

PRESCRIBING INFORMATION

**SEREVENT<sup>®</sup> DISKUS<sup>®</sup>**  
**(salmeterol xinafoate inhalation powder)**

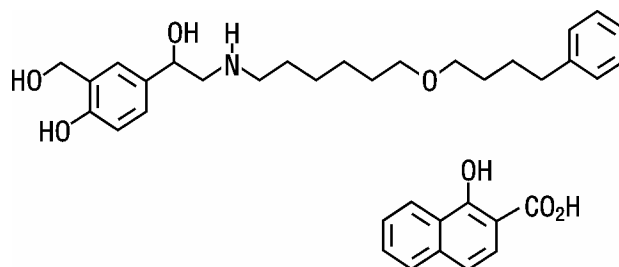
**FOR ORAL INHALATION ONLY**

**WARNING**

Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT<sup>®</sup> 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*).

**DESCRIPTION**

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



Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8, and the empirical formula is C<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>•C<sub>11</sub>H<sub>8</sub>O<sub>3</sub>. 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<sup>®</sup>, which is the delivery component, is an integral part of the drug

35 product. Each blister on the double-foil strip within the unit contains 50 mcg of salmeterol  
36 administered as the salmeterol xinafoate salt in 12.5 mg of formulation containing lactose (which  
37 contains milk proteins). After a blister containing medication is opened by activating the  
38 DISKUS, the medication is dispersed into the airstream created by the patient inhaling through  
39 the mouthpiece.

40 Under standardized in vitro test conditions, SEREVENT DISKUS delivers 47 mcg when  
41 tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and  
42 severely compromised lung function (mean forced expiratory volume in 1 second [FEV<sub>1</sub>] 20% to  
43 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS was 82.4 L/min (range,  
44 46.1 to 115.3 L/min).

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

## 47 **CLINICAL PHARMACOLOGY**

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

58 The pharmacologic effects of beta<sub>2</sub>-adrenoceptor agonist drugs, including salmeterol, are at  
59 least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes  
60 the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic  
61 AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition  
62 of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

63 In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast  
64 cell mediators, such as histamine, leukotrienes, and prostaglandin D<sub>2</sub>, from human lung.  
65 Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits  
66 platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when  
67 administered by the inhaled route. In humans, single doses of salmeterol administered via  
68 inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

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

73 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low or  
74 undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder  
75 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol  
76 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in  
77 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of  
78 167 pg/mL at 20 minutes and no accumulation with repeated doses.

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

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

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

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

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

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

101 The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied  
102 in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as  
103 inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as  
104 albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and adult  
105 patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent continuous  
106 electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month  
107 of therapy, and no clinically significant dysrhythmias were noted. Also, pediatric patients  
108 receiving 50-mcg doses of salmeterol inhalation powder (N = 67) underwent continuous  
109 electrocardiographic monitoring during two 12-hour periods after the first dose and after  
110 3 months of therapy, and no clinically significant dysrhythmias were noted.

111 In 24-week clinical studies in patients with chronic obstructive pulmonary disease (COPD),  
112 the incidence of clinically significant abnormalities on the predose electrocardiograms (ECGs) at

113 Weeks 12 and 24 in patients who received salmeterol 50 mcg was not different compared with  
114 placebo.

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

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

## 124 **CLINICAL TRIALS**

125 **Asthma:** During the initial treatment day in several multiple-dose clinical trials with  
126 SEREVENT DISKUS in patients with asthma, the median time to onset of clinically significant  
127 bronchodilatation ( $\geq 15\%$  improvement in FEV<sub>1</sub>) ranged from 30 to 48 minutes after a 50-mcg  
128 dose.

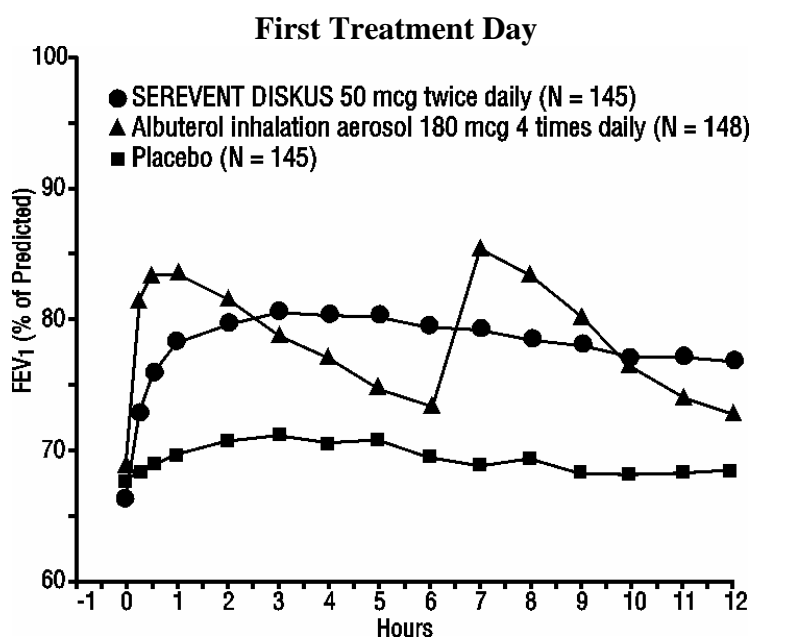
129 One hour after a single dose of 50 mcg of SEREVENT DISKUS, the majority of patients had  
130  $\geq 15\%$  improvement in FEV<sub>1</sub>. Maximum improvement in FEV<sub>1</sub> generally occurred within  
131 180 minutes, and clinically significant improvement continued for 12 hours in most patients.

132 In 2 randomized, double-blind studies, SEREVENT DISKUS was compared with albuterol  
133 inhalation aerosol and placebo in adolescent and adult patients with mild-to-moderate asthma  
134 (protocol defined as 50% to 80% predicted FEV<sub>1</sub>, actual mean of 67.7% at baseline), including  
135 patients who did and who did not receive concurrent inhaled corticosteroids. The efficacy of  
136 SEREVENT DISKUS was demonstrated over the 12-week period with no change in  
137 effectiveness over this time period (see Figure 1). There were no gender- or age-related  
138 differences in safety or efficacy. No development of tachyphylaxis to the bronchodilator effect  
139 was noted in these studies. FEV<sub>1</sub> measurements (mean change from baseline) from these two  
140 12-week studies are shown in Figure 1 for both the first and last treatment days.

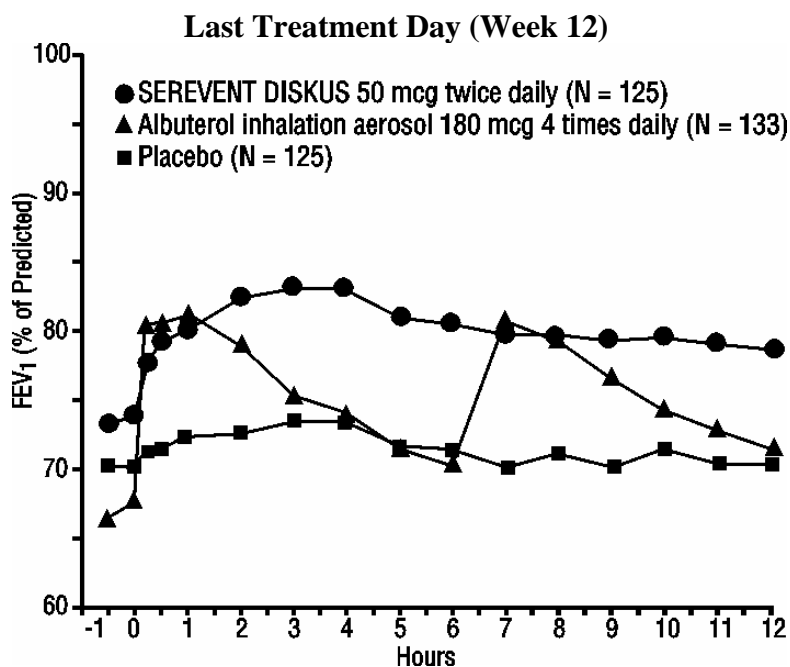
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142 **Figure 1. Serial 12-Hour FEV<sub>1</sub> From Two 12-Week**  
 143 **Clinical Trials in Patients With Asthma**

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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.

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

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

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

156 <sup>†</sup>Statistically superior to placebo (p<0.001).

157

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

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

172 In a randomized, double-blind, controlled study (N = 449), 50 mcg of SEREVENT DISKUS  
173 was administered twice daily to pediatric patients with asthma who did and who did not receive  
174 concurrent inhaled corticosteroids. The efficacy of salmeterol inhalation powder was  
175 demonstrated over the 12-week treatment period with respect to periodic serial peak expiratory  
176 flow (PEF) (36% to 39% postdose increase from baseline) and FEV<sub>1</sub> (32% to 33% postdose  
177 increase from baseline). Salmeterol was effective in demographic subgroup analyses (gender and  
178 age) and was effective when coadministered with other inhaled asthma medications such as  
179 short-acting bronchodilators and inhaled corticosteroids. A second randomized, double-blind,

180 placebo-controlled study (N = 207) with 50 mcg of salmeterol inhalation powder via an alternate  
181 device supported the findings of the trial with the DISKUS.

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

188 Two randomized, double-blind, controlled, parallel-group clinical trials (N = 997) enrolled  
189 patients (ages 18 to 82 years) with persistent asthma who were previously maintained but not  
190 adequately controlled on inhaled corticosteroid therapy. During the 2-week run-in period, all  
191 patients were switched to beclomethasone dipropionate 168 mcg twice daily. Patients still not  
192 adequately controlled were randomized to either the addition of SEREVENT Inhalation Aerosol  
193 42 mcg twice daily or an increase of beclomethasone dipropionate to 336 mcg twice daily. As  
194 compared to the doubled dose of beclomethasone dipropionate, the addition of SEREVENT  
195 Inhalation Aerosol resulted in statistically significantly greater improvements in pulmonary  
196 function and asthma symptoms, and statistically significantly greater reduction in supplemental  
197 albuterol use. The percent of patients who experienced asthma exacerbations overall was not  
198 different between groups (i.e., 16.2% in the group receiving SEREVENT Inhalation Aerosol  
199 versus 17.9% in the higher dose beclomethasone dipropionate group).

200 Two randomized, double-blind, parallel-group clinical trials (N = 925) enrolled patients (ages  
201 12 to 78 years) with persistent asthma who were previously maintained but not adequately  
202 controlled on prior therapy. During the 2- to 4-week run-in period, all patients were switched to  
203 fluticasone propionate 88 mcg twice daily. Patients still not adequately controlled were  
204 randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg twice daily or an  
205 increase of fluticasone propionate to 220 mcg twice daily. As compared to the increased (2.5  
206 times) dose of fluticasone propionate, the addition of SEREVENT Inhalation Aerosol resulted in  
207 statistically significantly greater improvements in pulmonary function and asthma symptoms,  
208 and statistically significantly greater reductions in supplemental albuterol use. Fewer patients  
209 receiving SEREVENT Inhalation Aerosol experienced asthma exacerbations than those  
210 receiving the higher dose of fluticasone propionate (8.8% versus 13.8%).

211 **Exercise-Induced Bronchospasm:** In 2 randomized, single-dose, crossover studies in  
212 adolescents and adults with EIB (N = 53), 50 mcg of SEREVENT DISKUS prevented EIB when  
213 dosed 30 minutes prior to exercise. For many patients, this protective effect against EIB was still  
214 apparent up to 8.5 hours following a single dose.  
215

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

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

217

218 In 2 randomized studies in children 4 to 11 years old with asthma and EIB (N = 50), a single  
219 50-mcg dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise,  
220 with protection lasting up to 11.5 hours in repeat testing following this single dose in many  
221 patients.

222 **Salmeterol Multi-center Asthma Research Trial:** The Salmeterol Multi-center Asthma  
223 Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting  
224 beta<sub>2</sub>-agonist-naïve patients with asthma (average age of 39 years, 71% Caucasian, 18% African  
225 American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol)  
226 42 mcg twice daily over 28 weeks compared to placebo when added to usual asthma therapy.

227 A planned interim analysis was conducted when approximately half of the intended number of  
228 patients had been enrolled (N = 26,355), which led to premature termination of the study. The  
229 results of the interim analysis showed that patients receiving salmeterol were at increased risk for  
230 fatal asthma events (see Table 3 and Figure 2). In the total population, a higher rate of asthma-  
231 related death occurred in patients treated with salmeterol than those treated with placebo (0.10%  
232 vs. 0.02%; relative risk 4.37 [95% CI 1.25, 15.34]).

233 Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death  
234 occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo  
235 (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also,  
236 asthma-related death occurred at a higher rate in patients treated with salmeterol than those  
237 treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the  
238 relative risks of asthma-related death were similar in Caucasians and African Americans, the  
239 estimate of excess deaths in patients treated with salmeterol was greater in African Americans  
240 because there was a higher overall rate of asthma-related death in African American patients (see  
241 Table 3).

242 The data from the SMART study are not adequate to determine whether concurrent use of  
243 inhaled corticosteroids or other asthma-controller therapy modifies the risk of asthma-related  
244 death.

245

246 **Table 3: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research**  
247 **Trial (SMART)**

	Salmeterol n (% <sup>*</sup> )	Placebo n (% <sup>*</sup> )	Relative Risk <sup>†</sup> (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients <sup>‡</sup> (95% Confidence Interval)
<b>Total Population<sup>§</sup></b> Salmeterol: N = 1,3176 Placebo: N = 1,3179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
<b>Caucasian</b> Salmeterol: N = 9,281 Placebo: N = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
<b>African American</b> Salmeterol: N = 2,366 Placebo: N = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

248 <sup>\*</sup> Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to  
249 study treatment to account for early withdrawal of patients from the study.

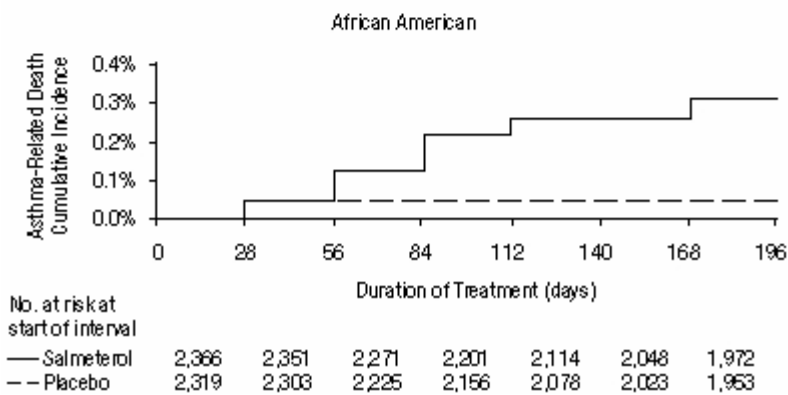
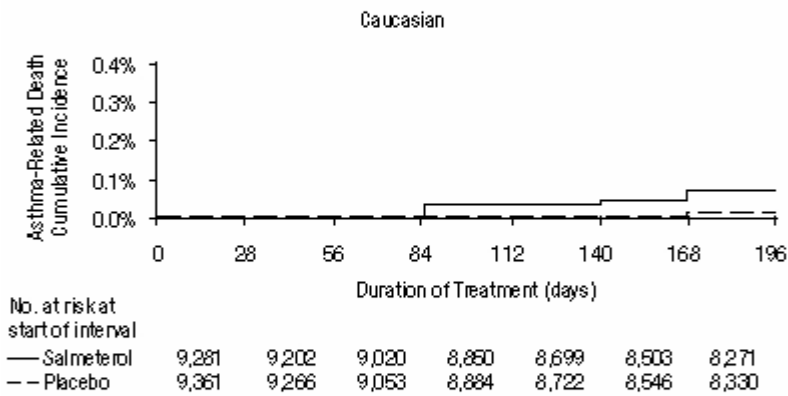
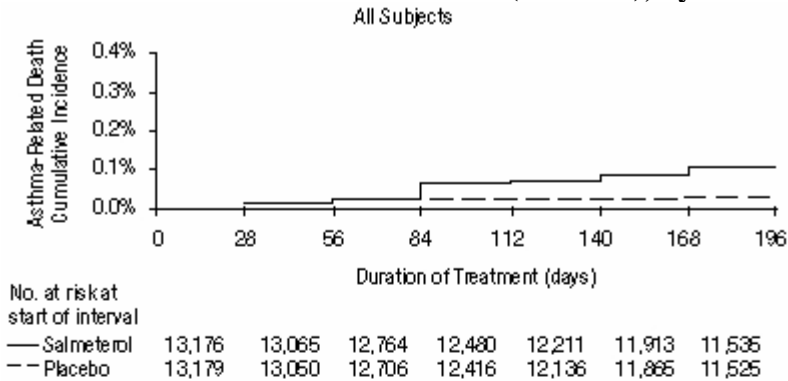
250 <sup>†</sup> Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the  
251 rate in the placebo group. The relative risk indicates how many more times likely an  
252 asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week  
253 treatment period.

254 <sup>‡</sup> Estimate of the number of additional asthma-related deaths in patients treated with salmeterol  
255 in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period.  
256 Estimate calculated as the difference between the salmeterol and placebo groups in the rates of  
257 asthma-related death multiplied by 10,000.

258 <sup>§</sup> The Total Population includes the following ethnic origins listed on the case report form:  
259 Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population  
260 includes those subjects whose ethnic origin was not reported. The results for Caucasian and  
261 African American subpopulations are shown above. No asthma-related deaths occurred in the  
262 Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149),  
263 or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death  
264 occurred in the placebo group in the subpopulation whose ethnic origin was not reported  
265 (salmeterol n = 130, placebo n = 127).

266

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



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271 **Chronic Obstructive Pulmonary Disease:** In 2 clinical trials evaluating twice-daily  
 272 treatment with SEREVENT DISKUS 50 mcg (N = 336) compared to placebo (N = 366) in  
 273 patients with chronic bronchitis with airflow limitation, with or without emphysema,  
 274 improvements in pulmonary function endpoints were greater with salmeterol 50 mcg than with  
 275 placebo. Treatment with SEREVENT DISKUS did not result in significant improvements in  
 276 secondary endpoints assessing COPD symptoms in either clinical trial. Both trials were

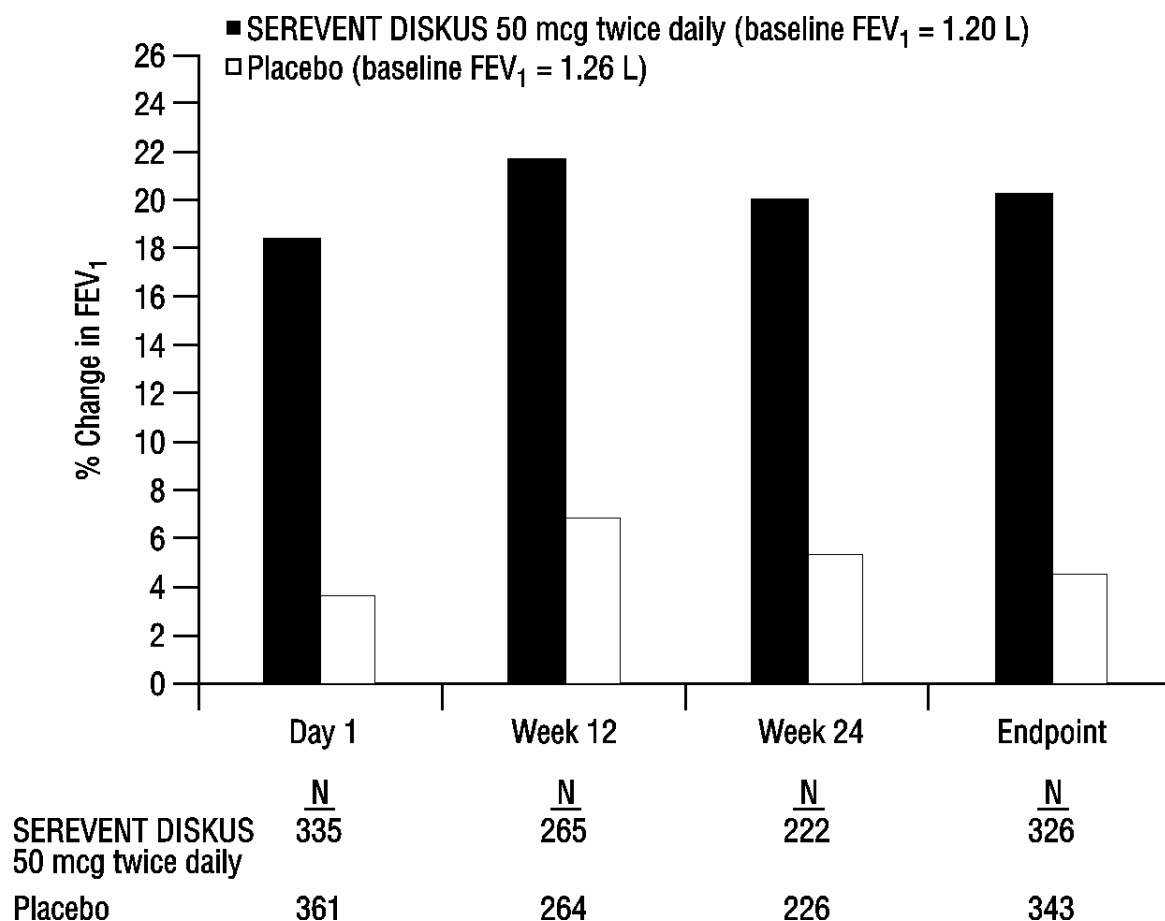
277 randomized, double-blind, parallel-group studies of 24 weeks' duration and were identical in  
 278 design, patient entrance criteria, and overall conduct.

279 Figure 3 displays the integrated 2-hour postdose FEV<sub>1</sub> results from the 2 clinical trials. The  
 280 percent change in FEV<sub>1</sub> refers to the change from baseline, defined as the predose value on  
 281 Treatment Day 1. To account for patient withdrawals during the study, Endpoint (last evaluable  
 282 FEV<sub>1</sub>) data are provided. Patients receiving SEREVENT DISKUS 50 mcg had significantly  
 283 greater improvements in 2-hour postdose FEV<sub>1</sub> at Endpoint (216 mL, 20%) compared to placebo  
 284 (43 mL, 5%). Improvement was apparent on the first day of treatment and maintained throughout  
 285 the 24 weeks of treatment.

286

287 **Figure 3. Mean Percent Change From Baseline in Postdose FEV<sub>1</sub> Integrated Data**  
 288 **From 2 Trials of Patients With Chronic Bronchitis and Airflow Limitation**

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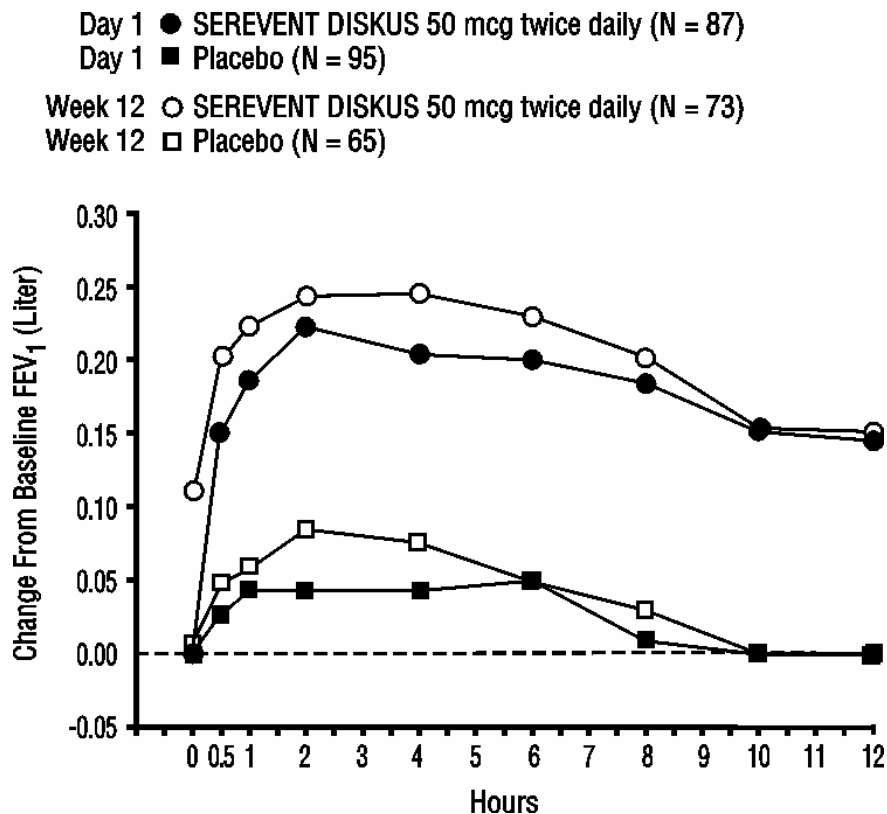
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292 **Onset of Action and Duration of Effect:** The onset of action and duration of effect of  
 293 SEREVENT DISKUS were evaluated in a subset of patients (n = 87) from 1 of the 2 clinical  
 294 trials discussed above. Following the first 50-mcg dose, significant improvement in pulmonary  
 295 function (mean FEV<sub>1</sub> increase of 12% or more and at least 200 mL) occurred at 2 hours. The  
 296 mean time to peak bronchodilator effect was 4.75 hours. As seen in Figure 4, evidence of

297 bronchodilatation was seen throughout the 12-hour period. Figure 4 also demonstrates that the  
298 bronchodilating effect after 12 weeks of treatment was similar to that observed after the first  
299 dose. The mean time to peak bronchodilator effect after 12 weeks of treatment was 3.27 hours.  
300

301 **Figure 4. Serial 12-Hour FEV<sub>1</sub> on the First Day and at Week**  
302 **12 of Treatment**

303



304

### 305 INDICATIONS AND USAGE

306 **Asthma:** SEREVENT DISKUS is indicated for long-term, twice-daily (morning and evening)  
307 administration in the maintenance treatment of asthma and in the prevention of bronchospasm in  
308 patients 4 years of age and older with reversible obstructive airway disease, including patients  
309 with symptoms of nocturnal asthma.

310 Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, the active ingredient in  
311 SEREVENT DISKUS, may increase the risk of asthma-related death (see WARNINGS).  
312 Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as  
313 additional therapy for patients not adequately controlled on other asthma-controller medications  
314 (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants  
315 initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. It is not  
316 indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting  
317 beta<sub>2</sub>-agonists or for patients whose asthma can be successfully managed by inhaled

318 corticosteroids or other controller medications along with occasional use of inhaled, short-acting  
319 beta<sub>2</sub>-agonists.

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

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

## 325 **CONTRAINDICATIONS**

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

## 329 **WARNINGS**

- 330 • **Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, the active ingredient in**  
331 **SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when**  
332 **treating patients with asthma, SEREVENT DISKUS should only be used as additional**  
333 **therapy for patients not adequately controlled on other asthma-controller medications**  
334 **(e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly**  
335 **warrants initiation of treatment with 2 maintenance therapies, including SEREVENT**  
336 **DISKUS.**
  - 337 ○ A large 28-week, placebo-controlled US study comparing the safety of salmeterol  
338 (SEREVENT Inhalation Aerosol) with placebo, each added to usual asthma therapy,  
339 showed an increase in asthma-related deaths in patients receiving salmeterol (see  
340 CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*). Given  
341 the similar basic mechanisms of action of beta<sub>2</sub>-agonists, it is possible that the findings  
342 seen in the SMART study represent a class effect.
  - 343 ○ A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide  
344 Surveillance (SNS) study, showed results similar to the SMART study. In the SNS  
345 study, the rate of asthma-related death was numerically, though not statistically  
346 significantly, greater in patients with asthma treated with salmeterol (42 mcg twice  
347 daily) than those treated with albuterol (180 mcg 4 times daily) added to usual asthma  
348 therapy.
- 349 • **The SNS and SMART studies enrolled patients with asthma. No studies have been**  
350 **conducted that were adequate to determine whether the rate of death in patients with**  
351 **COPD is increased by long-acting beta<sub>2</sub> adrenergic agonists.**
- 352 • **It is important to watch for signs of worsening asthma, such as increasing use of inhaled,**  
353 **short-acting beta<sub>2</sub>-agonists or a significant decrease in PEF or lung function. Such**  
354 **findings require immediate evaluation. Patients should be advised to seek immediate**  
355 **medical attention should their condition deteriorate.**

- 356 • **SEREVENT DISKUS should not be used to treat acute symptoms.** It is crucial to inform  
357 patients of this and prescribe an inhaled, short-acting beta<sub>2</sub>-agonist for this purpose and  
358 to warn them that increasing inhaled beta<sub>2</sub>-agonist use is a signal of deteriorating  
359 asthma that requires prompt consultation with a physician.
- 360 • **SEREVENT DISKUS should not be initiated in patients with significantly worsening or**  
361 **acutely deteriorating asthma, which may be a life-threatening condition.** Serious acute  
362 respiratory events, including fatalities, have been reported both in the United States and  
363 worldwide when SEREVENT has been initiated in this situation. Although it is not  
364 possible from these reports to determine whether SEREVENT contributed to these  
365 adverse events or simply failed to relieve the deteriorating asthma, the use of  
366 SEREVENT DISKUS in this setting is inappropriate.
- 367 • **SEREVENT DISKUS is not a substitute for inhaled or oral corticosteroids.**  
368 **Corticosteroids should not be stopped or reduced when SEREVENT DISKUS is**  
369 **initiated.**

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

372 **The following additional WARNINGS about SEREVENT DISKUS should be noted.**

373 1. **SEREVENT DISKUS Should Not Be Used as a Treatment for Acutely Deteriorating Asthma.**

374 SEREVENT DISKUS is intended for the maintenance treatment of asthma (see INDICATIONS  
375 AND USAGE) and should not be introduced in acutely deteriorating asthma, which is a  
376 potentially life-threatening condition. There are no data demonstrating that SEREVENT  
377 DISKUS provides greater efficacy than or additional efficacy to inhaled, short-acting  
378 beta<sub>2</sub>-agonists in patients with worsening asthma. Serious acute respiratory events, including  
379 fatalities, have been reported both in the United States and worldwide in patients receiving  
380 SEREVENT. In most cases, these have occurred in patients with severe asthma (e.g., patients  
381 with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical  
382 ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations)  
383 and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to  
384 usual medications; increasing need for inhaled, short-acting beta<sub>2</sub>-agonists; increasing need for  
385 systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden  
386 or progressive deterioration in pulmonary function). However, they have occurred in a few  
387 patients with less severe asthma as well. It was not possible from these reports to determine  
388 whether SEREVENT contributed to these events.

389 2. **SEREVENT DISKUS Should Not Be Used to Treat Acute Symptoms.** An inhaled,  
390 short-acting beta<sub>2</sub>-agonist, not SEREVENT DISKUS, should be used to relieve acute asthma or  
391 COPD symptoms. When prescribing SEREVENT DISKUS, the physician must also provide the  
392 patient with an inhaled, short-acting beta<sub>2</sub>-agonist (e.g., albuterol) for treatment of symptoms that  
393 occur acutely, despite regular twice-daily (morning and evening) use of SEREVENT DISKUS.

394 When beginning treatment with SEREVENT DISKUS, patients who have been taking  
395 inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., 4 times a day) should be instructed to

396 discontinue the regular use of these drugs and use them only for symptomatic relief of acute  
397 asthma or COPD symptoms (see PRECAUTIONS: Information for Patients).

398 3. Increasing Use of Inhaled, Short-Acting Beta<sub>2</sub>-Agonists Is a Marker of Deteriorating Asthma  
399 or COPD. The physician and patient should be alert to such changes. The patient's condition  
400 may deteriorate acutely over a period of hours or chronically over several days or longer. If the  
401 patient's inhaled, short-acting beta<sub>2</sub>-agonist becomes less effective, the patient needs more  
402 inhalations than usual, or the patient develops a significant decrease in PEF or lung function,  
403 these may be markers of destabilization of their disease. In this setting, the patient requires  
404 immediate reevaluation with reassessment of the treatment regimen, giving special consideration  
405 to the possible need for corticosteroids. If the patient uses 4 or more inhalations per day of an  
406 inhaled, short-acting beta<sub>2</sub>-agonist for 2 or more consecutive days, or if more than 1 canister  
407 (200 inhalations per canister) of inhaled, short-acting beta<sub>2</sub>-agonist is used in an 8-week period in  
408 conjunction with SEREVENT DISKUS, then the patient should consult the physician for  
409 reevaluation. **Increasing the daily dosage of SEREVENT DISKUS in this situation is not**  
410 **appropriate. SEREVENT DISKUS should not be used more frequently than twice daily**  
411 **(morning and evening) at the recommended dose of 1 inhalation.**

412 4. SEREVENT DISKUS Should Not Be Used in Conjunction With an Inhaled, Long-Acting  
413 Beta<sub>2</sub>-Agonist. SEREVENT DISKUS should not be used with other medications containing  
414 long-acting beta<sub>2</sub>-agonists.

415 5. SEREVENT DISKUS Is Not a Substitute for Oral or Inhaled Corticosteroids. There are no  
416 data demonstrating that SEREVENT DISKUS has a clinical anti-inflammatory effect and could  
417 be expected to take the place of corticosteroids. When initiating SEREVENT DISKUS in  
418 patients receiving oral or inhaled corticosteroids for treatment of asthma, patients should be  
419 continued on a suitable dose of corticosteroids to maintain clinical stability even if they feel  
420 better as a result of initiating SEREVENT DISKUS. Any change in corticosteroid dosage should  
421 be made ONLY after clinical evaluation (see PRECAUTIONS: Information for Patients).

422 6. The Recommended Dosage Should Not Be Exceeded. As with other inhaled beta<sub>2</sub>-adrenergic  
423 drugs, SEREVENT DISKUS should not be used more often or at higher doses than  
424 recommended. Fatalities have been reported in association with excessive use of inhaled  
425 sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the  
426 recommended dose) have been associated with clinically significant prolongation of the QTc  
427 interval, which has the potential for producing ventricular arrhythmias.

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

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

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

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

## 447 **PRECAUTIONS**

448 **General:** 1. Cardiovascular and Other Effects: No effect on the cardiovascular system is usually  
449 seen after the administration of inhaled salmeterol at recommended doses, but the cardiovascular  
450 and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood  
451 pressure, heart rate, excitement) can occur after use of salmeterol and may require  
452 discontinuation of SEREVENT DISKUS. SEREVENT DISKUS, like all sympathomimetic  
453 amines, should be used with caution in patients with cardiovascular disorders, especially  
454 coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive  
455 disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic  
456 amines.

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

460 2. Metabolic Effects: Doses of the related beta<sub>2</sub>-adrenoceptor agonist albuterol, when  
461 administered intravenously, have been reported to aggravate preexisting diabetes mellitus and  
462 ketoacidosis. Beta-adrenergic agonist medications may produce significant hypokalemia in some  
463 patients, possibly through intracellular shunting, which has the potential to produce adverse  
464 cardiovascular effects. The decrease in serum potassium is usually transient, not requiring  
465 supplementation.

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

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

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

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

- 478 **1. Patients should be informed that salmeterol may increase the risk of asthma-related**  
479 **death.**
- 480 2. SEREVENT DISKUS is not meant to relieve acute asthma or COPD symptoms and extra  
481 doses should not be used for that purpose. Acute symptoms should be treated with an  
482 inhaled, short-acting bronchodilator (the physician should provide the patient with such  
483 medication and instruct the patient in how it should be used).
- 484 3. The physician should be notified immediately if any of the following signs of seriously  
485 worsening asthma or COPD occur:
  - 486 • Decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonists
  - 487 • Need for more inhalations than usual of inhaled, short-acting beta<sub>2</sub>-agonists
  - 488 • Significant decrease in PEF or lung function as outlined by the physician
  - 489 • Use of 4 or more inhalations per day of a short-acting beta<sub>2</sub>-agonist for 2 or more days  
490 consecutively
  - 491 • Use of more than 1 canister (200 inhalations per canister) of an inhaled, short-acting  
492 beta<sub>2</sub>-agonist in an 8-week period.
- 493 4. Patients should not stop therapy with SEREVENT DISKUS for asthma or COPD without  
494 physician/provider guidance since symptoms may worsen after discontinuation.
- 495 5. SEREVENT DISKUS should not be used as a substitute for oral or inhaled corticosteroids.  
496 The dosage of these medications should not be changed and they should not be stopped  
497 without consulting the physician, even if the patient feels better after initiating treatment  
498 with SEREVENT DISKUS.
- 499 6. Patients should be cautioned regarding adverse effects associated with beta<sub>2</sub>-agonists, such  
500 as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 501 7. When patients are prescribed SEREVENT DISKUS, other medications for asthma and  
502 COPD should be used only as directed by the physician.
- 503 8. SEREVENT DISKUS should not be used with a spacer device.
- 504 9. Patients who are pregnant or nursing should contact the physician about the use of  
505 SEREVENT DISKUS.
- 506 10. The action of SEREVENT DISKUS may last up to 12 hours or longer. The recommended  
507 dosage (1 inhalation twice daily, morning and evening) should not be exceeded.
- 508 11. When used for the treatment of EIB, 1 inhalation of SEREVENT DISKUS should be taken  
509 30 minutes before exercise.
  - 510 • Additional doses of SEREVENT should not be used for 12 hours.
  - 511 • Patients who are receiving SEREVENT DISKUS twice daily should not use additional  
512 SEREVENT for prevention of EIB.
- 513 12. Effective and safe use of SEREVENT DISKUS includes an understanding of the way that it  
514 should be used:

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

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

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

529 **Drug Interactions: Short-Acting Beta<sub>2</sub>-Agonists:** In two 12-week, repetitive-dose  
530 adolescent and adult clinical trials in patients with asthma (N = 149), the mean daily need for  
531 additional beta<sub>2</sub>-agonist in patients using SEREVENT DISKUS was approximately 1½  
532 inhalations/day. Twenty-six percent (26%) of the patients in these trials used between 8 and  
533 24 inhalations of short-acting beta-agonist per day on 1 or more occasions. Nine percent (9%) of  
534 the patients in these trials averaged over 4 inhalations/day over the course of the 12-week trials.  
535 No increase in frequency of cardiovascular events was observed among the 3 patients who  
536 averaged 8 to 11 inhalations/day; however, the safety of concomitant use of more than  
537 8 inhalations/day of short-acting beta<sub>2</sub>-agonist with SEREVENT DISKUS has not been  
538 established. In 29 patients who experienced worsening of asthma while receiving SEREVENT  
539 DISKUS during these trials, albuterol therapy administered via either nebulizer or inhalation  
540 aerosol (1 dose in most cases) led to improvement in FEV<sub>1</sub> and no increase in occurrence of  
541 cardiovascular adverse events.

542 In 2 clinical trials in patients with COPD, the mean daily need for additional beta<sub>2</sub>-agonist for  
543 patients using SEREVENT DISKUS was approximately 4 inhalations/day. Twenty-four percent  
544 (24%) of the patients using SEREVENT DISKUS in these trials averaged 6 or more inhalations  
545 of albuterol per day over the course of the 24-week trials. No increase in frequency of  
546 cardiovascular events was observed among patients who averaged 6 or more inhalations per day.

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

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

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

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

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

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

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

587 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol  
588 caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at  
589 doses of 0.68 mg/kg and above (approximately 55 times the maximum recommended daily  
590 inhalation dose in adults and approximately 25 times the maximum recommended daily  
591 inhalation dose in children on a mg/m<sup>2</sup> basis). No tumors were seen at 0.21 mg/kg  
592 (approximately 15 times the maximum recommended daily inhalation dose in adults and  
593 approximately 8 times the maximum recommended daily inhalation dose in children on a mg/m<sup>2</sup>

594 basis). These findings in rodents are similar to those reported previously for other  
595 beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

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

601 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. No teratogenic effects occurred in  
602 rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily  
603 inhalation dose in adults on a mg/m<sup>2</sup> basis). In pregnant Dutch rabbits administered oral doses of  
604 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in  
605 adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects  
606 characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid  
607 openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the  
608 frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately  
609 20 times the maximum recommended daily inhalation dose in adults based on comparison of the  
610 AUCs).

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

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

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

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

631 **Pediatric Use:** The safety and efficacy of SEREVENT DISKUS has been evaluated in over  
632 2,500 patients aged 4 to 11 years with asthma, 346 of whom were administered SEREVENT  
633 DISKUS for 1 year. Based on available data, no adjustment of dosage of SEREVENT DISKUS

634 in pediatric patients is warranted for either asthma or EIB (see DOSAGE AND  
635 ADMINISTRATION).

636 In 2 randomized, double-blind, controlled clinical trials of 12 weeks' duration, SEREVENT  
637 DISKUS 50-mcg was administered to 211 pediatric patients with asthma who did and who did  
638 not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was  
639 demonstrated over the 12-week treatment period with respect to PEF and FEV<sub>1</sub>. SEREVENT  
640 DISKUS was effective in demographic subgroups (gender and age) of the population.  
641 SEREVENT DISKUS was effective when coadministered with other inhaled asthma  
642 medications, such as short-acting bronchodilators and inhaled corticosteroids. SEREVENT  
643 DISKUS was well tolerated in the pediatric population, and there were no safety issues identified  
644 specific to the administration of SEREVENT DISKUS to pediatric patients.

645 In 2 randomized studies in children 4 to 11 years old with asthma and EIB, a single 50-mcg  
646 dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise, with  
647 protection lasting up to 11.5 hours in repeat testing following this single dose in many patients.  
648 **Geriatric Use:** Of the total number of adolescent and adult patients with asthma who received  
649 SEREVENT DISKUS in chronic dosing clinical trials, 209 were 65 years of age and older. Of  
650 the total number of patients with COPD who received SEREVENT DISKUS in chronic dosing  
651 clinical trials, 167 were 65 years of age or older and 45 were 75 years of age or older. No  
652 apparent differences in the safety of SEREVENT DISKUS were observed when geriatric patients  
653 were compared with younger patients in clinical trials. As with other beta<sub>2</sub>-agonists, however,  
654 special caution should be observed when using SEREVENT DISKUS in geriatric patients who  
655 have concomitant cardiovascular disease that could be adversely affected by this class of drug.  
656 Data from the trials in patients with COPD suggested a greater effect on FEV<sub>1</sub> of SEREVENT  
657 DISKUS in the <65 years age-group, as compared with the ≥65 years age-group. However,  
658 based on available data, no adjustment of dosage of SEREVENT DISKUS in geriatric patients is  
659 warranted.

## 660 **ADVERSE REACTIONS**

661 **Data from a large, 28-week, placebo-controlled US study that compared the safety of**  
662 **salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy**  
663 **showed an increase in asthma-related deaths in patients receiving salmeterol (see**  
664 **WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research***  
665 ***Trial*).**

666 **Asthma:** Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of  
667 SEREVENT DISKUS in patients 12 years of age and older with asthma. Table 4 reports the  
668 incidence of adverse events in these 2 studies.

669

670 **Table 4. Adverse Event Incidence in Two 12-Week Adolescent and Adult Clinical Trials**  
671 **in Patients With Asthma**

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

672

673 Table 4 includes all events (whether considered drug-related or nondrug-related by the  
674 investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT  
675 DISKUS and were more common than in the placebo group.

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

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

682 **Ear, Nose, and Throat:** Sinus headache.

683 **Gastrointestinal:** Nausea.

684 **Mouth and Teeth:** Oral mucosal abnormality.

685 **Musculoskeletal:** Pain in joint.

686 **Neurological:** Sleep disturbance, paresthesia.

687 **Skin:** Contact dermatitis, eczema.

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

689 Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of  
690 SEREVENT DISKUS in patients aged 4 to 11 years with asthma. Table 5 includes all events  
691 (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate  
692 of 3% or greater in the group receiving SEREVENT DISKUS and were more common than in  
693 the placebo group.

694

695 **Table 5. Adverse Event Incidence in Two 12-Week Pediatric Clinical Trials in Patients**  
696 **With Asthma**

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

697  
698 The following events were reported at an incidence of 1% to 2% (3 to 4 patients) in the  
699 salmeterol group and with a higher incidence than in the albuterol and placebo groups:  
700 gastrointestinal signs and symptoms, lower respiratory signs and symptoms, photodermatitis, and  
701 arthralgia and articular rheumatism.

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

705 **Chronic Obstructive Pulmonary Disease:** Two multicenter, 24-week, controlled studies  
706 have evaluated twice-daily doses of SEREVENT DISKUS in patients with COPD. For  
707 presentation (Table 6), the placebo data from a third trial, identical in design, patient entrance  
708 criteria, and overall conduct but comparing fluticasone propionate with placebo, were integrated  
709 with the placebo data from these 2 studies (total N = 341 for salmeterol and 576 for placebo).

710

711 **Table 6. Adverse Events With  $\geq 3\%$  Incidence in US Controlled Clinical Trials With**  
712 **SEREVENT DISKUS in Patients With Chronic Obstructive Pulmonary Disease\***

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

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

717  
718 Other events occurring in the group receiving SEREVENT DISKUS that occurred at a  
719 frequency of 1% to <3% and were more common than in the placebo group were as follows:

720 **Endocrine and Metabolic:** Hyperglycemia.

721 **Eye:** Keratitis and conjunctivitis.

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

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

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

727 **Neurology:** Migraines.

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

729 **Psychiatry:** Anxiety.

730 **Skin:** Skin rashes.

731 Adverse reactions to salmeterol are similar in nature to those seen with other selective  
732 beta<sub>2</sub>-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions,  
733 including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor;  
734 nervousness; and paradoxical bronchospasm (see WARNINGS).

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

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

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

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

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

## 752 OVERDOSAGE

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

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

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

771 No deaths were seen in rats at an inhalation dose of 2.9 mg/kg (approximately 240 times the  
772 maximum recommended daily inhalation dose in adults and approximately 110 times the  
773 maximum recommended daily inhalation dose in children on a mg/m<sup>2</sup> basis) and in dogs at an  
774 inhalation dose of 0.7 mg/kg (approximately 190 times the maximum recommended daily  
775 inhalation dose in adults and approximately 90 times the maximum recommended daily  
776 inhalation dose in children on a mg/m<sup>2</sup> basis). By the oral route, no deaths occurred in mice at  
777 150 mg/kg (approximately 6,100 times the maximum recommended daily inhalation dose in  
778 adults and approximately 2,900 times the maximum recommended daily inhalation dose in  
779 children on a mg/m<sup>2</sup> basis) and in rats at 1,000 mg/kg (approximately 81,000 times the maximum  
780 recommended daily inhalation dose in adults and approximately 38,000 times the maximum  
781 recommended daily inhalation dose in children on a mg/m<sup>2</sup> basis).

## 782 **DOSAGE AND ADMINISTRATION**

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

787 **Asthma:** Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, the active ingredient in  
788 SEREVENT DISKUS, may increase the risk of asthma-related death (see WARNINGS).  
789 Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as  
790 additional therapy for patients not adequately controlled on other asthma-controller medications  
791 (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants  
792 initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. It is not  
793 indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting  
794 beta<sub>2</sub>-agonists or for patients whose asthma can be successfully managed by inhaled  
795 corticosteroids or other controller medications along with occasional use of inhaled, short-acting  
796 beta<sub>2</sub>-agonists.

797 For maintenance of bronchodilatation and prevention of symptoms of asthma, including the  
798 symptoms of nocturnal asthma, the usual dosage for adults and children 4 years of age and older  
799 is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). If a  
800 previously effective dosage regimen fails to provide the usual response, medical advice should  
801 be sought immediately as this is often a sign of destabilization of asthma. Under these

802 circumstances, the therapeutic regimen should be reevaluated. If symptoms arise in the period  
803 between doses, an inhaled, short-acting beta<sub>2</sub>-agonist should be taken for immediate relief.

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

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

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

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

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

## 822 HOW SUPPLIED

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

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

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

834  
835



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837 GlaxoSmithKline  
838 Research Triangle Park, NC 27709  
839

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## MEDICATION GUIDE

846

847

**SEREVENT<sup>®</sup> [*ser' uh-vent*] DISKUS<sup>®</sup>**

848

(salmeterol xinafoate inhalation powder)

849

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

853

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

855 SEREVENT DISKUS is a medicine called a long-acting beta<sub>2</sub>-agonist or LABA. LABA  
856 medicines are used in patients with asthma, exercise-induced bronchospasm (EIB), and chronic  
857 obstructive pulmonary disease (COPD). LABA medicines help the muscles around the airways  
858 in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These  
859 symptoms can happen when the muscles around the airways tighten. This makes it hard to  
860 breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right  
861 away.

862

863 • **In patients with asthma, LABA medicines such as SEREVENT DISKUS may increase**  
864 **the chance of death from asthma problems.** In a large asthma study, more patients who  
865 used salmeterol (SEREVENT) died from asthma problems compared with patients who did  
866 not use salmeterol (SEREVENT). Talk with your healthcare provider about this risk and the  
867 benefits of treating your asthma with SEREVENT DISKUS.

868

869 • **SEREVENT DISKUS does not relieve sudden symptoms. Always have a short-acting**  
870 **beta<sub>2</sub>-agonist medicine with you to treat sudden symptoms. If you do not have an**  
871 **inhaled, short-acting bronchodilator, contact your healthcare provider to have one**  
872 **prescribed for you.**

873

874 • **Do not stop using SEREVENT DISKUS unless told to do so by your healthcare provider**  
875 **because your symptoms might get worse.**

876

877 • **SEREVENT DISKUS:**

878 • **should not be the only medicine prescribed for your asthma**

- 879 • **should only be used if your healthcare provider decides that another asthma-controller**  
880 **medicine alone does not control your asthma or that you need 2 asthma-controller**  
881 **medicines**  
882
- 883 • **Call your healthcare provider if breathing problems worsen over time while using**  
884 **SEREVENT DISKUS. You may need different treatment.**  
885
- 886 • **Get emergency medical care if:**  
887 • **breathing problems worsen quickly, and**  
888 • **you use your short-acting beta<sub>2</sub>-agonist medicine, but it does not relieve your**  
889 **breathing problems**  
890

### 891 **What is SEREVENT DISKUS?**

892 SEREVENT DISKUS is a long-acting beta<sub>2</sub>-agonist medicine (LABA). SEREVENT DISKUS is  
893 used for asthma, exercise-induced bronchospasm (EIB), and chronic obstructive pulmonary  
894 disease (COPD) as follows:

#### 895 **Asthma**

896 SEREVENT DISKUS is used long term, twice a day, to control symptoms of asthma, and  
897 prevent symptoms such as wheezing in adults and children ages 4 and older.  
898

899

900 **Because LABA medicines such as SEREVENT DISKUS may increase the chance of death**  
901 **from asthma problems, SEREVENT DISKUS is not for adults and children with asthma**  
902 **who:**

- 903 • **are well controlled with another asthma-controller medicine, such as a low to medium dose**  
904 **of an inhaled corticosteroid**  
905 • **only need short-acting beta<sub>2</sub>-agonist medicines once in awhile**  
906

#### 907 **Exercise-Induced Bronchospasm (EIB)**

908 SEREVENT DISKUS is used for the prevention of wheezing caused by exercise in adults and  
909 children 4 years of age and older.  
910

#### 911 **Chronic Obstructive Pulmonary Disease (COPD)**

912 SEREVENT DISKUS is used long term, twice a day in controlling symptoms of COPD and  
913 preventing wheezing in adults with COPD.  
914

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

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

- 917 • **have heart problems**  
918 • **have high blood pressure**

- 919 • **have seizures**
- 920 • **have thyroid problems**
- 921 • **have diabetes**
- 922 • **have liver problems**
- 923 • **are pregnant or planning to become pregnant.** It is not known if SEREVENT DISKUS
- 924 may harm your unborn baby.
- 925 • **are breastfeeding.** It is not known if SEREVENT DISKUS passes into your milk and if it can
- 926 harm your baby.
- 927 • **are allergic to SEREVENT DISKUS, any other medicines, or food products**

928

929 Tell your healthcare provider about all the medicines you take including prescription and  
930 non-prescription medicines, vitamins, and herbal supplements. SEREVENT DISKUS and certain  
931 other medicines may interact with each other. This may cause serious side effects.

932

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

935

### 936 **How do I use SEREVENT DISKUS?**

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

941

- 942 • Children should use SEREVENT DISKUS with an adult's help, as instructed by the child's  
943 healthcare provider.

944

- 945 • Use SEREVENT DISKUS exactly as prescribed. **Do not use SEREVENT DISKUS more**  
946 **often than prescribed.**

947

- 948 • For asthma and COPD, the usual dose is 1 inhalation twice a day (morning and evening). The  
949 2 doses should be about 12 hours apart.

950

- 951 • For preventing exercise-induced bronchospasm, take 1 inhalation at least 30 minutes before  
952 exercise. Do not use SEREVENT DISKUS more often than every 12 hours. Do not use extra  
953 SEREVENT DISKUS before exercise if you already use it twice a day.

954

- 955 • If you miss a dose of SEREVENT DISKUS, just skip that dose. Take your next dose at your  
956 usual time. Do not take 2 doses at one time.

957

- 958 • Do not use a spacer device with SEREVENT DISKUS.

959

960 • Do not breathe into SEREVENT DISKUS.

961

962 • **While you are using SEREVENT DISKUS twice a day, do not use other medicines that**  
963 **contain a long-acting beta<sub>2</sub>-agonist or LABA for any reason. Other LABA medicines**  
964 **include ADVAIR DISKUS<sup>®</sup> (fluticasone propionate and salmeterol inhalation powder)**  
965 **or FORADIL<sup>®</sup> AEROLIZER<sup>™</sup> (formoterol fumarate inhalation powder).**

966

967 • Do not change or stop any of your medicines used to control or treat your breathing problems.  
968 Your healthcare provider will adjust your medicines as needed.

969

970 • Make sure you always have a short-acting beta<sub>2</sub>-agonist medicine with you. Use your  
971 short-acting beta<sub>2</sub>-agonist medicine if you have breathing problems between doses of  
972 SEREVENT DISKUS.

973

974 • **Call your healthcare provider or get medical care right away if:**

- 975 • your breathing problems worsen with SEREVENT DISKUS
- 976 • you need to use your short-acting beta<sub>2</sub>-agonist medicine more often than usual
- 977 • your short-acting beta<sub>2</sub>-agonist medicine does not work as well for you at relieving  
978 symptoms
- 979 • you need to use 4 or more inhalations of your short-acting beta<sub>2</sub>-agonist medicine for 2 or  
980 more days in a row
- 981 • you use 1 whole canister of your short-acting beta<sub>2</sub>-agonist medicine in 8 weeks' time
- 982 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers  
983 that are right for you.
- 984 • you have asthma and your symptoms do not improve after using SEREVENT DISKUS  
985 regularly for 1 week.

986

987 **What are the possible side effects with SEREVENT DISKUS?**

- 988 • **In patients with asthma, LABA medicines such as SEREVENT may increase the**  
989 **chance of death from asthma problems.** See “What is the most important information I  
990 should know about SEREVENT DISKUS?”

991

992 **Other possible side effects with SEREVENT DISKUS include:**

- 993 • **serious allergic reactions including rash, hives, swelling of the face, mouth, and**  
994 **tongue, and breathing problems.** Call your healthcare provider or get emergency  
995 medical care if you get any symptoms of a serious allergic reaction.
- 996 • **increased blood pressure**
- 997 • **a fast and irregular heartbeat**
- 998 • **chest pain**

- 999       • **headache**
- 1000       • **tremor**
- 1001       • **nervousness**
- 1002       • **throat irritation**

1003

1004       Tell your healthcare provider about any side effect that bothers you or that does not go away.

1005

1006       These are not all the side effects with SEREVENT DISKUS. Ask your healthcare provider or  
1007       pharmacist for more information.

1008

1009       **How do I store SEREVENT DISKUS?**

- 1010       • Store SEREVENT DISKUS at room temperature between 68° to 77° F (20° to 25° C).  
1011       Keep in a dry place away from heat and sunlight.
- 1012       • Safely discard SEREVENT DISKUS 6 weeks after you remove it from the foil pouch, or  
1013       after the dose indicator reads “0”, whichever comes first.
- 1014       • **Keep SEREVENT DISKUS and all medicines out of the reach of children.**

1015

1016       **General Information about SEREVENT DISKUS**

1017       Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not  
1018       use SEREVENT DISKUS for a condition for which it was not prescribed. Do not give your  
1019       SEREVENT DISKUS to other people, even if they have the same condition. It may harm them.

1020       This Medication Guide summarizes the most important information about SEREVENT  
1021       DISKUS. If you would like more information, talk with your healthcare provider or pharmacist.  
1022       You can ask your healthcare provider or pharmacist for information about SEREVENT DISKUS  
1023       that was written for healthcare professionals. You can also contact the company that makes  
1024       SEREVENT DISKUS (toll free) at 1-888-825-5249 or at [www.serevent.com](http://www.serevent.com).

1025

1026       **Instructions for Using SEREVENT DISKUS**

1027       Follow the instructions below for using your SEREVENT DISKUS. **You will breathe-in**  
1028       **(inhale) the medicine from the DISKUS.** If you have any questions, ask your healthcare  
1029       provider or pharmacist.



1030

1031

1032 **How to Use Your SEREVENT DISKUS**

1033 Take the SEREVENT DISKUS out of the box and foil overwrap pouch. Write the “**Pouch**  
1034 **opened**” and “**Use by**” dates on the label on top of the DISKUS. The “**Use by**” date is **6 weeks**  
1035 **from date of opening the pouch.**

1036

1037 • The DISKUS will be in the closed position when the pouch is opened.

1038

1039 • The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose  
1040 indicator number will decrease each time you use the DISKUS. After you have used 55  
1041 doses from the DISKUS, the numbers 5 to 0 will appear in **red** to warn you that there are  
1042 only a few doses left (*see Figure 1*). If you are using a “sample” DISKUS, the numbers 5  
1043 to 0 will appear in red after 23 doses.

1044



1045

1046

Figure 1

1047

1048 Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.

1049

1050 **1. OPEN**

1051 Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**. Push  
1052 your thumb away from you as far as it will go until the mouthpiece appears and snaps into  
1053 position (*see Figure 2*).

1054



Figure 2

1055

1056

1057

1058 **2. CLICK**

1059 Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the **lever**  
1060 away from you as far as it will go until it **clicks** (*see Figure 3*). The DISKUS is now ready to  
1061 use.

1062



Figure 3

1063

1064

1065

1066 Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a  
1067 decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the**  
1068 **DISKUS is ready:**

- 1069 • **Do not close the DISKUS.**
- 1070 • **Do not tilt the DISKUS.**
- 1071 • **Do not play with the lever.**
- 1072 • **Do not move the lever more than once.**

1073

### 1074 3. INHALE

1075 Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the  
1076 DISKUS level and away from your mouth (*see Figure 4*). **Remember, never breathe out**  
1077 **into the DISKUS mouthpiece.**

1078



Figure 4

1079

1080

1081

1082 Put the mouthpiece to your lips (*see Figure 5*). Breathe in quickly and deeply through the  
1083 DISKUS. Do not breathe in through your nose.

1084



1085

Figure 5

1086  
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1097  
1098  
1099  
1100

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

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

**4. Close THE DISKUS when you are finished taking a dose so that the DISKUS will be ready for you to take your next dose.** Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go (*see Figure 6*). The DISKUS will click shut. The lever will automatically return to its original position. The DISKUS is now ready for you to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4.)



Figure 6

1101  
1102  
1103  
1104  
1105  
1106  
1107  
1108  
1109  
1110  
1111  
1112  
1113  
1114  
1115

**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.

**Rx only**



1116

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1118 Research Triangle Park, NC 27709

1119

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1121 FORADIL AEROLIZER is a trademark of Novartis Pharmaceuticals Corporation.

1122

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1126

1127 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**