CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-692 /S024

Trade Name: Serevent Diskus

Generic Name: salmeterol xinafote inhalation powder

Sponsor: GlaxoSmithKline

Approval Date: August 11, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-692 /S024

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-692/S-024

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 Serevent Diskus (salmeterol xinafoate 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 20-692/S-024." 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 Akylah Green, Regulatory Project Manager, at (301) 827-5580.

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 05:48:28 PM
Signing for Dr. Chowdury in his absence in my role as Acting Director.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-692/S024

LABELING

PRESCRIBING INFORMATION

SEREVENT® DISKUS®

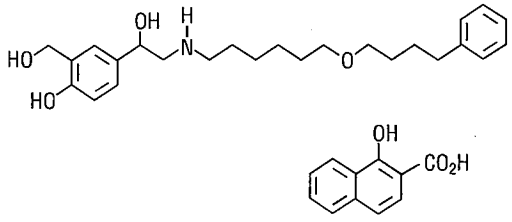
(salmeterol xinafoate inhalation powder)

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 and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).

DESCRIPTION

SEREVENT DISKUS (salmeterol xinafoate inhalation powder) contains salmeterol xinafoate as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The active component of the formulation is salmeterol base, a highly selective beta$_2$-adrenergic bronchodilator. The chemical name of salmeterol xinafoate is 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino] methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate. Salmeterol xinafoate 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.

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

Under standardized in vitro test conditions, SEREVENT DISKUS delivers 47 mcg when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in 1 second [FEV_1] 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS was 82.4 L/min (range, 46.1 to 115.3 L/min).

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

CLINICAL PHARMACOLOGY

Mechanism of Action: Salmeterol is a selective, long-acting beta-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: Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and excreted independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

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

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

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

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

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days.

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

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

The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and adult patients receiving 50-mcg doses of salmeterol inhalation powder (n = 60) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted. Also, pediatric patients receiving 50-mcg doses of salmeterol inhalation powder (n = 67) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 3 months of therapy, and no clinically significant dysrhythmias were noted.

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

No effect of treatment with salmeterol 50 mcg was observed on pulse rate and systolic and diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign measurements after the first dose (n = 91) and after 12 weeks of therapy (n = 74). Median

changes from baseline in pulse rate and systolic and diastolic blood pressure were similar for patients receiving either salmeterol or placebo (see ADVERSE REACTIONS).

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

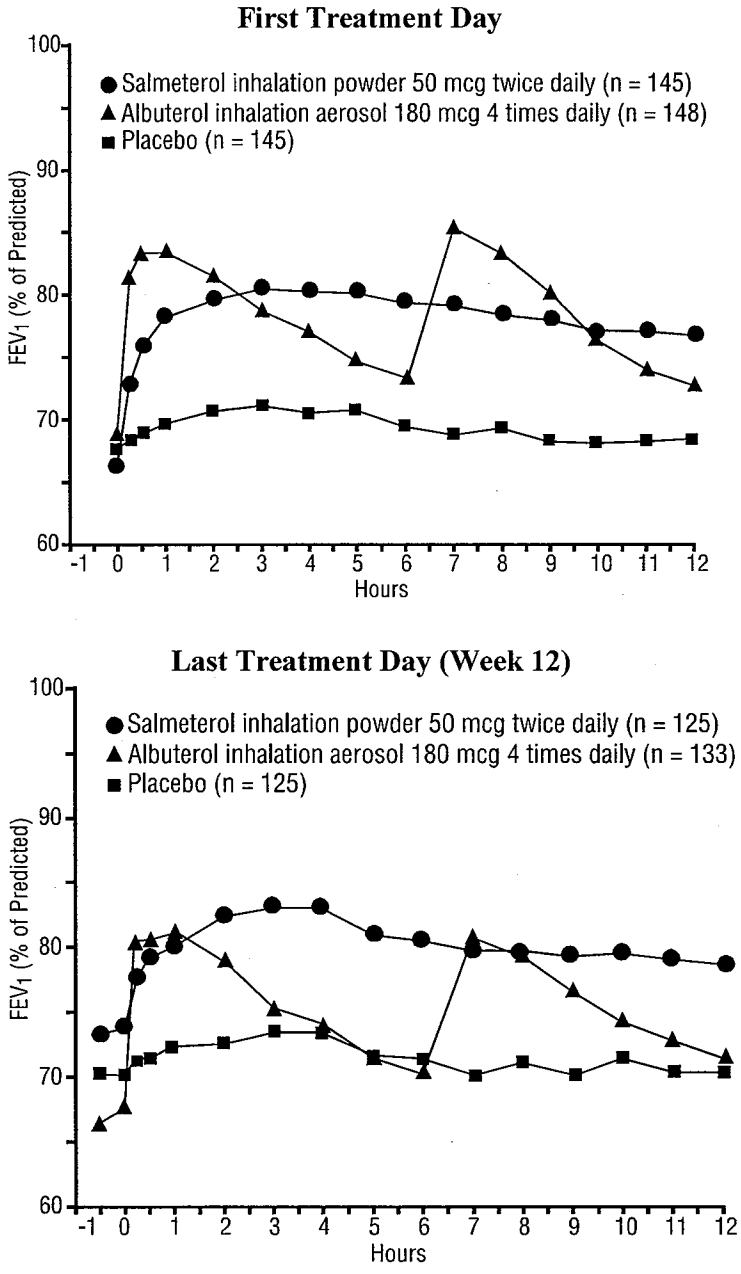
CLINICAL TRIALS

Asthma: During the initial treatment day in several multiple-dose clinical trials with salmeterol inhalation powder in patients with asthma, the median time to onset of clinically significant bronchodilatation (≥15% improvement in FEV_1) ranged from 30 to 48 minutes after a 50-mcg dose.

One hour after a single dose of 50 mcg of salmeterol inhalation powder, the majority of patients had ≥15% improvement in FEV_1. Maximum improvement in FEV_1 generally occurred within 180 minutes, and clinically significant improvement continued for 12 hours in most patients.

In 2 randomized, double-blind studies, salmeterol inhalation powder was compared with albuterol inhalation aerosol and placebo in adolescent and adult patients with mild-to-moderate asthma (protocol defined as 50% to 80% predicted FEV_1, actual mean of 67.7% at baseline), including patients who did and who did not receive concurrent inhaled corticosteroids. The efficacy of salmeterol inhalation powder was demonstrated over the 12-week period with no change in effectiveness over this time period (see Figure 1). There were no gender- or age-related differences in safety or efficacy. No development of tachyphylaxis to the bronchodilator effect has been noted in these studies. FEV_1 measurements (mean change from baseline) from these two 12-week studies are shown below for both the first and last treatment days.

Figure 1. Serial 12-Hour FEV_1 From Two 12-Week Clinical Trials in Patients with Asthma



During daily treatment with salmeterol inhalation powder for 12 weeks in adolescent and adult patients with mild-to-moderate asthma, the following treatment effects were seen:

Table 1. Daily Efficacy Measurements in Two 12-Week Clinical Trials (Combined Data)

Parameter	Time	Placebo	Salmeterol Inhalation Powder	Albuterol Inhalation Aerosol
No. of randomized subjects		152	149	148
Mean AM peak expiratory flow (L/min)	baseline	394	395	394
	12 weeks	396	427*	394
Mean % days with no asthma symptoms	baseline	14	13	12
	12 weeks	20	33	21
Mean % nights with no awakenings	baseline	70	63	68
	12 weeks	73	85*	71
Rescue medications (mean no. of inhalations per day)	baseline	4.2	4.3	4.3
	12 weeks	3.3	1.6†	2.2
Asthma exacerbations		14%	15%	16%

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

†Statistically superior to placebo ($p<0.001$).

Safe usage with maintenance of efficacy for periods up to 1 year has been documented.

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

In a randomized, double-blind, controlled study (n = 449), 50 mcg of salmeterol inhalation powder, via the DISKUS, was administered twice daily to pediatric patients with asthma who did and who did not receive concurrent inhaled corticosteroids. The efficacy of salmeterol inhalation powder was demonstrated over the 12-week treatment period with respect to periodic serial peak expiratory flow (PEF) (36% to 39% postdose increase from baseline) and FEV_1 (32% to 33% postdose increase from baseline). Salmeterol was effective in demographic subgroup analyses

(gender and age) and was effective when coadministered with other inhaled asthma medications such as short-acting bronchodilators and inhaled corticosteroids. A second randomized, double-blind, placebo-controlled study (n = 207) with 50 mcg of salmeterol inhalation powder via an alternate device supported the findings of the trial with the DISKUS.

Effects in Patients With Asthma on Concomitant Inhaled Corticosteroids: In 4 clinical trials in adult and adolescent patients with asthma (n = 1922), the effect of adding salmeterol to inhaled corticosteroid therapy was evaluated. The studies utilized the inhalation aerosol formulation of salmeterol xinafoate for a treatment period of 6 months. They compared the addition of salmeterol therapy to an increase (at least doubling) of the inhaled corticosteroid dose.

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

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

In 2 randomized, single-dose, crossover studies in adolescents and adults with exercise-induced bronchospasm (EIB) (n = 53), 50 mcg of salmeterol inhalation powder prevented EIB when dosed 30 minutes prior to exercise. For many patients, this protective effect against EIB was still apparent up to 8.5 hours following a single dose.

Table 2. Results of 2 Exercise-Induced Bronchospasm Studies in Adolescents and Adults

		Placebo (n = 52)		Salmeterol Inhalation Powder (n = 52)	
		n	% Total	n	% Total
0.5-Hour	% Fall in FEV_1				
postdose	<10%	15	29	31	60
exercise	≥10%,<20%	3	6	11	21
challenge	≥20%	34	65	10	19
Mean maximal % fall in FEV_1 (SE)		-25% (1.8)		-11% (1.9)	
8.5-Hour	% Fall in FEV_1				
postdose	<10%	12	23	26	50
exercise	≥10%,<20%	7	13	12	23
challenge	≥20%	33	63	14	27
Mean maximal % fall in FEV_1 (SE)		-27% (1.5)		-16% (2.0)	

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

Salmeterol Multi-center Asthma Research Trial: The Salmeterol Multi-center Asthma Research Trial (SMART) 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 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).

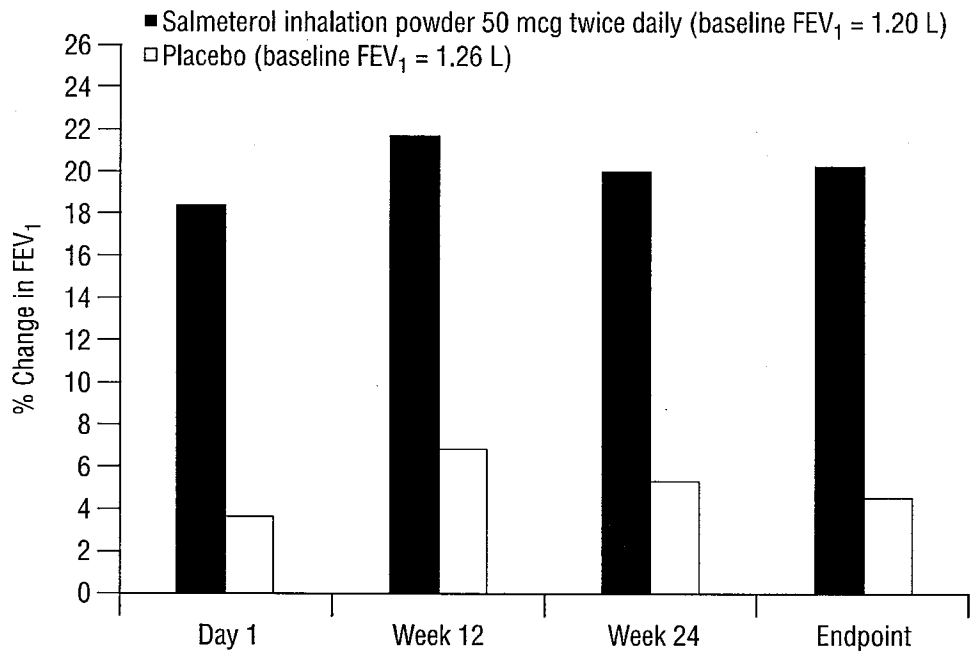
Due to the low rate of primary events in the study, the findings of the planned interim analysis were not conclusive. The analysis showed no significant difference for the primary endpoint for the total population. However, a higher number of asthma-related deaths or life-threatening experiences (36 vs. 23) 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, 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 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.

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

Figure 2 displays the integrated 2-hour postdose FEV_1 results from the 2 clinical trials. The percent change in FEV_1 refers to the change from baseline, defined as the predose value on Treatment Day 1. To account for patient withdrawals during the study, Endpoint (last evaluable FEV_1) data are provided. Patients receiving salmeterol 50 mcg had significantly greater improvements in 2-hour postdose FEV_1 at Endpoint (216 mL, 20%) compared to placebo (43 mL, 5%). Improvement was apparent on the first day of treatment and maintained throughout the 24 weeks of treatment.

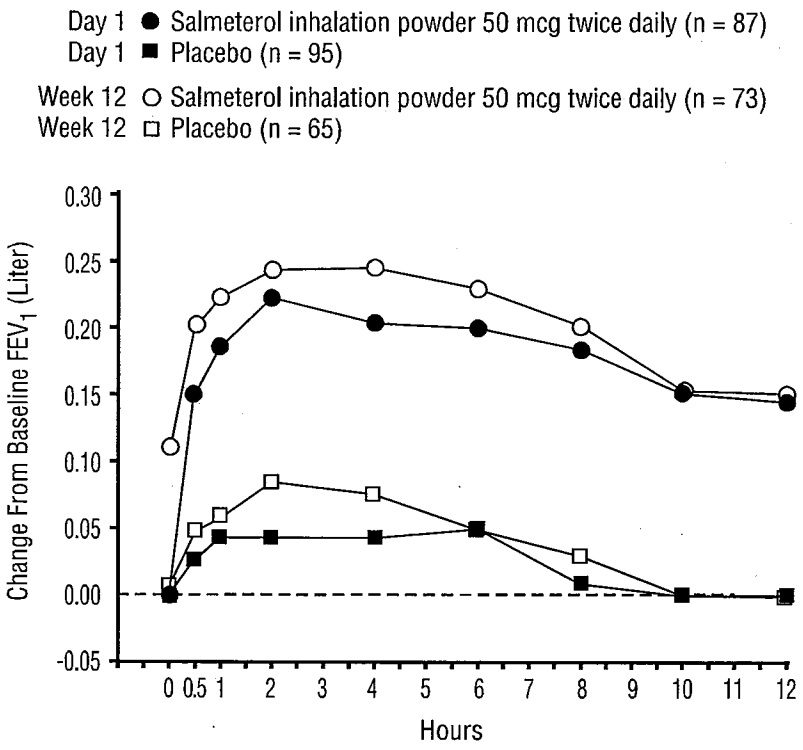
Figure 2. Mean Percent Change From Baseline in Postdose FEV_1 Integrated Data From 2 Trials of Patients With Chronic Bronchitis and Airflow Limitation



	N	N	N	N
Salmeterol inhalation powder 50 mcg twice daily	335	265	222	326
Placebo	361	264	226	343

Onset of Action and Duration of Effect: The onset of action and duration of effect of salmeterol were evaluated in a subset of patients (n = 87) from 1 of the 2 clinical trials discussed above. Following the first 50-mcg dose, significant improvement in pulmonary function (mean FEV_1 increase of 12% or more and at least 200 mL) occurred at 2 hours. The mean time to peak bronchodilator effect was 4.75 hours. As seen in Figure 3, evidence of bronchodilatation was seen throughout the 12-hour period. Figure 3 also demonstrates that the bronchodilating effect after 12 weeks of treatment was similar to that observed after the first dose. The mean time to peak bronchodilator effect after 12 weeks of treatment was 3.27 hours.

Figure 3. Serial 12-Hour FEV_1 on the First Day and at Week 12 of Treatment



INDICATIONS AND USAGE

Asthma: SEREVENT DISKUS is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting $beta_2$-agonists. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting $beta_2$-agonists.

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

SEREVENT DISKUS may be used alone or in combination with inhaled or systemic corticosteroid therapy.

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

CONTRAINDICATIONS

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

WARNINGS

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 CLINICAL TRIALS: Asthma: *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 patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol (180 mcg 4 times daily) added to usual asthma therapy.

SEREVENT DISKUS SHOULD NOT BE INITIATED IN PATIENTS WITH PATIENTS WITH SIGNIFICANTLY WORSENING OR ACUTELY DETERIORATING ASTHMA, WHICH MAY BE A LIFE-THREATENING CONDITION. Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide when SEREVENT has been initiated in this situation.

Although it is not possible from these reports to determine whether SEREVENT contributed to these adverse events or simply failed to relieve the deteriorating asthma, the use of SEREVENT DISKUS in this setting is inappropriate.

SEREVENT DISKUS SHOULD NOT BE USED TO TREAT ACUTE SYMPTOMS. It is crucial to inform patients of this and prescribe an inhaled, short-acting beta$_2$-agonist for this purpose as well as warn them that increasing inhaled beta$_2$-agonist use is a signal of deteriorating asthma.

SEREVENT DISKUS IS NOT A SUBSTITUTE FOR INHALED OR ORAL CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced when SEREVENT DISKUS is initiated.

(See PRECAUTIONS: Information for Patients and the accompanying Patient's Instructions for Use.)

1. Do Not Introduce SEREVENT DISKUS as a Treatment for Acutely Deteriorating Asthma: SEREVENT DISKUS is intended for the maintenance treatment of asthma (see INDICATIONS AND USAGE) and should not be introduced in acutely deteriorating asthma, which is a

potentially life-threatening condition. There are no data demonstrating that SEREVENT DISKUS provides greater efficacy than or additional efficacy to inhaled, short-acting beta$_2$-agonists in patients with worsening asthma. Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide in patients receiving SEREVENT. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled, short-acting 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 SEREVENT contributed to these events or simply failed to relieve the deteriorating asthma.

2. Do Not Use SEREVENT DISKUS to Treat Acute Symptoms: An inhaled, short-acting beta$_2$-agonist, not SEREVENT DISKUS, should be used to relieve acute asthma or COPD symptoms. When prescribing SEREVENT DISKUS, the physician must also provide the patient with an inhaled, short-acting beta$_2$-agonist (e.g., albuterol) for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of SEREVENT DISKUS.

When beginning treatment with SEREVENT DISKUS, patients who have been taking 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 and use them only for symptomatic relief of acute asthma or COPD symptoms (see PRECAUTIONS: Information for Patients).

3. Watch for Increasing Use of Inhaled, Short-Acting Beta$_2$-Agonists, Which Is a Marker of Deteriorating Asthma or COPD: The patient's condition may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalations than usual, or the patient develops a significant decrease in PEF or lung function, these may be markers of destabilization of their disease. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for corticosteroids. If the patient uses 4 or more inhalations per day of an inhaled, short-acting beta$_2$-agonist for 2 or more consecutive days, or if more than 1 canister (200 inhalations per canister) of inhaled, short-acting beta$_2$-agonist is used in an 8-week period in conjunction with SEREVENT DISKUS, then the patient should consult the physician for reevaluation. **Increasing the daily dosage of SEREVENT DISKUS in this situation is not appropriate. SEREVENT DISKUS should not be used more frequently than twice daily (morning and evening) at the recommended dose of 1 inhalation.**

4. Do Not Use SEREVENT DISKUS as a Substitute for Oral or Inhaled Corticosteroids: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g.,

corticosteroids. There are no data demonstrating that SEREVENT DISKUS has a clinical anti-inflammatory effect and could be expected to take the place of corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on a suitable dose to maintain clinical stability even if they feel better as a result of initiating SEREVENT DISKUS. Any change in corticosteroid dosage should be made ONLY after clinical evaluation (see PRECAUTIONS: Information for Patients).

5. Do Not Exceed Recommended Dosage: As with other inhaled $beta_2$-adrenergic drugs, SEREVENT DISKUS should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias.

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

7. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of SEREVENT DISKUS, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

8. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving SEREVENT DISKUS.

9. Cardiovascular Disorders: SEREVENT DISKUS, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. SEREVENT DISKUS, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of SEREVENT DISKUS at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce 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.

PRECAUTIONS

General: 1. Cardiovascular and Other Effects: No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol at recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of salmeterol and may require discontinuation of the drug. Salmeterol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac

arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

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

2. Metabolic 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 long-term administration of salmeterol at recommended doses.

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

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

1. The action of SEREVENT DISKUS may last up to 12 hours or longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not be exceeded.

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

3. SEREVENT DISKUS is not meant to relieve acute asthma or COPD symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting bronchodilator (the physician should provide the patient with such medication and instruct the patient in how it should be used).

4. Patients should not stop therapy with SEREVENT DISKUS for asthma or COPD without physician/provider guidance since symptoms may worsen after discontinuation.

5. • When used for the treatment of EIB, 1 inhalation of SEREVENT DISKUS should be taken 30 minutes before exercise.
   • Additional doses of SEREVENT should not be used for 12 hours.
   • Patients who are receiving SEREVENT DISKUS twice daily should not use additional SEREVENT for prevention of EIB.

6. The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma or COPD:
   • 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 PEF or lung function as outlined by the physician,
- use of 4 or more inhalations per day of a short-acting beta$_2$-agonist for 2 or more days consecutively,
- use of more than 1 canister (200 inhalations per canister) of an inhaled, short-acting beta$_2$-agonist in an 8-week period.

7. SEREVENT DISKUS should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with SEREVENT DISKUS.

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

9. When patients are prescribed SEREVENT DISKUS, other medications for asthma and COPD should be used only as directed by the physician.

10. SEREVENT DISKUS should not be used with a spacer device.

11. If you are pregnant or nursing, contact your physician about the use of SEREVENT DISKUS.

12. Effective and safe use of SEREVENT DISKUS includes an understanding of the way that it should be used:

- Never exhale into the DISKUS.
- Never attempt to take the DISKUS apart.
- Always activate and use the DISKUS in a level, horizontal position.
- Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
- Always keep the DISKUS in a dry place.
- Discard **6 weeks** after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads "0"), whichever comes first.

13. For the proper use of SEREVENT DISKUS and to attain maximum benefit, the patient should read and follow carefully the Patient's Instructions for Use accompanying the product.

Drug Interactions: ***Short-Acting Beta-Agonists:*** In the two 12-week, repetitive-dose adolescent and adult clinical trials in patients with asthma (n = 149), the mean daily need for additional beta$_2$-agonist in patients using salmeterol inhalation powder was approximately 1½ inhalations/day. Twenty-six percent (26%) of the patients in these trials used between 8 and 24 inhalations of short-acting beta-agonist per day on 1 or more occasions. Nine percent (9%) of the patients in these trials averaged over 4 inhalations/day over the course of the 12-week trials. No increase in frequency of cardiovascular events was observed among the 3 patients who averaged 8 to 11 inhalations per day; however, the safety of concomitant use of more than 8 inhalations per day of short-acting beta$_2$-agonist with salmeterol inhalation powder has not been established. In 29 patients who experienced worsening of asthma while receiving salmeterol inhalation powder during these trials, albuterol therapy administered via either nebulizer or inhalation aerosol (1 dose in most cases) led to improvement in FEV_1 and no increase in occurrence of cardiovascular adverse events.

In 2 clinical trials in patients with COPD, the mean daily need for additional beta$_2$-agonist for patients using salmeterol inhalation powder was approximately 4 inhalations/day. Twenty-four percent (24%) of the patients using salmeterol inhalation powder in these trials averaged 6 or more inhalations of albuterol per day over the course of the 24-week trials. No increase in frequency of cardiovascular events was observed among patients who averaged 6 or more inhalations per day.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol on the vascular system may be potentiated by these agents.

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

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: In an 18-month carcinogenicity study in CD-mice, salmeterol xinafoate at oral doses of 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose in adults and children based on

comparison of the area under the plasma concentration versus time curves [AUCs]) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (approximately 3 times the maximum recommended daily inhalation doses in adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 times the maximum recommended daily inhalation dose in adults and approximately 25 times the maximum recommended daily inhalation dose in children on a mg/m^2 basis). No tumors were seen at 0.21 mg/kg (approximately 15 times the maximum recommended daily inhalation dose in adults and approximately 8 times the maximum recommended daily inhalation dose in children on a mg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in male and female rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. No teratogenic effects occurred in rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans. There are no adequate and well-controlled studies with SEREVENT DISKUS in pregnant women. SEREVENT DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice and rats (approximately 410 and 810 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

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

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

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

In 2 randomized, double-blind, controlled clinical trials of 12 weeks' duration, salmeterol 50-mcg powder was administered to 211 pediatric asthma patients who did and who did not receive concurrent inhaled corticosteroids. The efficacy of salmeterol inhalation powder was demonstrated over the 12-week treatment period with respect to PEF and FEV_1. Salmeterol inhalation powder was effective in demographic subgroups (gender and age) of the population. Salmeterol was effective when coadministered with other inhaled asthma medications, such as short-acting bronchodilators and inhaled corticosteroids. Salmeterol inhalation powder was well tolerated in the pediatric population, and there were no safety issues identified specific to the administration of salmeterol inhalation powder to pediatric patients.

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

Geriatric Use: Of the total number of adolescent and adult patients with asthma who received salmeterol inhalation powder in chronic dosing clinical trials, 209 were 65 years of age and older. Of the total number of patients with COPD who received salmeterol inhalation powder in chronic dosing clinical trials, 167 were 65 years of age or older and 45 were 75 years of age or older. No apparent differences in the safety of SEREVENT inhalation powder were observed when geriatric patients were compared with younger patients in clinical trials. As with other $beta_2$-agonists, however, special caution should be observed when using SEREVENT DISKUS in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Data from the trials in patients with COPD suggested a greater effect on FEV_1 of salmeterol inhalation powder in the <65 years age-group, as compared with the ≥65 years age-group. However, based on available data, no adjustment of salmeterol dosage in geriatric patients is warranted.

ADVERSE REACTIONS

Adverse reactions to salmeterol are similar in nature to reactions to other selective beta$_2$-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor; nervousness; and paradoxical bronchospasm (see WARNINGS).

Asthma: Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of salmeterol inhalation powder in patients 12 years of age and older with asthma. Table 3 reports the incidence of adverse experiences in these 2 studies.

Table 3. Adverse Experience Incidence in Two 12-Week Adolescent and Adult Clinical Trials in Patients With Asthma

	Percent of Patients		
Adverse Experience Type	Placebo (N = 152)	Salmeterol Inhalation Powder 50 mcg Twice Daily (N = 149)	Albuterol Inhalation Aerosol 180 mcg 4 Times Daily (N = 150)
Ear, nose, and throat			
Nasal/sinus congestion, pallor	6	9	8
Rhinitis	4	5	4
Neurological			
Headache	9	13	12
Respiratory			
Asthma	1	3	<1
Tracheitis/bronchitis	4	7	3
Influenza	2	5	5

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

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

Other adverse experiences that occurred in the group receiving salmeterol inhalation powder in these studies with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

Ear, Nose, and Throat: Sinus headache.

Gastrointestinal: Nausea.

Mouth and Teeth: Oral mucosal abnormality.

Musculoskeletal: Pain in joint.

Neurological: Sleep disturbance, paresthesia.

Skin: Contact dermatitis, eczema.

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

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

Table 4. Adverse Experience Incidence in Two 12-Week Pediatric Clinical Trials in Patients With Asthma

	Percent of Patients		
Adverse Experience Type	Placebo (N = 215)	Salmeterol Inhalation Powder 50 mcg Twice Daily (N = 211)	Albuterol Inhalation Powder 200 mcg 4 Times Daily (N = 115)
Ear, nose, and throat			
Ear signs and symptoms	3	4	9
Pharyngitis	3	6	3
Neurological			
Headache	14	17	20
Respiratory			
Asthma	2	4	<1
Skin			
Skin rashes	3	4	2
Urticaria	0	3	2

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

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

Chronic Obstructive Pulmonary Disease (COPD): Two multicenter, 24-week, controlled studies have evaluated twice-daily doses of salmeterol inhalation powder administered via the DISKUS in patients with COPD. For presentation (Table 5), the placebo data from a third trial, identical in design, patient entrance criteria, and overall conduct but comparing fluticasone propionate with placebo, were integrated with the placebo data from these 2 studies (total N = 341 for salmeterol and 576 for placebo).

Table 5. Adverse Experiences With ≥3% Incidence in US Controlled Clinical Trials With Salmeterol Inhalation Powder in Patients With Chronic Obstructive Pulmonary Disease*

	Percent of Patients	
Adverse Experience Type	Placebo (N = 576)	Salmeterol Inhalation Powder 50 mcg Twice Daily (N = 341)
Cardiovascular		
Hypertension	2	4
Ear, nose, and throat		
Throat irritation	6	7
Nasal congestion/blockage	3	4
Sinusitis	2	4
Ear signs and symptoms	1	3
Gastrointestinal		
Nausea and vomiting	3	3
Lower respiratory		
Cough	4	5
Rhinitis	2	4
Viral respiratory infection	4	5
Musculoskeletal		
Musculoskeletal pain	10	12
Muscle cramps and spasms	1	3
Neurological		
Headache	11	14
Dizziness	2	4
Average duration of exposure (days)	128.9	138.5

*Table 5 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group treated with salmeterol inhalation powder and were more common in the group treated with salmeterol inhalation powder than in the placebo group.

Other experiences occurring in the group treated with salmeterol inhalation powder that occurred at a frequency of 1% to <3% and were more common than in the placebo group were as follows:

Endocrine and Metabolic: Hyperglycemia.

Eye: Keratitis and conjunctivitis.

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

Lower Respiratory: Lower respiratory signs and symptoms.

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

Neurology: Migraines.

Non-Site Specific: Pain, edema and swelling.

Psychiatry: Anxiety.

Skin: Skin rashes.

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

In extensive US and worldwide postmarketing experience with salmeterol, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS no. 1), 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.

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

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

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

OVERDOSAGE

The expected signs and symptoms with overdosage of SEREVENT DISKUS are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with SEREVENT DISKUS may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with SEREVENT DISKUS can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

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

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

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

DOSAGE AND ADMINISTRATION

SEREVENT DISKUS should be administered by the orally inhaled route only (see Patient's Instructions for Use). The patient must not exhale into the DISKUS and the DISKUS should only be activated and used in a level, horizontal position.

Asthma: For maintenance of bronchodilatation and prevention of symptoms of asthma, including the symptoms of nocturnal asthma, the usual dosage for adults and children 4 years of age and older is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be reevaluated and additional therapeutic options, such as inhaled or systemic corticosteroids, should be considered. If symptoms arise in the period between doses, an inhaled, short-acting $beta_2$-agonist should be taken for immediate relief.

Chronic Obstructive Pulmonary Disease (COPD): For maintenance treatment of bronchospasm associated with COPD (including chronic bronchitis and emphysema), the usual dosage for adults is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart).

For both asthma and COPD, adverse effects are more likely to occur with higher doses of salmeterol, and more frequent administration or administration of a larger number of inhalations is not recommended.

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

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

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

HOW SUPPLIED

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

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

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

GlaxoSmithKline
Research Triangle Park, NC 27709

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August 2003 RL-2032

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-692/S024

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 and 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 deaths ~ 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=? ~ .

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 ~ , 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 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 ~ Clinical Trials: ~ 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 ~

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 ✕ 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 experience ——, 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

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/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 and 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.

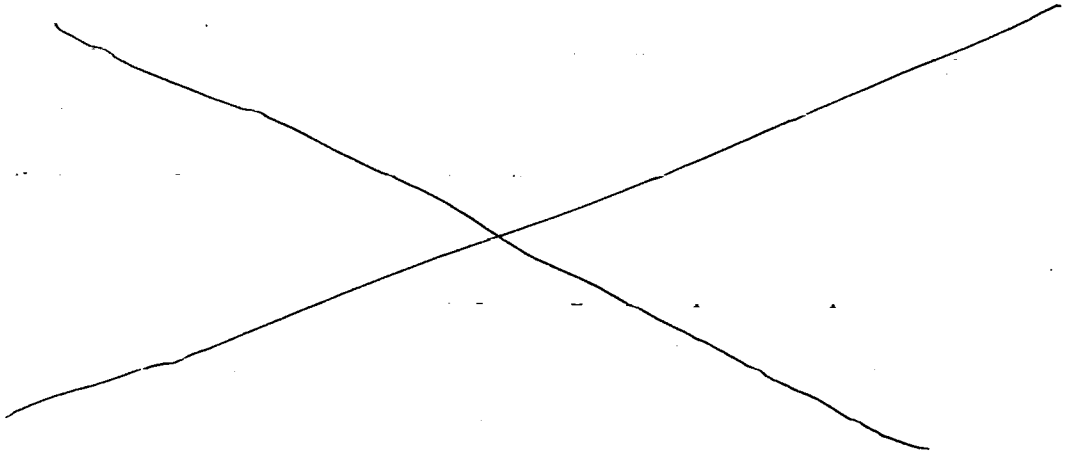
6. Add the following text as a boxed warning preceding the Description section of the labels.

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

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/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

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/s/

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

August 6, 2003

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709

Tel. 919 483 2100
www.gsk.com

Badrul A. Chowdhury, M.D., Director
Division of Pulmonary and Allergy Drug Products
Center for Drug Evaluation and Research II
Food and Drug Administration
PKLN, Room 10B-45/HFD-570
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-692; SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder)
Supplement: Prior Approval, Labeling

Dear Dr. Chowdhury:

Please find enclosed revised labeling, as discussed with the Division, to incorporate the results of the Serevent Multicenter Asthma Research Trial (SMART) as a boxed warning. The enclosed labeling is identical to the labeling submitted in draft on July 31, 2003 (IND Serial No ——— and agreed to by the Division on August 1, 2003.

The statistical data tables that support the labeling changes along with the 'Dear Healthcare Professional' letter and envelope submitted concurrently to NDA 20-236 Serevent Inhalation Aerosol are incorporated herein by cross reference.

Please contact me at (919) 483-4490 if there are any questions or comments regarding this submission.

Sincerely,

C. Elaine Jones

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