

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-692 S001/002

FINAL PRINTED LABELING

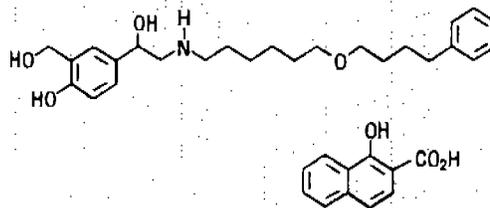
PRODUCT INFORMATION

SEREVENT[®] DISKUS[®]

(salmeterol xinafoate inhalation powder)

For Oral Inhalation Only

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



The molecular weight of salmeterol xinafoate is 603.8, and the empirical formula is C₂₅H₃₇NO₄•C₁₁H₈O₃. Salmeterol xinafoate is a white to off-white powder. 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 device containing a double-foil blister strip of a powder formulation of salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 50 mcg of salmeterol administered as the salmeterol xinafoate salt in 12.5 mg of formulation containing lactose. When a blister containing medication is opened by activating the device, the medication is dispersed into the air stream created when the patient inhales through the mouthpiece.

The amount of drug delivered to the lung will depend on patient factors such as inspiratory flow. Under standardized in vitro testing, SEREVENT DISKUS delivers 47 mcg when tested at 60 L/min flow rate for 3 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in 1 second [FEV₁] 0.65 L [range, 0.35 to 0.92 L]; 20% to 30% predicted FEV₁), mean peak inspiratory flow (PIF) through SEREVENT DISKUS was 82.4 L/min (range, 46.1 to 115.3 L/min). The emitted dose of salmeterol xinafoate determined in an in vitro experiment modeling these patient-generated flow rates was 46 mcg (range, 45 to 51 mcg).

CLINICAL PHARMACOLOGY:

Mechanism of Action: Salmeterol is a long-acting beta-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta₂-adrenoceptors compared with

isoproterenol, which has approximately equal agonist activity on beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

Pharmacokinetics: Salmeterol acts locally in the lung; plasma levels therefore do not predict therapeutic effect. Because of the low therapeutic dose, systemic levels of salmeterol inhalation powder are low or undetectable after inhalation of recommended doses (50 mcg 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 seven asthmatic patients; plasma concentrations were very low, with mean peak concentrations of 167 ± 75 pg/mL and no accumulation with repeated doses. Oral administration of 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) to two healthy subjects gave peak plasma salmeterol concentrations of about 650 pg/mL at about 45 minutes; the terminal elimination half-life was about 5.5 hours (one volunteer only).

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

Salmeterol is 94% to 98% bound to human plasma proteins in vitro over the concentration range of 8 to 7,722 ng of base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

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

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 cardiovascular effects (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.

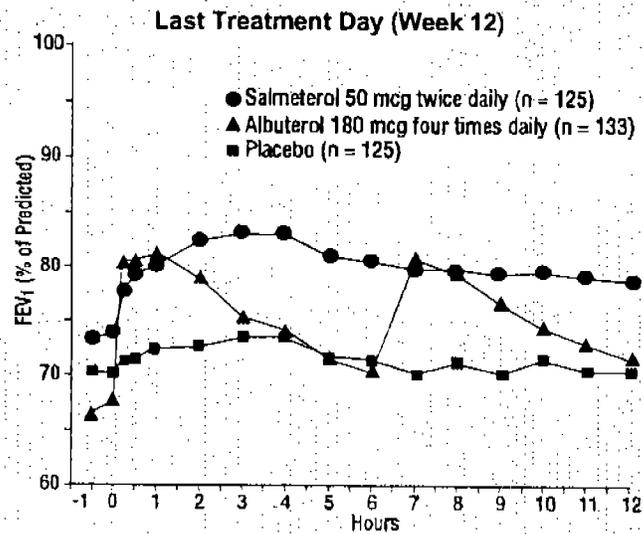
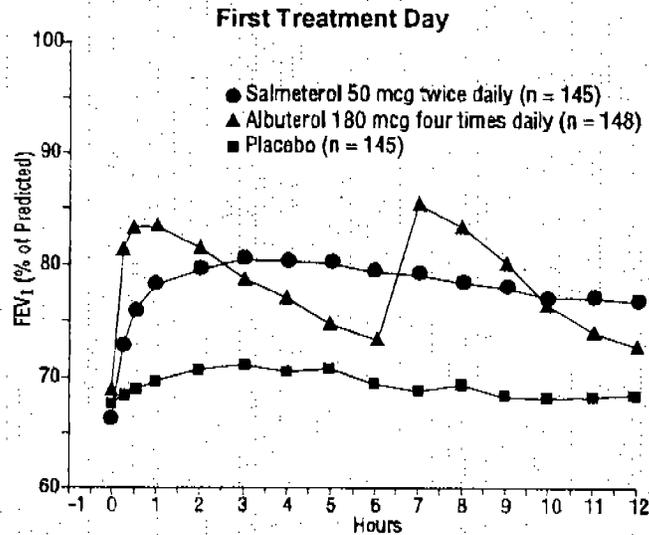
Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Clinical Trials: 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 ($\geq 15\%$ 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 $\geq 15\%$ 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 two large, 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. 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.

FEV₁, As Percent of Predicted, From Two Large 12-Week Clinical Trials



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 Large 12-Week Clinical Trials (Combined Data)

Parameter	Time	Placebo	SEREVENT	Albuterol
No. of randomized subjects		152	149	148
Mean AM peak expiratory flow rate (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 aerosol were compared to placebo in two 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 two randomized, single-dose, crossover comparisons of salmeterol inhalation powder/salmeterol powder and salmeterol aerosol for the prevention of exercise-induced bronchospasm. Therefore, while SEREVENT DISKUS was comparable to SEREVENT[®] (salmeterol xinafoate) Inhalation Aerosol in clinical trials in mild-to-moderate asthmatics, it should not be assumed that the SEREVENT Inhalation Aerosol and SEREVENT DISKUS drug products will produce clinically equivalent outcomes in all patients.

In a large, randomized, double-blind, controlled study ($n = 449$), 50 mcg of salmeterol inhalation powder/salmeterol powder, via the SEREVENT DISKUS, was administered twice daily to pediatric asthma patients who did and who did not receive concurrent inhaled corticosteroids. The efficacy of salmeterol inhalation powder/salmeterol powder was demonstrated over the 12-week treatment period with respect to

periodic serial peak expiratory flow (36% to 39% postdose increase from baseline) and FEV₁ (32% to 33% postdose increase from baseline). Salmeterol was effective in demographic subgroup analyses (gender and age) and was effective when coadministered with other inhaled asthma medications such as short-acting bronchodilators and inhaled corticosteroids. A second large, randomized, double-blind, placebo-controlled study (n = 207) with 50 mcg of ~~salmeterol inhalation powder~~ ~~salmeterol powder~~ via an alternate device supported the findings of the trial with SEREVENT DISKUS.

In two randomized, single-dose, crossover studies in adolescents and adults with exercise-induced bronchospasm (EIB) (n = 53), 50 mcg of ~~salmeterol inhalation powder~~ ~~salmeterol powder~~ significantly 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 Two Exercise-Induced Bronchospasm Studies in Adolescents and Adults

		Placebo (n = 52)		SEREVENT DISKUS (n = 52)	
		n	% Total	n	% Total
0.5 Hour postdose exercise challenge	% Fall in FEV ₁				
	<10%	15	29	31	60
	=10%, <20%	3	6	11	21
	=20%	34	65	10	19
Mean maximal % fall in FEV ₁ (SE)		-25% (1.8)		-11% (1.9)	
8.5 Hour postdose exercise challenge	% Fall in FEV ₁				
	<10%	12	23	26	50
	=10%, <20%	7	13	12	23
	=20%	33	63	14	27
Mean maximal % fall in FEV ₁ (SE)		-27% (1.5)		-16% (2.0)	

In two randomized studies in children 4 to 11 years old with asthma and EIB (n = 50), a single 50-mcg dose of ~~salmeterol inhalation powder~~ ~~salmeterol powder~~ significantly 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.

INDICATIONS AND USAGE: SEREVENT DISKUS inhalation powder 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 beta₂-agonists. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting beta₂-agonists.

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

SEREVENT DISKUS may be used with or without concurrent inhaled or systemic corticosteroid therapy.

CONTRAINDICATIONS: SEREVENT DISKUS is contraindicated in patients with a history of hypersensitivity to salmeterol or any of its components.

WARNINGS:

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

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

SEREVENT DISKUS SHOULD NOT BE USED TO TREAT ACUTE SYMPTOMS. It is crucial to inform patients of this and prescribe an inhaled, short-acting beta₂-agonist for this purpose as well as warn them that increasing inhaled beta₂-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 beta₂-agonists in patients with worsening asthma. Serious acute respiratory events, including fatalities, have been reported, both in the United States and worldwide, in patients receiving SEREVENT. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function; intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled, short-acting beta₂-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT contributed to these events or simply failed to relieve the deteriorating asthma.

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

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

3. Watch for Increasing Use of Inhaled, Short-Acting Beta₂-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 beta₂-agonist becomes less effective or the patient needs more inhalations than usual, this 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 corticosteroids. If the patient uses four or more inhalations per day of an inhaled, short-acting beta₂-agonist for 2 or more consecutive days, or if more than one canister (200 inhalations per canister) of inhaled, short-acting beta₂-agonist is used in an 8-week period in conjunction with SEREVENT DISKUS, then the patient should consult the physician for reevaluation. **Increasing the daily dosage of SEREVENT DISKUS in this situation is not appropriate. SEREVENT DISKUS should not be used more frequently than twice daily (morning and evening) at the recommended dose of one 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, or reduce the dose 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 beta₂-adrenergic drugs, SEREVENT DISKUS should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QT_c interval, which has the potential for producing ventricular arrhythmias.

6. Paradoxical Bronchospasm: Inhalation of salmeterol xinafoate can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, SEREVENT DISKUS should be discontinued immediately and alternative therapy 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.

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 QT_c interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, SEREVENT DISKUS, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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 beta₂-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. No effects on glucose have been seen with SEREVENT DISKUS at recommended doses. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of SEREVENT DISKUS at recommended doses.

Information for Patients: See illustrated PATIENT'S INSTRUCTIONS FOR USE.

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. The action of SEREVENT DISKUS may last up to 12 hours or longer. The recommended dosage (one inhalation twice daily, morning and evening) should not be exceeded.
2. SEREVENT 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 beta₂-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient in how it should be used).
3. •When used for the treatment of EIB, one inhalation of SEREVENT DISKUS inhalation powder should be taken 30 minutes before exercise.
 - Additional doses of SEREVENT should not be used for 12 hours.
 - Patients who are receiving SEREVENT DISKUS inhalation powder twice daily should not use additional SEREVENT for prevention of EIB.
4. 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 beta₂-agonists
 - Need for more inhalations than usual of inhaled, short-acting beta₂-agonists
 - Use of four or more inhalations per day of a short-acting beta₂-agonist for 2 or more days consecutively
 - Use of more than one canister of an inhaled, short-acting beta₂-agonist in an 8-week period (i.e., canister with 200 inhalations)
5. SEREVENT DISKUS should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with SEREVENT DISKUS.
6. Patients should be cautioned regarding common adverse cardiovascular effects, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
7. In patients receiving SEREVENT DISKUS, other inhaled medications should be used only as directed by the physician.
8. SEREVENT DISKUS should not be used with a spacer.
9. If you are pregnant or nursing, contact your physician about use of SEREVENT DISKUS.
10. Effective and safe use of the DISKUS device includes an understanding of the way that it should be used:
 - Never exhale into the DISKUS device.
 - Always activate and use the DISKUS device in a level, horizontal position.
 - Never wash the mouthpiece or any part of the DISKUS device. KEEP IT DRY.

Drug Interactions: Short-Acting Beta-Agonists: In the two 12-week, repetitive-dose adolescent and adult clinical trials (n = 149), the mean daily need for additional beta₂-agonist use in patients using salmeterol inhalation powder was approximately 1½ inhalations per day. Twenty-six percent of the patients in these trials used between 8 and 24 inhalations of short-acting beta-agonist per day on one or more occasions. Nine percent of the patients in these trials averaged over 4 inhalations per day over the course of the 12-week trials. No observed increase in frequency of cardiovascular events was noted among the 3 patients who used

an average of 8 to 11 inhalations per day; however, the safety of concomitant use of more than 8 inhalations per day of short-acting beta₂-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 (one dose in most cases) led to improvement in FEV₁ and no increase in occurrence of cardiovascular adverse events.

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 SEREVENT when administered concurrently.

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

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as SEREVENT DISKUS, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma 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. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

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 60 times the maximum recommended daily inhalation dose in adults and

approximately 30 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 20 times the maximum recommended daily inhalation dose in adults and approximately 9 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 170 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 170 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, sternal 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 1700 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.

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 for relief of bronchospasm 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 with use of SEREVENT by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when salmeterol xinafoate is administered to a nursing woman.

Pediatric Use: The safety and efficacy of salmeterol inhalation powder ~~salmeterol powder~~ has been evaluated in over 2500 patients aged 4 to 11 years with asthma, 346 of whom were administered salmeterol inhalation powder ~~salmeterol 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 two 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 peak expiratory flow and FEV₁. 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 two randomized studies in children 4 to 11 years old with asthma and EIB, a single 50-mcg dose of salmeterol inhalation powder significantly 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 patients who received salmeterol inhalation powder in adolescent and adult chronic dosing clinical trials, 209 were 65 years of age and older. No apparent differences in the efficacy and safety of SEREVENT inhalation powder were observed when geriatric patients were compared with younger patients in clinical trials. As with other beta₂-agonists, however, special caution should be observed when using SEREVENT inhalation powder in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. 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 beta₂-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor; nervousness; and paradoxical bronchospasm (see WARNINGS).

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT inhalation powder in patients 12 years of age and older with asthma. The following table reports the incidence of adverse events in these two studies:

Table 3: Adverse Experience Incidence in Two Large 12-Week Adolescent and Adult Clinical Trials

Adverse Event Type	Percent of Patients		
	Placebo n = 152	SEREVENT Inhalation Powder 50 mcg twice daily n = 149	Albuterol Inhalation Aerosol 180 mcg four 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

The table above includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of $\geq 3\%$ in the SEREVENT inhalation powder treatment group and were more common in the SEREVENT inhalation powder group than in the placebo group.

Pharyngitis, sinusitis, upper respiratory tract infection, and cough occurred at $\geq 3\%$ 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 events occurring in the SEREVENT inhalation powder group at a frequency of 1% to 3% and at a greater rate than in placebo were as follows:

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. The following table includes all events (whether considered drug-related or non-drug related by the investigator) that occurred at a rate of $\geq 3\%$ in the SEREVENT inhalation powder treatment group and were more common in the SEREVENT inhalation powder group than in the placebo group.

Table 4: Adverse Experience Incidence in Two Large 12-Week Pediatric Clinical Trials

Adverse Event Type	Percent of Patients		
	Placebo n = 215	SEREVENT INHALATION POWDER T. Powder 50 mcg twice daily n = 211	Albuterol Powder 200 mcg four 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 events were reported at an incidence of 1% to 2% (3 to 4 patients) in the salmeterol group and with a higher incidence than in the albuterol and placebo groups: gastrointestinal signs and symptoms, lower respiratory signs and symptoms, photodermatitis, and arthralgia and articular rheumatism.

Observed During Clinical Practice: In extensive United States and worldwide postmarketing experience with SEREVENT, 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 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.

The following events have also been identified during postapproval use of SEREVENT in clinical practice. 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 a combination of their seriousness, frequency of reporting, or potential causal connection to SEREVENT.

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

Cardiovascular: Cases of hypertension, arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), and anaphylaxis.

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 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 QT_c 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 250 times the maximum recommended daily inhalation dose in adults and approximately 120 times the maximum recommended daily inhalation dose in children on a mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 200 times the maximum recommended daily inhalation dose in adults and approximately 95 times the maximum recommended daily inhalation dose in children on a mg/m² basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6500 times the maximum recommended daily inhalation dose in adults and approximately 3100 times the maximum recommended daily inhalation dose in children on a mg/m² basis) and in rats at 1000 mg/kg (approximately 86,000 times the maximum recommended daily inhalation dose in adults and approximately 41,000 times the maximum recommended daily inhalation dose in children on a mg/m² basis).

DOSAGE AND ADMINISTRATION: SEREVENT DISKUS inhalation powder should be administered by the orally inhaled route only (see PATIENT'S INSTRUCTIONS FOR USE). 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 one inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). 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. The patient must not exhale into the device and the device should only be activated and used in a level, horizontal position.

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

NDA 20-692/S-001, S-002

Page 20

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 beta₂-agonist should be taken for immediate relief.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with SEREVENT inhalation powder, efficacy and safety of 50 mcg given twice daily (morning and evening) did not differ from that in younger patients. Consequently, no dosage adjustment is recommended.

Prevention of Exercise-Induced Bronchospasm (EIB): One inhalation of SEREVENT DISKUS inhalation powder 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 inhalation powder 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 inhalation powder is supplied as a disposable, teal green colored device containing 60 blisters. The DISKUS inhalation device is packaged within a teal green colored, plastic-coated foil pouch (NDC 0173-0521-00).

SEREVENT DISKUS is also supplied in an institutional pack of one teal green colored, disposable DISKUS inhalation device containing 28 blisters. The DISKUS inhalation device is packaged within a teal green colored, plastic-coated foil pouch (NDC 0173-0520-00).

Store at controlled room temperature, 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 and should be discarded after every blister has been used (when the dose indicator reads "0") or 6 weeks after removal from the moisture-protective foil overwrap pouch, whichever comes first. Do not attempt to take the device apart.

Rx only

GlaxoWellcome

Glaxo Wellcome Inc.

Research Triangle Park, NC 27709

US Patent Nos. 4,992,474; 5,225,445; 5,380,922; 5,590,645; and Des. 342,994

©Copyright 1997 Glaxo Wellcome Inc. All rights reserved.

September 1998

RL-628

PATIENT'S INSTRUCTIONS FOR USE

SEREVENT[®] DISKUS[®]
(salmeterol xinafoate
inhalation powder)

For Oral Inhalation Only

(illustration of device with parts labeled:

Outer Case
Mouthpiece
Lever
Thumbgrip
Dose Indicator)

Before using your SEREVENT DISKUS, read complete instructions carefully.

Children should use SEREVENT DISKUS under adult supervision, as instructed by the patient's doctor.

When you take the SEREVENT DISKUS out of the box and foil overwrap pouch, write the "Use by" date on the label in the space provided on the device (6 weeks from date of opening). The DISKUS[®] inhalation device will be in the closed position. The **dose indicator** on the top of the DISKUS tells you how many doses are left. After the DISKUS has delivered 55 doses (23 doses for the institutional or sample pack), numbers 5 to 0 will appear in **red** to warn you that there are only a few doses left (see *Figure 1*).

Figure 1

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

Figure 2

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

Figure 3

Every time the lever is pushed back, a dose is made available for inhaling. This is shown by the dose counter. **At this point do not close the device, play with the lever, or advance the lever more than once because this will release doses that will be wasted.**

3. Holding the DISKUS level and away from your mouth, breathe out as far as is comfortable (*see Figure 4*). **(Remember, never breathe out into the DISKUS mouthpiece.)**

Figure 4

4. Put the mouthpiece to your lips (*see Figure 5*). Breathe in steadily and deeply through the DISKUS, not through your nose.

Figure 5

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

7. To close the DISKUS, put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go (see Figure 6). The DISKUS will click shut. The lever will automatically return to its original position and will reset. The DISKUS is now ready for your next scheduled dose. (Repeat steps 1 through 7.)

Figure 6

8. REMEMBER:

- Never exhale into the DISKUS device.
- Always activate and use the DISKUS device in a level, horizontal position.
- Never wash the mouthpiece or any part of the DISKUS device. KEEP IT DRY.

DOSAGE: Use only as directed by your doctor.

WARNINGS: SEREVENT DISKUS is different from your other asthma medications. SEREVENT DISKUS provides a relatively longer duration of effect. The bronchodilation action of SEREVENT DISKUS usually lasts for at least 12 hours. Therefore, it is important that you carefully read and understand the following information:

- 1. Do not use SEREVENT DISKUS more frequently than two times daily, morning and evening, approximately 12 hours apart, at the recommended dose of one inhalation each time.**
- 2. Do not use SEREVENT DISKUS to relieve sudden asthma symptoms** (e.g., sudden severe onset or worsening of wheezing, cough, chest tightness, and/or shortness of breath that has been diagnosed by your doctor as due to asthma). **If you experience sudden asthma symptoms while using SEREVENT DISKUS, you should not take more SEREVENT DISKUS to relieve these symptoms.** Instead, you should treat these sudden asthma symptoms with a different medication that has been prescribed by your doctor (e.g., an inhaled, short-acting bronchodilator such as albuterol). If you do not have an inhaled, short-acting bronchodilator, contact your doctor to have one prescribed for you.

3. If you are using SEREVENT DISKUS for exercise-induced bronchospasm, one inhalation should be taken 30 minutes before exercise.

AdditionalAdditional doses of SEREVENT should not be taken for 12 hours. If you are using SEREVENT DISKUS twice daily, you should not use additionaladditional SEREVENT for the protection of exercise-induced bronchospasm.

4. While you are using SEREVENT DISKUS, tell your doctor immediately if you are getting worse, as indicated by any of the following situations.

- Your inhaled, short-acting, ~~inhaled~~ bronchodilator becomes less effective for treatment of sudden asthma symptoms.
- You need more inhalations than usual of your inhaled, short-acting bronchodilator for treatment of sudden asthma symptoms.
- You are using four or more inhalations per day of your inhaled, short-acting bronchodilator for 2 or more days consecutively.
- You use more than one canister of a inhaled, short-acting bronchodilator in an 8-week period (i.e., there are 200 inhalations per canister).

5. Use other inhaled medications only as prescribed by your doctor.

6. Do not use SEREVENT DISKUS as a substitute for oral or inhaled corticosteroids. If you have been prescribed corticosteroids, you should not change your dosage of these medications or stop taking these medications without talking to your doctor, even if you feel better.

Store at controlled room temperature, 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 and should be discarded after every blister has been used (when the dose indicator reads "0") or 6 weeks after removal from the moisture-protective foil overwrap pouch, whichever comes first. Do not attempt to take the device apart.

Your doctor has determined that this product is likely to help your personal health. **USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.** If you have any questions about the use of SEREVENT DISKUS, consult with your doctor.

NDA 20-692/S-001, S-002

Page 25

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

Made in England

September 1998

22 **Page(s) Redacted**

**DRAFT
LABELING**