inhalation Aerosol. Post-hoc subgroup analyses revealed no significant increase in respiratory or asthma-related episodes in Caucasian patients. In African-Americans, the study showed a small, though statistically significantly greater, number of primary events (20 vs. 7), asthma-related deaths, life-threatening experiences (19 vs. 4), and asthma-related deaths (8 vs. 1), in patients taking SEREVENT Inhalation Aerosol compared to those taking placebo. Even though SMART did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African-American patients, and difficulties in enrollment. The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids,

such as fluticasone propionate, a component of ADVAIR DISKUS, provides protection from this risk. Therefore, it is not known whether the findings seen with SEREVENT Inhalation Aerosol would apply to ADVAIR DISKUS.

Findings similar to the SMART study findings were reported in a prior 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma-related death was numerically, though not statistically greater in asthma patients treated with salmeterol (42mcg twice daily) versus albuterol (180mcg four times daily) added to usual asthma therapy.

Given the similar basic mechanisms of action of $beta_2$-agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect.

7. Add the following sentence to the Information for Patients subsection of the WARNINGS section:

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

Submit draft labeling as a prior approval supplement to this application. Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

In addition, submit a draft "Dear Health Care Professional" letter with this supplemental NDA.

The requested supplements should be submitted within 14 days.

If you have any questions, call Akilah Green, Regulatory Project Manager, at 301-827-5580.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury
7/21/03 05:09:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDAs 20-236, 20-692, and 21-077
INDs 30,905 and 50,703

GlaxoSmithKline
Five Moore Drive
P.O. Box 13398
Research Triangle Park, No 27709-3398

Attention: C. Elaine Jones, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Jones:

Please refer to your new drug application (NDA) for Serevent (salmeterol) Inhalation Aerosol, Serevent (salmeterol) Diskus, and Advair (salmeterol and fluticasone dipropionate) Diskus.

We have reviewed the preliminary data submitted regarding the SMART trial and your June 19, 2003, submission to INDs 30,905 and 50,703.

We request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drugs:

Modify the existing labels for SEREVENT Inhalation Aerosol and SEREVENT DISKUS (NDAs 20-236 and 20-692) as follows.

1. Add the following text as a boxed warning preceding the Description section of the labels.

DATA FROM A LARGE PLACEBO-CONTROLLED STUDY THAT ASTHMA-RELATED DEATHS

2. Add the following text to the CLNICAL PHARMACOLOGY: Clinical Trials section:

Salmeterol Multi-center Asthma Research Trial: The Salmeterol Multi-center Asthma Research Trial (SMART) enrolled long-acting beta$_2$-agonist-naive patients with asthma (average age of 39 years, 71% Caucasian, 18% African-American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol, 42mcg twice daily over 28 weeks) compared to placebo when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths, respiratory-related life-threatening experiences (intubation and mechanical ventilation). A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N=2

Due to the low rate of primary events in the study, the findings of the planned interim analysis were not conclusive. analysis showed no significant difference for the primary endpoint for the total population, In African-Americans, the study showed a small, though statistically significantly greater, number of primary events compared to those taking placebo. The numbers of patients from other were too small to draw any conclusions in these populations. Even though SMART did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African-American patients, and difficulties in enrollment.

3. Delete the following statement from the

4. Add the following text to the WARNINGS section.

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED SUGGEST THAT SALMETEROL MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. Data from this study, called the Salmeterol Multi-center Asthma Research Trial (SMART), further suggest that the risk might be greater in African-American patients, in whom the increased risk was statistically significant at the time of the interim analysis. These results led to stopping the study prematurely (see Salmeterol Multi-center Asthma Research Trial). The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids provides protection from this risk. Given the similar basic mechanisms of action of beta$_2$-agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect. Findings similar to the SMART study findings were reported in a prior 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma-related death was numerically, though not statistically greater in asthma patients treated with salmeterol (42mcg twice daily) versus albuterol (180mcg four times a day) added to usual asthma therapy.

5. Add the words "asthma or" to the following sentence in the Information for Patients section: "Patients should not stop SEREVENT for *asthma or* COPD without physician/provider guidance since symptoms may recur after discontinuation."

Modify the existing labels for ADVAIR DISKUS products as follows.

6. Add the following text as a boxed warning preceding the Description section of the labels.

DATA FROM A LARGE PLACEBO-CONTROLLED STUDY THAT

ASTHMA-RELATED DEATHS

7. Add the following text to the WARNINGS section.

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED SUGGEST THAT SALMETEROL, A COMPONENT OF ADVAIR DISKUS, MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS

Submit draft labeling as a prior approval supplement to this application. Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

In addition, submit a draft "Dear Health Care Professional" letter with this supplemental NDA.

The requested supplements should be submitted within 14 days.

If you have any questions, call Akilah Green, Regulatory Project Manager, at 301-827-5580.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury
6/27/03 05:23:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDAs 20-077/S-020, 20-692/S-025 and 20-236/S-029

GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Research Triangle Park , NC 27709

Attention: C. Elaine Jones, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Jones:

We acknowledge receipt on August 29, 2003, of your August 29, 2003, submissions that you intended to be supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Advair Diskus (fluticasone propionate/salmeterol inhalation powder), Serevent Diskus (salmeterol inhalation powder) and Serevent (salmeterol) Inhalation Aerosol.

The submissions contain full data sets for the Smart study as well as additional information regarding rare serious asthma episodes or asthma-related death associated with the use of salmeterol from clinical studies by GlaxoSmithKline, worldwide spontaneous reports and the literature. The summaries of these data was used as support for the approval of supplements, NDA 21-077/S-019, NDA 20-692/S-024, and NDA 20-236/S-028.

We wish to advise you that since no changes to the labeling are being proposed we consider these submissions to be correspondences to supplements, NDA 21-077/S-019, NDA 20-692/S-024, and NDA 20-236/S-028. Therefore, they will not be accepted as supplements but will be retained in the files.

If you have any questions, call Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Division Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury
2/11/04 10:55:31 AM