SEREVENT® DISKUS®
(salmeterol xinafoate inhalation powder)

For Oral Inhalation Only

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-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) (see WARNINGS and CLINICAL TRIALS: Asthma: Salmeterol Multi-center Asthma Research Trial). 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 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 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 LABA is recommended.

DESCRIPTION

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

\[
\begin{align*}
\text{HO} & \quad \text{N} & \quad \text{OH} & \quad \text{O} & \quad \text{COOH} \\
\text{HO} & \quad \text{N} & \quad \text{OH} & \quad \text{O} & \quad \text{COOH}
\end{align*}
\]

Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is C_{25}H_{37}NO_{4}\cdot C_{11}H_{8}O_{3}. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

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

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

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

**CLINICAL PHARMACOLOGY**

**Mechanism of Action:** Salmeterol is a long-acting beta\textsubscript{2}-adrenergic agonist. In vitro studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta\textsubscript{2}-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on beta\textsubscript{1}- and beta\textsubscript{2}-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more selective for beta\textsubscript{2}-adrenoceptors than albuterol. Although beta\textsubscript{2}-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta\textsubscript{1}-adrenoceptors are the predominant receptors in the heart, there are also beta\textsubscript{2}-adrenoceptors in the human heart.
comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta2-agonists may have cardiac effects.

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

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

**Pharmacokinetics:** Salmeterol 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 has been 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 cytochrome P450 3A4 (CYP 3A4). Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of α-hydroxysalmeterol in vitro.

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

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days.
Special Populations: The pharmacokinetics of salmeterol base has not been studied in elderly patients nor in patients with hepatic or renal impairment. Since salmeterol is predominantly cleared by hepatic metabolism, liver function impairment may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Drug Interactions: Salmeterol is a substrate of CYP3A4.

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. 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.

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.

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

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

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

No effect of treatment with salmeterol 50 mcg was observed on pulse rate and systolic and diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign measurements after the first dose (N = 91) and after 12 weeks of therapy (N = 74). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar for patients receiving either salmeterol or placebo (see ADVERSE REACTIONS).

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

**CLINICAL TRIALS**

**Asthma:** During the initial treatment day in several multiple-dose clinical trials with SEREVENT DISKUS in patients with asthma, the median time to onset of clinically significant bronchodilatation (≥15% improvement in FEV₁) 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 FEV₁. Maximum improvement in FEV₁ generally occurred within 180 minutes, and clinically significant improvement continued for 12 hours in most patients.

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 FEV₁, 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. FEV₁ measurements (mean change from baseline) from these two 12-week studies are shown in Figure 1 for both the first and last treatment days.
Table 1 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 1. Daily Efficacy Measurements in Two 12-Week Clinical Trials (Combined Data)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time</th>
<th>Placebo</th>
<th>SEREVENT DISKUS</th>
<th>Albuterol Inhalation Aerosol</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of randomized subjects</td>
<td></td>
<td>152</td>
<td>149</td>
<td>148</td>
</tr>
<tr>
<td>Mean AM peak expiratory flow (L/min)</td>
<td>baseline</td>
<td>394</td>
<td>395</td>
<td>394</td>
</tr>
<tr>
<td>Mean % days with no asthma symptoms</td>
<td>12 weeks</td>
<td>14</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Mean % nights with no awakenings</td>
<td>12 weeks</td>
<td>70</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>Rescue medications (mean no. of inhalations per day)</td>
<td>baseline</td>
<td>4.2</td>
<td>4.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Asthma exacerbations</td>
<td>12 weeks</td>
<td>3.3</td>
<td>1.6†</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14%</td>
<td>15%</td>
</tr>
</tbody>
</table>

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

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

SEREVENT DISKUS and SEREVENT® (salmeterol xinafoate) Inhalation Aerosol were compared to 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 exercise-induced bronchospasm (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.

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

**Effects in Patients With Asthma on Concomitant Inhaled Corticosteroids:** In 4
clinical trials in adult and adolescent patients with asthma (N = 1,922), the effect of adding
salmeterol to inhaled corticosteroid therapy was evaluated. The studies utilized the inhalation
aerosol formulation of salmeterol xinafoate for a treatment period of 6 months. They compared
the addition of salmeterol therapy to an increase (at least doubling) of the inhaled corticosteroid
dose.

Two randomized, double-blind, controlled, parallel-group clinical trials (N = 997) enrolled
patients (ages 18 to 82 years) with persistent asthma who were previously maintained but not
adequately controlled on inhaled corticosteroid therapy. During the 2-week run-in period, all
patients were switched to beclomethasone dipropionate 168 mcg twice daily. Patients still not
adequately controlled were randomized to either the addition of SEREVENT Inhalation Aerosol
42 mcg twice daily or an increase of beclomethasone dipropionate to 336 mcg twice daily. As
compared to the doubled dose of beclomethasone dipropionate, the addition of 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, parallel-group clinical trials (N = 925) enrolled patients (ages
12 to 78 years) with persistent asthma who were previously maintained but not adequately
controlled on prior therapy. During the 2- to 4-week run-in period, all patients were switched to
fluticasone propionate 88 mcg twice daily. Patients still not adequately controlled were
randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg twice daily or an
increase of fluticasone propionate to 220 mcg twice daily. As compared to the increased (2.5
times) dose of fluticasone propionate, the addition of 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%).

**Exercise-Induced Bronchospasm:** In 2 randomized, single-dose, crossover studies in
adolescents and adults with EIB (N = 53), 50 mcg of SEREVENT DISKUS prevented EIB when
dosed 30 minutes prior to exercise. For many patients, this protective effect against EIB was still
apparent up to 8.5 hours following a single dose.
Table 2. Results of 2 Exercise-Induced Bronchospasm Studies in Adolescents and Adults

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 52)</th>
<th>SEREVENT DISKUS (N = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% Total</td>
</tr>
<tr>
<td>0.5-Hour postdose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10%, &lt;20%</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>≥20%</td>
<td>34</td>
<td>65</td>
</tr>
<tr>
<td>Mean maximal % fall in FEV&lt;sub&gt;1&lt;/sub&gt; (SE)</td>
<td>-25% (1.8)</td>
<td>-11% (1.9)</td>
</tr>
<tr>
<td>8.5-Hour postdose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10%, &lt;20%</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>≥20%</td>
<td>33</td>
<td>63</td>
</tr>
<tr>
<td>Mean maximal % fall in FEV&lt;sub&gt;1&lt;/sub&gt; (SE)</td>
<td>-27% (1.5)</td>
<td>-16% (2.0)</td>
</tr>
</tbody>
</table>

In 2 randomized studies in children 4 to 11 years old 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.

**Salmeterol Multi-center Asthma Research Trial:** The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta<sub>2</sub>-agonist–naive patients with asthma (average age of 39 years, 71% Caucasian, 18% African American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared to placebo when added to usual asthma therapy. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355), which led to premature termination of the study. The results of the interim analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events (see Table 3 and Figure 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% vs. 0.02%; relative risk 4.37 [95% CI 1.25, 15.34]).

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also, asthma-related death occurred at a higher rate in patients treated with salmeterol than those treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American patients (see
Table 3). Post-hoc analyses in pediatric patients 12 to 18 years of age 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% (2/1653) and the placebo group (0.12%) (2/1622) [relative risk 1.0, 95% CI 0.1-7.2]. All cause hospitalization, however, was increased in the salmeterol group (2%) (35/1653) vs. the placebo group (<1%) (16/1622) [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 3: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)

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

* Life-table 28-week estimate, adjusted according to the patients’ actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.
† Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week treatment period.
‡ Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.
§ The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and “Other.” In addition, the Total Population includes those 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

Chronic Obstructive Pulmonary Disease: In 2 clinical trials evaluating twice-daily
treatment with SEREVENT DISKUS 50 mcg (N = 336) compared to placebo (N = 366) in patients with chronic bronchitis with airflow limitation, with or without emphysema, improvements in pulmonary function endpoints were greater with salmeterol 50 mcg than with placebo. Treatment with 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 FEV₁ results from the 2 clinical trials. The percent change in FEV₁ 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 FEV₁) data are provided. Patients receiving SEREVENT DISKUS 50 mcg had significantly greater improvements in 2-hour postdose FEV₁ at Endpoint (216 mL, 20%) compared to placebo (43 mL, 5%). Improvement was apparent on the first day of treatment and maintained throughout the 24 weeks of treatment.

**Figure 3. Mean Percent Change From Baseline in Postdose FEV₁ Integrated Data From 2 Trials of Patients With Chronic Bronchitis and Airflow Limitation**

**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 FEV₁ 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 FEV₁ on the First Day and at Week 12 of Treatment

**INDICATIONS AND USAGE**

**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 4 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma. Long-acting beta₂-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death (see WARNINGS). 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). 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 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 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 LABA
is recommended.

**Exercise Induced Bronchospasm:** SEREVENT DISKUS is also indicated for prevention
of exercise induced bronchospasm in patients 4 years of age and older. Use of SEREVENT
DISKUS as a single agent for the prevention of exercise induced bronchospasm 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 exercise induced bronchospasm may
be clinically indicated, but the treatment of asthma should include a long-term asthma control
medication, such as an inhaled corticosteroid.

**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 COPD (including emphysema and chronic bronchitis).

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

**WARNINGS**

**Asthma Related Death**
Long-acting beta₂-adrenergic agonists, 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 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
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 LABA is recommended.

SMART and SNS
A large 28-week, placebo-controlled US study comparing the safety of salmeterol (SEREVENT
Inhalation Aerosol) with placebo, each added to usual asthma therapy, showed an increase in
asthma-related deaths in patients receiving salmeterol (see CLINICAL TRIALS: Asthma:
Salmeterol Multi-center Asthma Research Trial). Given the similar basic mechanisms of action
of beta2-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 long-acting beta2-adrenergic agonists.
• It is important to watch for signs of worsening asthma, such as increasing use of
inhaled, short-acting beta2-agonists or a significant decrease in PEF or lung function.
Such findings require immediate evaluation. Patients should be advised to seek
immediate medical attention should their condition deteriorate.
• **SEREVENT DISKUS should not be used to treat acute symptoms.** It is crucial to inform patients of this and prescribe an inhaled, short-acting beta₂-agonist for this purpose and to warn them that increasing inhaled beta₂-agonist use is a signal of deteriorating asthma that requires prompt consultation with a physician.

• **SEREVENT DISKUS should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition.** Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide when SEREVENT has been initiated in this situation. Although it is not possible from these reports to determine whether SEREVENT contributed to these adverse events or simply failed to relieve the deteriorating asthma, the use of SEREVENT DISKUS in this setting is inappropriate.

• **SEREVENT DISKUS is not a substitute for inhaled or oral corticosteroids.** Corticosteroids should not be stopped or reduced when SEREVENT DISKUS is initiated.

See PRECAUTIONS: Information for Patients and the Medication Guide accompanying the product.

The following additional WARNINGS about SEREVENT DISKUS should be noted.

1. **SEREVENT DISKUS should not be used as a treatment for acutely deteriorating asthma.** SEREVENT DISKUS should not be introduced in acutely deteriorating asthma, which is a potentially life-threatening condition. There are no data demonstrating that SEREVENT DISKUS provides greater efficacy than or additional efficacy to inhaled, short-acting beta₂-agonists in patients with worsening asthma. Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide in patients receiving SEREVENT. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled, short-acting beta₂-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT contributed to these events.

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

When beginning treatment with SEREVENT DISKUS, patients who have been taking
inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute asthma or COPD symptoms (see PRECAUTIONS: Information for Patients).

3. **Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma or COPD.** The physician and patient should be alert to such changes. The patient’s condition may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient’s inhaled, short-acting beta₂-agonist becomes less effective, the patient needs more inhalations than usual, or the patient develops a significant decrease in PEF or lung function, these may be markers of destabilization of their disease. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for corticosteroids. If the patient uses 4 or more inhalations per day of an inhaled, short-acting beta₂-agonist for 2 or more consecutive days, or if more than 1 canister (200 inhalations per canister) of inhaled, short-acting beta₂-agonist is used in an 8-week period in conjunction with SEREVENT DISKUS, then the patient should consult the physician for reevaluation.

**Increasing the daily dosage of SEREVENT DISKUS in this situation is not appropriate.** SEREVENT DISKUS should not be used more frequently than twice daily (morning and evening) at the recommended dose of 1 inhalation.

4. **SEREVENT DISKUS should not be used in conjunction with an inhaled, long-acting beta₂-agonist.** SEREVENT DISKUS should not be used with other medications containing inhaled, long-acting beta₂-agonists.

5. **SEREVENT DISKUS is not a substitute for oral or inhaled corticosteroids.** There are no data demonstrating that SEREVENT DISKUS has a clinical anti-inflammatory effect and could be expected to take the place of corticosteroids. When initiating SEREVENT DISKUS in patients receiving oral or inhaled corticosteroids for treatment of asthma, patients should be continued on a suitable dose 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 (see PRECAUTIONS: Information for Patients).

6. **The recommended dosage should not be exceeded.** As with other inhaled beta₂-adrenergic drugs, SEREVENT DISKUS should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias.

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

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

9. Upper airway symptoms. Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving SEREVENT DISKUS.

10. Cardiovascular disorders. SEREVENT DISKUS, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. SEREVENT DISKUS, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of SEREVENT DISKUS at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown.

11. Potential drug interactions. 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 CYP 3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir,itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Drug Interactions).

PRECAUTIONS

General: Cardiovascular Effects: No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol at recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of salmeterol and may require discontinuation of SEREVENT DISKUS. SEREVENT DISKUS, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

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

Metabolic Effects: Doses of the related beta2-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic agonist medications may produce significant hypokalemia in some
patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

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

Information for Patients: Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document.

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

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

1. Patients should be informed that salmeterol increases the risk of asthma-related death and may increase the risk of asthma-related hospitalizations 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. 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.

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

3. The physician should be notified immediately if any of the following signs of seriously worsening asthma or COPD occur:
   • decreasing effectiveness of inhaled, short-acting beta2-agonists;
   • need for more inhalations than usual of inhaled, short-acting beta2-agonists;
   • significant decrease in PEF or lung function as outlined by the physician;
   • use of 4 or more inhalations per day of a short-acting beta2-agonist for 2 or more days consecutively;
   • use of more than 1 canister (200 inhalations per canister) of an inhaled, short-acting beta2-agonist in an 8-week period.

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

5. SEREVENT DISKUS should not be used as a substitute for oral or inhaled corticosteroids.

The dosage of these medications should not be changed and they should not be stopped
without consulting the physician, even if the patient feels better after initiating treatment with SEREVENT DISKUS.

6. Patients should be cautioned regarding adverse effects associated with beta2-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

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

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

9. Patients who are pregnant or nursing should contact the physician about the use of SEREVENT DISKUS.

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

11. When used for the treatment of EIB, 1 inhalation of SEREVENT DISKUS should be taken 30 minutes before exercise.

   • Additional doses of SEREVENT should not be used for 12 hours.

   • Patients who are receiving SEREVENT DISKUS twice daily should not use additional SEREVENT for prevention of EIB.

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

   • Never exhale into the DISKUS.

   • Never attempt to take the DISKUS apart.

   • Always activate and use the DISKUS in a level, horizontal position.

   • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.

   • Always keep the DISKUS in a dry place.

   • Discard 6 weeks after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads “0”), whichever comes first.

13. For the proper use of SEREVENT DISKUS and to attain maximum benefit, the patient should read and follow carefully the Instructions for Using SEREVENT DISKUS in the Medication Guide accompanying the product.

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

**Drug Interactions: 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\text{max} increased 1.4-fold). Three (3) subjects were withdrawn due to beta2-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.

**Short-Acting Beta₂-Agonists:** In two 12-week, repetitive-dose adolescent and adult clinical trials in patients with asthma (N = 149), the mean daily need for additional beta₂-agonist in patients using SEROVENT 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 beta₂-agonist with SEROVENT DISKUS has not been established. In 29 patients who experienced worsening of asthma while receiving SEROVENT DISKUS during these trials, albuterol therapy administered via either nebulizer or inhalation aerosol (1 dose in most cases) led to improvement in FEV₁ and no increase in occurrence of cardiovascular adverse events.

In 2 clinical trials in patients with COPD, the mean daily need for additional beta₂-agonist for patients using SEROVENT DISKUS was approximately 4 inhalations/day. Twenty-four percent (24%) of the patients using SEROVENT 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 events was observed among patients who averaged 6 or more inhalations per day.

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

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

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

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

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

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

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** In an 18-month oral
carcinogenicity study in CD-mice, salmeterol xinafoate caused a dose-related increase in the
incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus,
and ovarian cysts at doses of 1.4 mg/kg and above (approximately 20 times the maximum
recommended daily inhalation dose in adults and children based on comparison of the area under
the plasma concentration versus time curves [AUCs]). The incidence of leiomyosarcomas was
not statistically significant. No tumors were seen at 0.2 mg/kg (approximately 3 times the
maximum recommended daily inhalation doses in adults and children based on comparison of
the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol
caus ed a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at
doses of 0.68 mg/kg and above (approximately 55 times the maximum recommended daily
inhalation dose in adults and approximately 25 times the maximum recommended daily
inhalation dose in children on a mg/m² basis). No tumors were seen at 0.21 mg/kg
(approximately 15 times the maximum recommended daily inhalation dose in adults and
approximately 8 times the maximum recommended daily inhalation dose in children on a mg/m²
basis). These findings in rodents are similar to those reported previously for other
beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian
gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo
in a rat micronucleus test. No effects on fertility were identified in male and female rats treated
with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum
recommended daily inhalation dose in adults on a mg/m² basis).

**Pregnancy:** **Teratogenic Effects:** Pregnancy Category C. No teratogenic effects occurred in
rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily
inhalation dose in adults on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of
1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in
adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects
characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid
openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans. There are no adequate and well-controlled studies with SEREVENT DISKUS in pregnant women. SEREVENT DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice and rats (approximately 410 and 810 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m² basis).

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

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

**Pediatric Use:** 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 LABA should ordinarily be used to ensure adherence with both drugs (see INDICATIONS AND USAGE and WARNINGS).

The safety and efficacy of SEREVENT DISKUS in adolescents (12 years and older) has been established based on adequate and well-controlled trials conducted in adults and adolescents (see CLINICAL TRIALS). A large 28-week, placebo-controlled US study, comparing salmeterol (SEREVENT Inhalation Aerosol) and placebo, added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (see CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*). Post-hoc analyses in pediatric patients 12 to 18 years of age 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% (2/1653) and the placebo group (0.12%) (2/1622) [relative risk 1.0, 95% CI 0.1-7.2]. All cause hospitalization, however, was increased in
the salmeterol group (2%) (35/1653) vs. the placebo group (<1%) (16/1622) [relative risk 2.1, 95% CI 1.1-3.7].

The safety and efficacy of SEREVENT DISKUS has 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 (see DOSAGE AND ADMINISTRATION).

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 PEF and FEV₁. SEREVENT DISKUS was effective in demographic subgroups (gender and age) of the population.

In 2 randomized studies in children 4 to 11 years old 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.

Geriatric Use: Of the total number of adolescent and adult patients with asthma who received SEREVENT DISKUS in chronic dosing clinical trials, 209 were 65 years of age and older. Of the total number of patients with COPD who received SEREVENT DISKUS in chronic dosing clinical trials, 167 were 65 years of age or older and 45 were 75 years of age or older. No apparent differences in the safety of SEREVENT DISKUS were observed when geriatric patients were compared with younger patients in clinical trials. As with other beta₂-agonists, however, special caution should be observed when using SEREVENT 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 FEV₁ 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.

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

Asthma: Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT DISKUS in patients 12 years of age and older with asthma. Table 4 reports the incidence of adverse events in these 2 studies.
Table 4. Adverse Event Incidence in Two 12-Week Adolescent and Adult Clinical Trials in Patients With Asthma

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N = 152)</th>
<th>SEREVENT DISKUS 50 mcg Twice Daily (N = 149)</th>
<th>Albuterol Inhalation Aerosol 180 mcg 4 Times Daily (N = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear, nose, and throat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal/sinus congestion, pallor</td>
<td>6</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>1</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Tracheitis/bronchitis</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Influenza</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 4 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in 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.

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

- **Ear, Nose, and Throat**: Sinus headache.
- **Gastrointestinal**: Nausea.
- **Mouth and Teeth**: Oral mucosal abnormality.
- **Musculoskeletal**: Pain in joint.
- **Neurological**: Sleep disturbance, paresthesia.
- **Skin**: Contact dermatitis, eczema.
- **Miscellaneous**: Localized aches and pains, pyrexia of unknown origin.

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of SEREVENT DISKUS in patients aged 4 to 11 years with asthma. Table 5 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common than in the placebo group.
Table 5. Adverse Event Incidence in Two 12-Week Pediatric Clinical Trials in Patients With Asthma

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 215)</td>
</tr>
<tr>
<td></td>
<td>SEREVENT DISKUS 50 mcg Twice Daily (N = 211)</td>
</tr>
<tr>
<td></td>
<td>Albuterol Inhalation Powder 200 mcg 4 Times Daily (N = 115)</td>
</tr>
<tr>
<td>Ear, nose, and throat</td>
<td></td>
</tr>
<tr>
<td>Ear signs and symptoms</td>
<td>3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>2</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Skin rashes</td>
<td>3</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0</td>
</tr>
</tbody>
</table>

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

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.

**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 6), 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 6. Adverse Events With ≥3% Incidence in US Controlled Clinical Trials With SEREVENT DISKUS in Patients With Chronic Obstructive Pulmonary Disease*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percent of Patients</th>
<th>Placebo (N = 576)</th>
<th>SEREVENT DISKUS 50 mcg Twice Daily (N = 341)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Ear, nose, and throat</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Throat irritation</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Nasal congestion/blockage</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Ear signs and symptoms</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Lower respiratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Viral respiratory infection</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Muscle cramps and spasms</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Average duration of exposure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(days)</td>
<td>128.9</td>
<td>138.5</td>
<td></td>
</tr>
</tbody>
</table>

* Table 6 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT DISKUS and were more common in the group receiving SEREVENT DISKUS than in the placebo group.

Other events occurring in the group receiving SEREVENT DISKUS that occurred at a frequency of 1% to <3% and were more common than in the placebo group were as follows:

**Endocrine and Metabolic:** Hyperglycemia.

**Eye:** Keratitis and conjunctivitis.

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

**Lower Respiratory:** Lower respiratory signs and symptoms.

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

**Neurology:** Migraines.

**Non-Site Specific:** Pain, edema and swelling.

**Psychiatry:** Anxiety.

**Skin:** Skin rashes.

Adverse reactions to salmeterol are similar in nature to those seen with other selective beta2-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor; nervousness; and paradoxical bronchospasm (see WARNINGS).

**Observed During Clinical Practice:** In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of salmeterol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These 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), 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.

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

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

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

**OVERDOSAGE**

The expected signs and symptoms with overdosage of SEREVENT DISKUS are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Overdosage with SEREVENT DISKUS may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with SEREVENT DISKUS can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

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

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

No deaths were seen in rats at an inhalation dose of 2.9 mg/kg (approximately 240 times the maximum recommended daily inhalation dose in adults and approximately 110 times the maximum recommended daily inhalation dose in children on a mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 times the maximum recommended daily inhalation dose in adults and approximately 90 times the maximum recommended daily inhalation dose in children on a mg/m² basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6,100 times the maximum recommended daily inhalation dose in adults and approximately 2,900 times the maximum recommended daily inhalation dose in children on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 81,000 times the maximum recommended daily inhalation dose in adults and approximately 38,000 times the maximum recommended daily inhalation dose in children on a mg/m² basis).

DOSAGE AND ADMINISTRATION

SEREVENT DISKUS should be administered by the orally inhaled route only (see Instructions for Using SEREVENT DISKUS in the Medication Guide accompanying the product). The patient must not exhale into the DISKUS and the DISKUS should only be activated and used in a level, horizontal position.

Asthma: Long-acting beta₂-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death (see WARNINGS).

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 Patients 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 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 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 LABA is recommended.

For bronchodilatation and prevention of symptoms of asthma, including the symptoms of nocturnal asthma, the usual dosage for adults and children 4 years of age and older is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be reevaluated. If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

**Chronic Obstructive Pulmonary Disease:** For maintenance treatment of bronchospasm associated with COPD (including chronic bronchitis and emphysema), the usual dosage for adults is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). For both asthma and COPD, adverse effects are more likely to occur with higher doses of salmeterol, and more frequent administration or administration of a larger number of inhalations is not recommended.

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

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

**Prevention of Exercise-Induced Bronchospasm:** Use of SEREVENT DISKUS as a single agent for the prevention of exercise induced bronchospasm 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 exercise induced bronchospasm 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 4 to 11 years of age. **Additional doses of SEREVENT should not be used for 12 hours after the administration of this drug. Patients who are receiving SEREVENT DISKUS twice daily should not use additional SEREVENT for prevention of EIB.**

**HOW SUPPLIED**

SEREVENT DISKUS is supplied as a disposable teal green unit containing 60 blisters. The drug product is packaged within a teal green, 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 teal green, 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. SEREVENT DISKUS 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. The DISKUS is not reusable. Do not attempt to take the DISKUS apart.
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:**
SEEREVENT 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 SEEREVENT DISKUS?**

*Do not take SEEREVENT 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 SEEREVENT DISKUS. Ask your healthcare provider if you are not sure. See the end of this Medication Guide for a complete list of ingredients in SEEREVENT DISKUS.

**What should I tell my healthcare provider before using SEEREVENT 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 SEEREVENT DISKUS may harm your unborn baby.
- are breastfeeding. It is not known if SEEREVENT DISKUS passes into your milk and if it can harm your baby.
- are allergic to SEEREVENT DISKUS, any other medicines, or food products. See the end of this Medication Guide for a complete list of ingredients in SEEREVENT DISKUS.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. SEEREVENT 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 SEEREVENT DISKUS?**

See the step-by-step instructions for using the SEEREVENT DISKUS at the end of this Medication Guide. Do not use SEEREVENT 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 SEEREVENT DISKUS with an adult’s help, as instructed by the child’s
1086 healthcare provider.

1087 • Use SEREVENT DISKUS exactly as prescribed. Do not use SEREVENT DISKUS more
1088 often than prescribed.
1089 • For asthma and COPD, the usual dose is 1 inhalation 2 times each day (morning and
1090 evening). The 2 doses should be about 12 hours apart.
1091 • For preventing exercise-induced bronchospasm, take 1 inhalation at least 30 minutes before
1092 exercise. Do not use SEREVENT DISKUS more often than every 12 hours. Do not use extra
1093 SEREVENT DISKUS before exercise if you already use it 2 times each day.
1094 • If you miss a dose of SEREVENT DISKUS, just skip that dose. Take your next dose at your
1095 usual time. Do not take 2 doses at one time.
1096 • Do not use a spacer device with SEREVENT DISKUS.
1097 • Do not breathe into SEREVENT DISKUS.
1098 • While you are using SEREVENT DISKUS 2 times each day, do not use other medicines that
1099 contain a long-acting beta2-agonist or LABA for any reason. Ask your healthcare provider or
1100 pharmacist for a list of these medicines.
1101 • Do not stop using SEREVENT DISKUS or any of your asthma medicines unless told to do
1102 so by your healthcare provider because your symptoms might get worse. Your healthcare
1103 provider will change your medicines as needed.
1104 • SEREVENT DISKUS does not relieve sudden symptoms. Always have a rescue inhaler
1105 medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting
1106 bronchodilator, contact your healthcare provider to have one prescribed for you.
1107 • Call your healthcare provider or get medical care right away if:
1108 • your breathing problems worsen with SEREVENT DISKUS
1109 • you need to use your rescue inhaler medicine more often than usual
1110 • your rescue inhaler medicine does not work as well for you at relieving symptoms
1111 • you need to use 4 or more inhalations of your rescue inhaler medicine for 2 or more days
1112 in a row
1113 • you use 1 whole canister of your rescue inhaler medicine in 8 weeks’ time
1114 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers
1115 that are right for you.
1116 • you have asthma and your symptoms do not improve after using SEREVENT DISKUS
1117 regularly for 1 week.
1118 • after a change in your asthma medicines you have any worsening of your asthma
1119 symptoms or an increase in the need for your rescue inhaler medicine.

1120 What are the possible side effects with SEREVENT DISKUS?
1121 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
1206 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).

1209

Figure 2

1210

2. CLICK

1213

1214 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.

1217

Figure 3

1218

1219

1220

1221 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:

1224

• 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.)

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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