HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SEREVENT DISKUS safely and effectively. See full prescribing information for SEREVENT DISKUS.

SEREVENT DISKUS (salmeterol xinafoate inhalation powder)
FOR ORAL INHALATION

Initial U.S. Approval: 1994

WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death. A US study showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. (5.1)**
- **Prescribe SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. (1.1, 5.1)**
- **Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. (5.1)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	November 2010
Indications and Usage (1.1, 1.2)	November 2010
Dosage and Administration (2.1, 2.2)	November 2010
Warnings and Precautions, Asthma-Related Death (5.1)	November 2010

----------INDICATIONS AND USAGE----------

SEREVENT DISKUS is a LABA indicated for:

- Treatment of asthma in patients aged 4 years and older. (1.1)
- Prevention of exercise-induced bronchospasm (EIB) in patients aged 4 years and older. (1.2)
- Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). (1.3)

Important limitation:

- Not indicated for the relief of acute bronchospasm. (1.1, 1.3)

---------- DOSAGE AND ADMINISTRATION ----------

For oral inhalation only.

- Treatment of asthma in patients ≥4 years: 1 inhalation twice daily in addition to concomitant treatment with an inhaled corticosteroid. (2.1)
- EIB: One inhalation at least 30 minutes before exercise
- Maintenance treatment of bronchospasm associated with COPD: 1 inhalation twice daily. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

DISKUS device containing salmeterol (50 mcg) as an oral inhalation powder. (3)

----------CONTRAINDICATIONS----------

- Asthma: Without concomitant use of a long-term asthma control medication such an inhaled corticosteroid.
- Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Asthma-related death and asthma-related hospitalizations: Long-acting beta$_2$-adrenergic agonists increase the risk. Prescribe for asthma only as concomitant therapy with an inhaled corticosteroid. (5.1)
- Deterioration of disease and acute episodes: Do not initiate during rapidly deteriorating asthma. Do not use to treat acute symptoms. (5.2)
- Corticosteroids: Not a substitute for corticosteroids. Patients with asthma must take a concomitant inhaled corticosteroid. (5.3)
- Use with additional long-acting beta$_2$-agonist: Do not use in combination because of risk of overdose (5.4)
- Paradoxical bronchospasm: Discontinue SEREVENT DISKUS and institute alternative therapy if paradoxical bronchospasm occurs. (5.5)
- Patients with cardiovascular or central nervous system disorders: Use with caution because of beta-adrenergic stimulation. (5.6)
- Strong cytochrome P450 3A4 inhibitors (e.g., ketoconazole): Risk of cardiovascular effects. Use not recommended with SEREVENT DISKUS. (5.8)
- Coexisting conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.9)
- Metabolic effects: Be alert to hypokalemia and hyperglycemia. (5.10)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (incidence ≥5%) are:

- Asthma: Headache, influenza, nasal/sinus congestion, pharyngitis, rhinitis tracheitis/bronchitis. (6.1)
- COPD: Cough, headache, musculoskeletal pain, throat irritation, viral respiratory infection. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Use not recommended. May increase risk of cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of salmeterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

---------- USE IN SPECIFIC POPULATIONS ----------

Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved MEDICATION GUIDE.

Revised: 12/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT® DISKUS®, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.

1 INDICATIONS AND USAGE

1.1 Treatment of Asthma

SEREVENT DISKUS is indicated for the treatment of asthma and in the prevention of bronchospasm only as concomitant therapy with a long-term asthma control medication, such as an inhaled corticosteroid, in patients aged 4 years and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma. LABA, such as salmeterol, the

active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death *[see Warnings and Precautions (5.1)]*. Use of SEREVENT DISKUS for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated *[see Contraindications (4)]*. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.

Important Limitation of Use: SEREVENT DISKUS is NOT indicated for the relief of acute bronchospasm.

1.2 Prevention of Exercise-Induced Bronchospasm

SEREVENT DISKUS is also indicated for prevention of exercise-induced bronchospasm (EIB) in patients aged 4 years and older. Use of SEREVENT DISKUS as a single agent for the prevention of EIB may be clinically indicated in patients who do not have persistent asthma. In patients with persistent asthma, use of SEREVENT DISKUS for the prevention of EIB may be clinically indicated, but the treatment of asthma should include a long-term asthma control medication, such as an inhaled corticosteroid.

1.3 Maintenance Treatment of Chronic Obstructive Pulmonary Disease

SEREVENT DISKUS is indicated for the long-term twice-daily (morning and evening) administration in the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) (including emphysema and chronic bronchitis).

Important Limitation of Use: SEREVENT DISKUS is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

SEREVENT DISKUS should be administered by the orally inhaled route only.

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

(more than 1 inhalation twice daily) is not recommended. Patients using SEREVENT DISKUS should not use additional LABA for any reason. *[See Warnings and Precautions (5.4, 5.6).]*

2.1 Asthma

LABA, such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death *[see Warnings and Precautions (5.1)]*.

Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid is contraindicated. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For patients with asthma less than 18 years of age who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.

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

2.2 Exercise-Induced Bronchospasm

Use of SEREVENT DISKUS as a single agent for the prevention of EIB may be clinically indicated in patients who do not have persistent asthma. In patients with persistent asthma, use of SEREVENT DISKUS for the prevention of EIB may be clinically indicated, but the treatment of asthma should include a long-term asthma control medication, such as an inhaled corticosteroid. 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 aged 4 to 11 years. 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.

2.3 Chronic Obstructive Pulmonary Disease

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

3 DOSAGE FORMS AND STRENGTHS

Disposable teal green device with 60 blisters containing salmeterol (50 mcg) as an oral inhalation powder formulation. An institutional pack containing 28 blisters is also available.

4 CONTRAINDICATIONS

Because of the risk of asthma-related death and hospitalization, use of SEREVENT DISKUS for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated *[see Warnings and Precautions (5.1)]*.

SEREVENT DISKUS is contraindicated as primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required *[see Warnings and Precautions (5.2)]*.

SEREVENT DISKUS is contraindicated in patients with severe hypersensitivity to milk proteins *[see Warnings and Precautions (5.7), Adverse Reactions (6.3), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

LABA, such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Pediatric and Adolescent Patients: **Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require**

addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.

The Salmeterol Multi-center Asthma Research Trial (SMART) was a large 28-week placebo-controlled US study comparing the safety of salmeterol (SEREVENT Inhalation Aerosol) with placebo, each added to usual asthma therapy, that showed an increase in asthma-related deaths in patients receiving salmeterol *[see Clinical Studies (14.1)]*. Given the similar basic mechanisms of action of beta$_2$-agonists, the findings seen in the SMART study are considered a class effect.

A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate of asthma-related death was numerically, though not statistically significantly, greater in patients with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol (180 mcg 4 times daily) added to usual asthma therapy.

The SNS and SMART studies enrolled patients with asthma. No studies have been conducted that were adequate to determine whether the rate of death in patients with COPD is increased by LABA.

5.2 Deterioration of Disease and Acute Episodes

SEREVENT DISKUS should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. SEREVENT DISKUS has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of SEREVENT DISKUS in this setting is not appropriate.

Serious acute respiratory events, including fatalities, have been reported when salmeterol has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, previous life-threatening acute asthma exacerbations) and in some patients with acutely deteriorating asthma (e.g., patients with significantly increasing symptoms; increasing need for inhaled, short-acting beta$_2$-agonists; decreasing response to usual medications; increasing need for systemic corticosteroids; recent emergency room visits; deteriorating lung function). However, these events have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for adding additional inhaled

corticosteroid or initiating systemic corticosteroids. Patients should not use more than 1 inhalation twice daily (morning and evening) of SEREVENT DISKUS.

SEREVENT DISKUS should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting $beta_2$-agonist, not SEREVENT DISKUS, should be used to relieve acute symptoms such as shortness of breath. 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 acute symptoms.

When beginning treatment with SEREVENT DISKUS, patients who have been taking oral or inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

5.3 SEREVENT DISKUS is Not a Substitute for Corticosteroids

There are no data demonstrating that SEREVENT DISKUS has a clinical anti-inflammatory effect such as that associated with corticosteroids. When initiating and throughout treatment with SEREVENT DISKUS in patients receiving oral or inhaled corticosteroids for treatment of asthma, patients must continue taking a suitable dosage of corticosteroids to maintain clinical stability even if they feel better as a result of initiating SEREVENT DISKUS. Any change in corticosteroid dosage should be made ONLY after clinical evaluation.

5.4 Excessive Use of SEREVENT DISKUS and Use With Other Long-Acting $Beta_2$-Agonists

As with other inhaled $beta_2$-adrenergic drugs, SEREVENT DISKUS should not be used more often or at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using SEREVENT DISKUS should not use an additional LABA (e.g., formoterol fumarate, arformorterol tartrate) for any reason.

5.5 Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, SEREVENT DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SEREVENT DISKUS, it should be treated immediately with an inhaled, short-acting bronchodilator; SEREVENT DISKUS should be discontinued immediately; and alternative therapy should be instituted. Upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving SEREVENT DISKUS.

5.6 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia *[see Overdosage (10)]*. Therefore, SEREVENT DISKUS, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Salmeterol can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. 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. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.7 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SEREVENT DISKUS, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm. There have been reports of anaphylactic reactions in patients with severe milk protein allergy; therefore, patients with severe milk protein allergy should not take SEREVENT DISKUS *[see Contraindications (4)]*.

5.8 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Because of the potential for drug interactions and the potential for increased risk of cardiovascular adverse events, the concomitant use of SEREVENT DISKUS with strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended *[see Drug Interactions (7.1)]*.

5.9 Coexisting Conditions

SEREVENT DISKUS, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.10 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2)]*. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant and dose-related changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SEREVENT DISKUS at recommended doses.

6 ADVERSE REACTIONS

LABA, including salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death. Data from a large 28-week placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving

salmeterol. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients *[see Warnings and Precautions (5.1), Clinical Studies (14.1)]*.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Asthma

Adult and Adolescent Patients Aged 12 Years and Older: Two multicenter, 12-week, controlled studies evaluated twice-daily doses of SEREVENT DISKUS in patients aged 12 years and older with asthma. Table 1 reports the incidence of adverse reactions in these 2 studies.

Table 1. Adverse Reaction Incidence in Two 12-Week Clinical Trials in Adult and Adolescent Patients With Asthma

	Percent of Patients		
Adverse Event	Placebo (N = 152)	SEREVENT DISKUS 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 1 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common than in the placebo group.

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

Additional Adverse Reactions: Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were reported more frequently by patients with asthma treated with SEREVENT DISKUS compared with patients treated with placebo include the following: contact dermatitis, eczema, localized aches and pains, nausea, oral

mucosal abnormality, pain in joint, paresthesia, pyrexia of unknown origin, sinus headache, and sleep disturbance.

Pediatric Patients Aged 4 to 11 Years: Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT DISKUS in patients aged 4 to 11 years with asthma. Table 2 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common than in the placebo group.

Table 2. Adverse Reaction Incidence in Two 12-Week Pediatric Clinical Trials in Patients With Asthma

	Percent of Patients		
Adverse Event	Placebo (N = 215)	SEREVENT DISKUS 50 mcg Twice Daily (N = 211)	Albuterol Inhalation Aerosol 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 events were reported at an incidence of >1% in the salmeterol group and with a higher incidence than in the albuterol and placebo groups: gastrointestinal signs and symptoms, lower respiratory signs and symptoms, photodermatitis, and arthralgia and articular rheumatism.

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

Laboratory Test Abnormalities: Elevation of hepatic enzymes was reported in ≥1% of patients in clinical trials. The elevations were transient and did not lead to discontinuation from the studies. In addition, there were no clinically relevant changes noted in glucose or potassium.

6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

Two multicenter, 24-week, controlled studies have evaluated twice-daily doses of SEREVENT DISKUS in patients with COPD. For presentation (Table 3), 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 3. Adverse Reactions With ≥3% Incidence in US Controlled Clinical Trials With SEREVENT DISKUS in Patients With Chronic Obstructive Pulmonary Disease[a]

	Percent of Patients	
Adverse Event	Placebo (N = 576)	SEREVENT DISKUS 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

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

Additional Adverse Reactions: Other events occurring in the group receiving SEREVENT DISKUS that occurred at a frequency of ≥1% and were more common than in the placebo group were as follows: anxiety; arthralgia and articular rheumatism; bone and skeletal pain; candidiasis mouth/throat; dental discomfort and pain; dyspeptic symptoms; edema and

swelling; gastrointestinal infections; hyperglycemia; hyposalivation; keratitis and conjunctivitis; lower respiratory signs and symptoms; migraines; muscle pain; muscle stiffness, tightness, and rigidity; musculoskeletal inflammation; pain; and skin rashes.

Adverse reactions to salmeterol are similar in nature to those seen with other selective beta$_2$-adrenoceptor agonists, e.g., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm; headache; tremor; nervousness; and paradoxical bronchospasm.

Laboratory Abnormalities: There were no clinically relevant changes in these trials. Specifically, no changes in potassium were noted.

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of salmeterol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to salmeterol or a combination of these factors.

In extensive US and worldwide postmarketing experience with salmeterol, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating *[see Warnings and Precautions (5.2)]*, but they have also occurred in a few patients with less severe asthma. It was not possible from these reports to determine whether salmeterol contributed to these events.

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

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

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

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

In a drug interaction study in 20 healthy subjects, coadministration of salmeterol (50 mcg twice daily) and ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold). Three (3) subjects were withdrawn due to beta$_2$-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong

CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

SEREVENT DISKUS should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol on the vascular system may be potentiated by these agents.

7.3 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, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 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 relevance of these effects is not known, caution is advised in the coadministration of SEREVENT DISKUS with nonpotassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. 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.

No teratogenic effects occurred in rats at oral doses approximately 160 times the maximum recommended daily inhalation dose (MRHD) on an mg/m^2 basis. In pregnant Dutch rabbits administered oral doses approximately 50 times the MRHD 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 such effects occurred at an oral dose approximately 20 times the MRHD based on comparison of the AUCs.

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at an oral dose approximately 1,600 times the MRHD on an 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.

8.2 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.

8.3 Nursing Mothers

Plasma levels of salmeterol, a component of SEREVENT DISKUS, after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. 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.

8.4 Pediatric Use

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs *[see Indications and Usage (1.1), Warnings and Precautions (5.1)]*.

The safety and efficacy of SEREVENT DISKUS in adolescents (aged 12 years and older) has been established based on adequate and well-controlled trials conducted in adults and adolescents *[see Clinical Studies (14.1)]*. A large 28-week placebo-controlled US study comparing salmeterol (SEREVENT Inhalation Aerosol) and placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol *[see Clinical Studies (14.1)]*. Post-hoc analyses in pediatric patients aged 12 to 18 years were also performed. Pediatric patients accounted for approximately 12% of patients in each treatment arm. Respiratory-related death or life-threatening experience occurred at a similar rate in the salmeterol group (0.12% [2/1,653]) and the placebo group (0.12% [2/1,622]; relative risk: 1.0 [95% CI: 0.1, 7.2]). All-cause hospitalization, however, was increased in the salmeterol group (2% [35/1,653]) versus the placebo group (<1% [16/1,622]; relative risk: 2.1 [95% CI: 1.1, 3.7]).

The safety and efficacy of SEREVENT DISKUS have been evaluated in over 2,500 patients aged 4 to 11 years with asthma, 346 of whom were administered SEREVENT DISKUS for 1 year. Based on available data, no adjustment of dosage of SEREVENT DISKUS in pediatric patients is warranted for either asthma or EIB.

In 2 randomized, double-blind, controlled clinical trials of 12 weeks' duration, SEREVENT DISKUS 50 mcg was administered to 211 pediatric patients with asthma who did and who did not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was demonstrated over the 12-week treatment period with respect to peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV_1). SEREVENT DISKUS was effective in demographic subgroups (gender and age) of the population.

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

8.5 Geriatric Use

Of the total number of adolescent and adult patients with asthma who received SEREVENT DISKUS in chronic dosing clinical trials, 209 were aged 65 years or older. Of the total number of patients with COPD who received SEREVENT DISKUS in chronic dosing clinical trials, 167 were aged 65 years or older and 45 were aged 75 years or older. No apparent differences in the safety of SEREVENT DISKUS were observed when geriatric patients were compared with younger patients in clinical trials. As with other $beta_2$-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 SEREVENT DISKUS in the <65 years age-group, as compared with the ≥65 years age-group. However, based on available data, no adjustment of dosage of SEREVENT DISKUS in geriatric patients is warranted.

8.6 Hepatic Impairment

The pharmacokinetics of salmeterol base has not been studied in patients with hepatic 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.

10 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 following: 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, insomnia. 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.

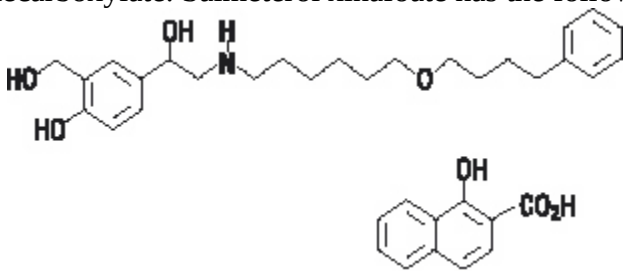
Treatment consists of discontinuation of SEREVENT DISKUS together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis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

No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg (approximately 240 and 110 times the MRHD for adults and children, respectively, on an mg/m^2 basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 and 90 times the MRHD for adults and children, respectively, on an mg/m^2 basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6,100 and 2,900 times the MRHD for adults and

children, respectively, on an mg/m^2 basis) and in rats at 1,000 mg/kg (approximately 81,000 and 38,000 times the MRHD for adults and children, respectively, on an mg/m^2 basis).

11 DESCRIPTION

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

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 (which contains milk proteins). After a blister containing medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, 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 FEV_1 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS® inhalation device was 82.4 L/min (range: 46.1 to 115.3 L/min).

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Salmeterol is a selective LABA. 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 their presence raises 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.

12.2 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 Warnings and Precautions (5.6, 5.10)]*. 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 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 (6.1)]*.

Concomitant Use of SEREVENT DISKUS With Other Respiratory Medications: *Short-Acting Beta$_2$-Agonists:* In 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 SEREVENT DISKUS was approximately 1½ inhalations/day. Twenty-six percent (26%) of the patients in these trials used between 8 and 24 inhalations of short-acting beta-agonist per day on 1 or more occasions. Nine percent (9%) of the patients in these trials averaged over 4 inhalations/day over the course of the 12-week trials. No increase in frequency of cardiovascular events was observed among the 3 patients who averaged 8 to 11 inhalations/day; however, the safety of concomitant use of more than 8 inhalations/day of short-acting $beta_2$-agonist with SEREVENT DISKUS has not been established. In 29 patients who experienced worsening of asthma while receiving SEREVENT DISKUS during these trials, albuterol therapy administered via either nebulizer or inhalation aerosol (1 dose in most cases) led to improvement in 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 SEREVENT DISKUS was approximately 4 inhalations/day. Twenty-four percent (24%) of the patients using SEREVENT DISKUS in these trials averaged 6 or more inhalations of albuterol per day over the course of the 24-week trials. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations per day.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving 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 patients receiving SEREVENT DISKUS concurrently with a theophylline product had adverse event rates similar to those in 302 patients receiving SEREVENT DISKUS without theophylline. Based on the available data, the concomitant administration of methylxanthines with SEREVENT DISKUS did not alter the observed adverse event profile.

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

12.3 Pharmacokinetics

Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Absorption: Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in

7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/mL at 20 minutes and no accumulation with repeated doses.

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

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

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to α-hydroxysalmeterol (aliphatic oxidation) by CYP3A4. Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of α-hydroxysalmeterol in vitro.

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

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

Drug Interactions: *Inhibitors of Cytochrome P450 3A4: Ketoconazole:* In a placebo-controlled crossover drug interaction study in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76 [90% CI: 10.66, 23.31]) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist–mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

Erythromycin: In a repeat-dose study in 13 healthy subjects, concomitant administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with and without erythromycin 1.4 [90% CI: 0.96, 2.03], p = 0.12), a 3.6-beat/min increase in heart rate ([95% CI: 0.19, 7.03], p<0.04), a 5.8-msec increase in QTc interval ([95% CI: -6.14, 17.77], p = 0.34), and no change in plasma potassium.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 20 times the MRHD for adults and children based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at 0.2 mg/kg (approximately 3 times the MRHD for adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 and 25 times the MRHD for adults and children, respectively, on an mg/m^2 basis). No tumors were seen at 0.21 mg/kg (approximately 15 and 8 times the MRHD for adults and children, respectively, on an 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 rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the MRHD for adults on an mg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: 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 relevance of these findings is unknown.

Reproductive Toxicology Studies: No teratogenic effects occurred in rats at oral doses up to 2 mg/kg (approximately 160 times the MRHD on an mg/m^2 basis).

In Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times and above the MRHD 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 such effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the MRHD 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 MRHD on an mg/m^2 basis).

Salmeterol crossed the placenta following oral administration to mice and rats.

14 CLINICAL STUDIES

14.1 Asthma

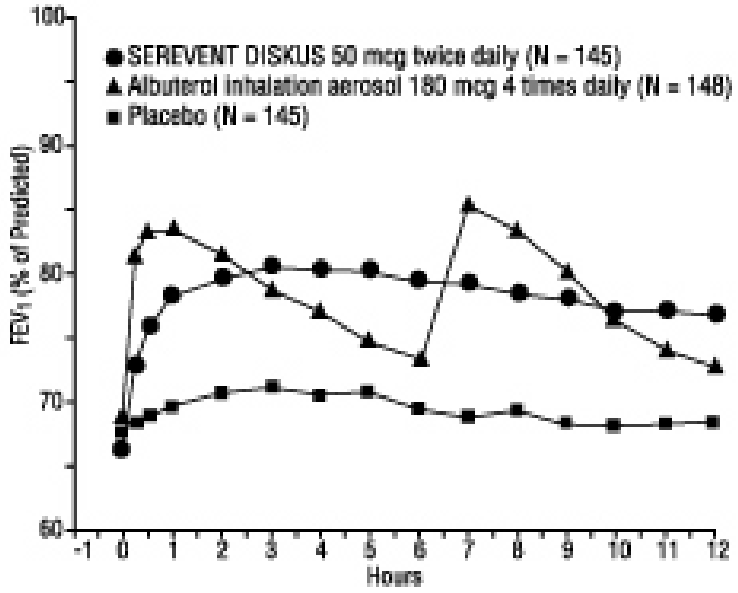
The initial studies supporting the approval of SEREVENT DISKUS for the treatment of asthma did not require the regular use of inhaled corticosteroids. However, for the treatment of

asthma, SEREVENT DISKUS is currently indicated only as concomitant therapy with an inhaled corticosteroid *[see Indications and Usage (1.1)]*.

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

First Treatment Day



Last Treatment Day (Week 12)

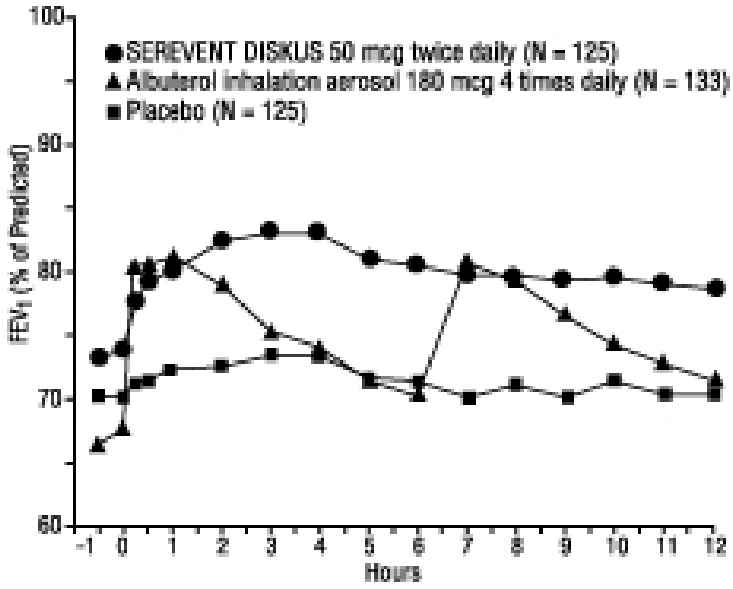


Table 4 shows the treatment effects seen during daily treatment with SEREVENT DISKUS for 12 weeks in adolescent and adult patients with mild-to-moderate asthma.

Table 4. Daily Efficacy Measurements in Two 12-Week Clinical Trials (Combined Data)

Parameter	Time	Placebo	SEREVENT DISKUS	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[a]	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[a]	71
Rescue medications (mean no. of inhalations per day)	Baseline	4.2	4.3	4.3
	12 weeks	3.3	1.6[b]	2.2
Asthma exacerbations (%)		14	15	16

[a]Statistically superior to placebo and albuterol ($p<0.001$).

[b]Statistically superior to placebo ($p<0.001$).

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

SEREVENT DISKUS and SEREVENT Inhalation Aerosol were compared with placebo in 2 additional randomized double-blind clinical trials in adolescent and adult patients with mild-

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

Patients on Concomitant Inhaled Corticosteroids: In 4 clinical trials in adult and adolescent patients with asthma (N = 1,922), the effect of adding SEREVENT Inhalation Aerosol to inhaled corticosteroid therapy was evaluated over a 24-week treatment period. The studies 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 (aged 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 (BDP) 168 mcg twice daily. Patients still not adequately controlled were randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg twice daily or an increase of BDP to 336 mcg twice daily. As compared with the doubled dose of BDP, the addition of SEREVENT Inhalation Aerosol resulted in statistically significantly greater improvements in pulmonary function and asthma symptoms, and statistically significantly greater reduction in supplemental albuterol use. The percent of patients who experienced asthma exacerbations overall was not different between groups (i.e., 16.2% in the group receiving SEREVENT Inhalation Aerosol versus 17.9% in the higher-dose beclomethasone dipropionate group).

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

Table 5 shows the treatment effects seen during daily treatment with SEREVENT Inhalation Aerosol for 24 weeks in adolescent and adult patients with mild-to-moderate asthma.

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

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

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

Salmeterol Multi-center Asthma Research Trial: The SMART study was a randomized double-blind study that enrolled LABA-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 with placebo when added to usual asthma therapy.

A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355), which led to premature termination of the study. The results of the interim analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events (see Table 5 and Figure 2). In the total population, a higher rate of asthma-related death occurred in patients treated with salmeterol than those treated with placebo (0.10% versus 0.02%, relative risk: 4.37 [95% CI: 1.25, 15.34]).

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo (0.07% versus 0.01%, relative risk: 5.82 [95% CI: 0.70, 48.37]). In African Americans also, asthma-related death occurred at a higher rate in patients treated with salmeterol than those treated with placebo (0.31% versus 0.04%, relative risk: 7.26 [95% CI: 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American patients (see Table 5).

Post-hoc analyses in pediatric patients aged 12 to 18 years were also performed. Pediatric patients accounted for approximately 12% of patients in each treatment arm. Respiratory-related death or life-threatening experience occurred at a similar rate in the salmeterol group (0.12%

[2/1,653]) and the placebo group (0.12% [2/1,622]); relative risk: 1.0 [95% CI: 0.1, 7.2]). All-cause hospitalization, however, was increased in the salmeterol group (2% [35/1,653]) versus the placebo group (<1% [16/1,622]; relative risk: 2.1 [95% CI: 1.1, 3.7]).

The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control therapy mitigates the risk of asthma-related death.

Table 5: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)

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

[a] Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

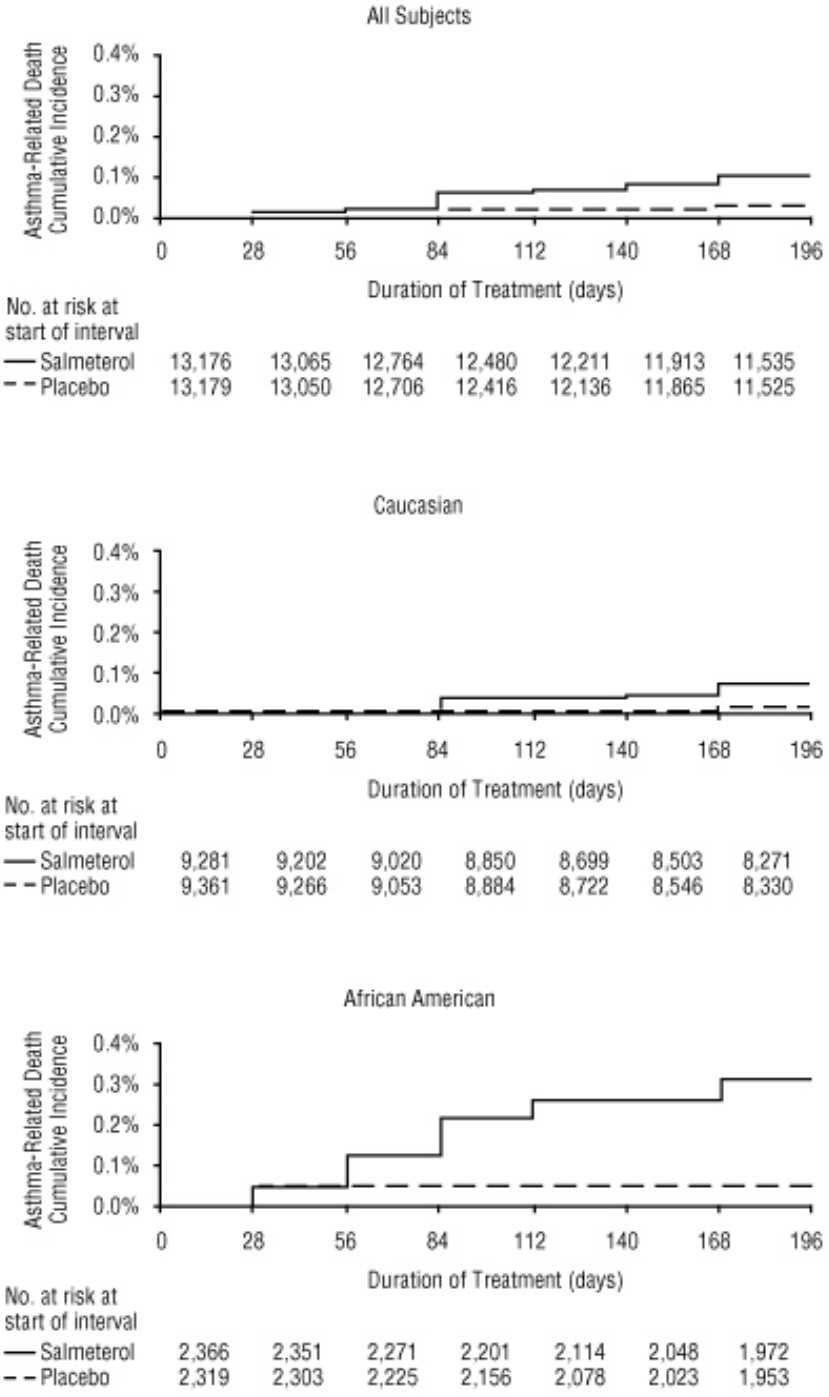
[b] Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week treatment period.

[c] Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

[d] The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those patients whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma-related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death

occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n = 130, placebo n = 127).

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



14.2 Exercise-Induced Bronchospasm

In 2 randomized, single-dose, crossover studies in adolescents and adults with EIB (N = 52), 50 mcg of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise. For some patients, this protective effect against EIB was still apparent up to 8.5 hours following a single dose (see Table 6).

Table 6. Results of 2 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 2 randomized studies in children aged 4 to 11 years with asthma and EIB (N = 50), a single 50-mcg dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise, with protection lasting up to 11.5 hours in repeat testing following this single dose in many patients.

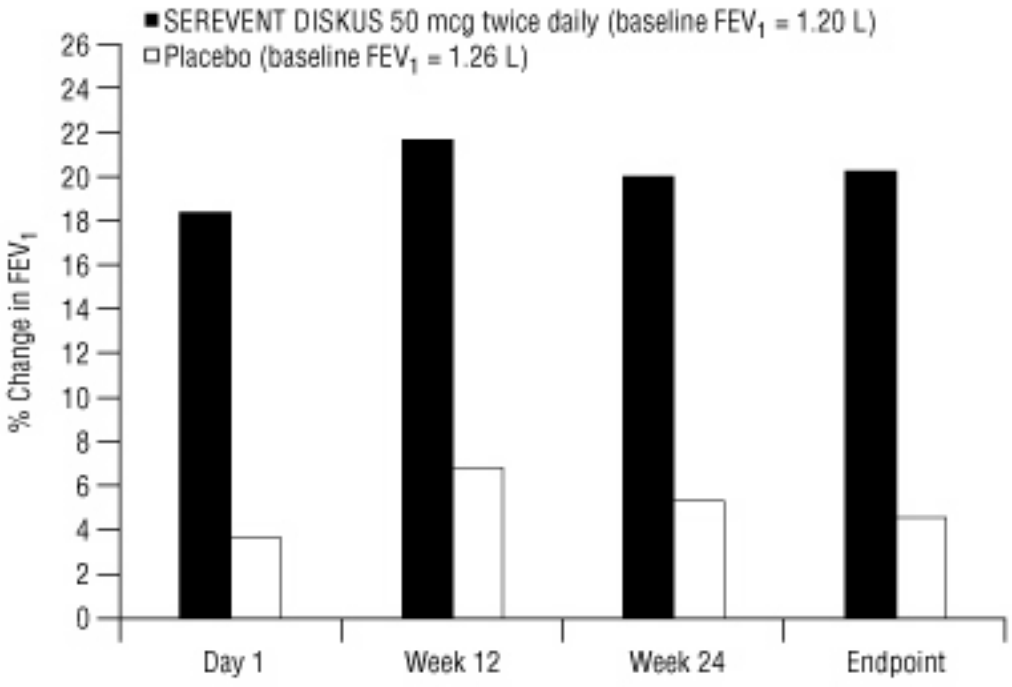
14.3 Chronic Obstructive Pulmonary Disease

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

Figure 3 displays the integrated 2-hour postdose 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 SEREVENT DISKUS 50 mcg had significantly greater improvements in 2-hour postdose FEV_1 at Endpoint (216 mL, 20%) compared with

placebo (43 mL, 5%). Improvement was apparent on the first day of treatment and maintained throughout the 24 weeks of treatment.

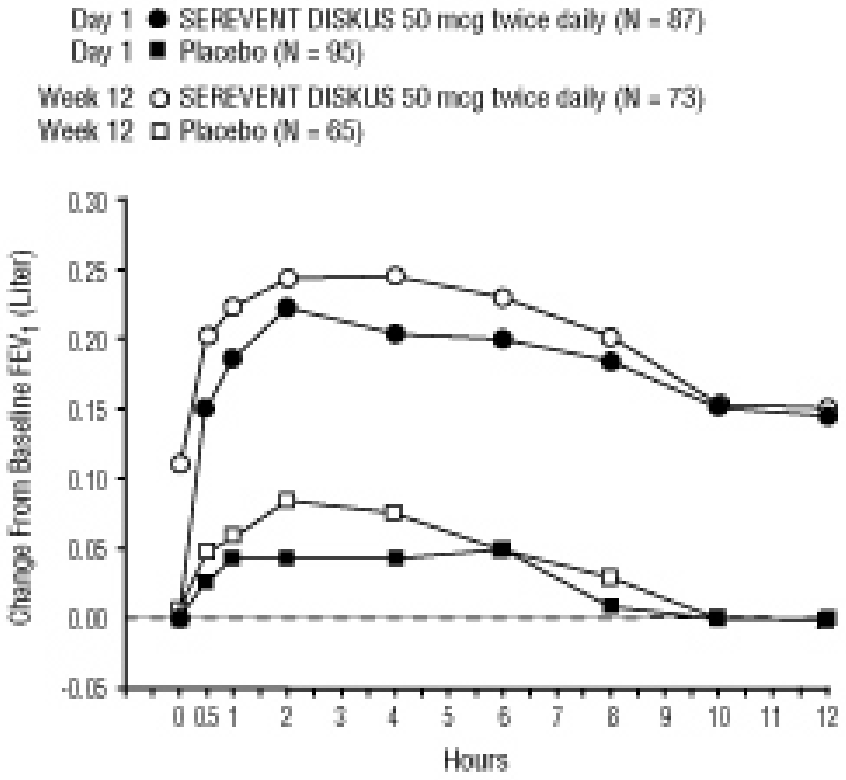
Figure 3. Mean Percent Change From Baseline in Postdose FEV_1 Integrated Data From 2 Trials of Patients With Chronic Bronchitis and Airflow Limitation



	N	N	N	N
SEREVENT DISKUS 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 SEREVENT DISKUS were evaluated in a subset of patients (n = 87) from 1 of the 2 clinical trials discussed above. Following the first 50-mcg dose, significant improvement in pulmonary function (mean FEV_1 increase of 12% or more and at least 200 mL) occurred at 2 hours. The mean time to peak bronchodilator effect was 4.75 hours. As seen in Figure 4, evidence of bronchodilatation was seen throughout the 12-hour period. Figure 4 also demonstrates that the bronchodilating effect after 12 weeks of treatment was similar to that observed after the first dose. The mean time to peak bronchodilator effect after 12 weeks of treatment was 3.27 hours.

Figure 4. Serial 12-Hour FEV_1 on the First Day and at Week 12 of Treatment



16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide.

17.1 Asthma-Related Death

Patients should be informed that salmeterol increases the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and

adolescent patients. Patients should be informed that SEREVENT DISKUS should not be the only therapy for the treatment of asthma and must only be used as additional therapy when long-term asthma control medications (e.g., inhaled corticosteroids) do not adequately control asthma symptoms. They should also be informed that currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Patients should be informed that when SEREVENT DISKUS is added to their treatment regimen they must continue to use their long-term asthma control medication.

17.2 Not for Acute Symptoms

SEREVENT DISKUS is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist such as albuterol. The physician should provide the patient with such medication and instruct the patient in how it should be used.

Patients should be instructed to notify their physicians immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting $beta_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists
- Significant decrease in lung function as outlined by the physician

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

17.3 SEREVENT DISKUS is Not a Substitute for Corticosteroids

All patients with asthma should be advised that they must also continue regular maintenance treatment with an inhaled corticosteroid if they are taking SEREVENT DISKUS.

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.

17.4 Do Not Use Additional Long-Acting $Beta_2$-Agonists

When patients are prescribed SEREVENT DISKUS, other LABA should not be used.

17.5 Risks Associated With Beta-Agonist Therapy

Patients should be informed of adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

17.6 Treatment of Exercised-Induced Bronchospasm

When used for the treatment of EIB, 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.

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GlaxoSmithKline
Research Triangle Park, NC 27709

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MEDICATION GUIDE

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

Read the Medication Guide that comes with SEREVENT DISKUS before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about SEREVENT DISKUS?

SEREVENT DISKUS can cause serious side effects, including:

1. **People with asthma who take long-acting beta$_2$-adrenergic agonist (LABA) medicines such as salmeterol (SEREVENT DISKUS), have an increased risk of death from asthma problems.**
   - Call your healthcare provider if breathing problems worsen over time while using SEREVENT DISKUS. You may need a different treatment.
   - Get emergency medical care if:
     - breathing problems worsen quickly, and
     - you use your rescue inhaler medicine, but it does not relieve your breathing problems.
2. **Do not use SEREVENT DISKUS as your only asthma medicine. SEREVENT DISKUS must only be used with a long-term asthma-control medicine, such as an inhaled corticosteroid.**
3. When your asthma is well controlled, your healthcare provider may tell you to stop taking SEREVENT DISKUS. Your healthcare provider will decide if you can stop SEREVENT DISKUS without loss of asthma control. You will continue taking your long-term asthma-control medicine, such as an inhaled corticosteroid.

4. Children and adolescents who take LABA medicines may have an increased risk of being hospitalized for asthma problems.

What is SEREVENT DISKUS?

- SEREVENT DISKUS is a LABA medicine. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.
- SEREVENT DISKUS is used for asthma, exercise-induced bronchospasm (EIB), and chronic obstructive pulmonary disease (COPD) as follows:

Asthma:

SEREVENT DISKUS is used in adults and children aged 4 years and older, with a long-term asthma control medicine, such as an inhaled corticosteroid:

- to control symptoms of asthma, and
- to prevent symptoms such as wheezing.

LABA medicines, such as SEREVENT DISKUS, increase the risk of death from asthma problems. SEREVENT DISKUS is not for adults and children with asthma who are well controlled with a long-term asthma-control medicine, such as a low to medium dose of an inhaled corticosteroid medicine.

Exercise-Induced Bronchospasm:

SEREVENT DISKUS is used to prevent wheezing caused by exercise in adults and children aged 4 years and older.

- If you have EIB only, your healthcare provider may prescribe only SEREVENT DISKUS for your condition.
- If you have EIB and asthma, your healthcare provider should also prescribe an asthma control medicine, such as an inhaled corticosteroid.

Chronic Obstructive Pulmonary Disease:

SEREVENT DISKUS is used long term, 2 times each day (morning and evening) to control symptoms of COPD and prevent wheezing in adults with COPD.

Who should not use SEREVENT DISKUS?

Do not take SEREVENT DISKUS:

- to treat your asthma without an asthma medicine known as an inhaled corticosteroid
- if you are allergic to salmeterol or any of the ingredients in SEREVENT DISKUS. Ask your healthcare provider if you are not sure. See the end of this Medication Guide for a complete

list of ingredients in SEREVENT DISKUS.

What should I tell my healthcare provider before using SEREVENT DISKUS?

Tell your healthcare provider about all of your health conditions, including if you:

- have heart problems
- have high blood pressure
- have seizures
- have thyroid problems
- have diabetes
- have liver problems
- are pregnant or planning to become pregnant. It is not known if SEREVENT DISKUS may harm your unborn baby.
- are breastfeeding. It is not known if SEREVENT DISKUS passes into your milk and if it can harm your baby.
- are allergic to SEREVENT DISKUS, any other medicines, or food products. See the end of this Medication Guide for a complete list of ingredients in SEREVENT DISKUS.

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

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

How do I use SEREVENT DISKUS?

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

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

- If you miss a dose of SEREVENT DISKUS, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.
- Do not use a spacer device with SEREVENT DISKUS.
- Do not breathe into SEREVENT DISKUS.
- While you are using SEREVENT DISKUS 2 times each day, do not use other medicines that contain a long-acting beta$_2$-agonist orLABA for any reason. Ask your healthcare provider or pharmacist for a list of these medicines.
- Do not stop using SEREVENT DISKUS or any of your asthma medicines unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- SEREVENT DISKUS does not relieve sudden symptoms. Always have a rescue inhaler medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.
- Call your healthcare provider or get medical care right away if:
  - your breathing problems worsen with SEREVENT DISKUS
  - you need to use your rescue inhaler medicine more often than usual
  - your rescue inhaler medicine does not work as well for you at relieving symptoms
  - you need to use 4 or more inhalations of your rescue inhaler medicine for 2 or more days in a row
  - you use 1 whole canister of your rescue inhaler medicine in 8 weeks' time
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  - you have asthma and your symptoms do not improve after using SEREVENT DISKUS regularly for 1 week.
  - after a change in your asthma medicines you have any worsening of your asthma symptoms or an increase in the need for your rescue inhaler medicine.

What are the possible side effects with SEREVENT DISKUS?
SEREVENT DISKUS can cause serious side effects, including:

- **See "What is the most important information I should know about SEREVENT DISKUS?"**
- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling of the face, mouth, and tongue
  - breathing problems.

- **sudden breathing problems immediately after inhaling your medicine**
- **effects on heart**
  - increased blood pressure
  - a fast and irregular heartbeat
  - chest pain
- **effects on nervous system**
  - tremor
  - nervousness
- **changes in blood (sugar, potassium)**

Common side effects of SEREVENT DISKUS include:

Asthma in adults and children:

- headache
- nasal congestion
- bronchitis
- throat irritation
- runny nose
- flu

Chronic obstructive pulmonary disease:

- headache
- musculoskeletal pain
- throat irritation
- cough
- respiratory infection

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with SEREVENT DISKUS. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store SEREVENT DISKUS?

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

General Information about SEREVENT DISKUS

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

This Medication Guide summarizes the most important information about SEREVENT DISKUS. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about SEREVENT DISKUS that was written for healthcare professionals. You can also contact the company that makes SEREVENT DISKUS (toll free) at 1-888-825-5249 or at www.serevent.com.

What are the ingredients in SEREVENT DISKUS?

Active ingredient: salmeterol xinafoate
Inactive ingredient: lactose (contains milk proteins)

Instructions for Using SEREVENT DISKUS

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

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

- The DISKUS will be in the closed position when the pouch is opened.

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

Figure 1

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

1. OPEN

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

Figure 2

2. CLICK

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

Figure 3

Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the DISKUS is ready:**

- **Do not close the DISKUS.**
- **Do not tilt the DISKUS.**
- **Do not play with the lever.**
- **Do not move the lever more than once.**

3. INHALE

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

Figure 4

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

Figure 5

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

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

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

to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4.)

Figure 6

Remember:

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

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

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GlaxoSmithKline

GlaxoSmithKline
Research Triangle Park, NC 27709

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