

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.

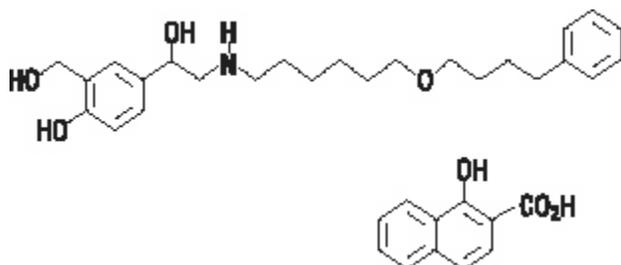
Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, 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

40 as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The active component
41 of the formulation is salmeterol base, a highly selective beta₂-adrenergic bronchodilator. The
42 chemical name of salmeterol xinafoate is 4-hydroxy-α¹-[[[6-(4-phenylbutoxy)hexyl]amino]
43 methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate. Salmeterol xinafoate has
44 the following chemical structure:

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48 Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical
49 formula is C₂₅H₃₇NO₄•C₁₁H₈O₃. It is freely soluble in methanol; slightly soluble in ethanol,
50 chloroform, and isopropanol; and sparingly soluble in water.

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

59 Under standardized in vitro test conditions, SEREVENT DISKUS delivers 47 mcg when
60 tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and
61 severely compromised lung function (mean forced expiratory volume in 1 second [FEV₁] 20% to
62 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS was 82.4 L/min (range,
63 46.1 to 115.3 L/min).

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

66 CLINICAL PHARMACOLOGY

67 **Mechanism of Action:** Salmeterol is a long-acting beta₂-adrenergic agonist. In vitro studies
68 and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta₂-
69 adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on
70 beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more
71 selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the
72 predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the
73 predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart

74 comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors
75 has not been established, but they raise the possibility that even highly selective beta₂-agonists
76 may have cardiac effects.

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

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

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

92 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low or
93 undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder
94 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol
95 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in
96 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of
97 167 pg/mL at 20 minutes and no accumulation with repeated doses.

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

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

104 An in vitro study using human liver microsomes showed that salmeterol is extensively
105 metabolized to α -hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP 3A4).
106 Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of
107 α -hydroxysalmeterol in vitro.

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

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

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

119 **Drug Interactions:** Salmeterol is a substrate of CYP3A4.

120 **Inhibitors of Cytochrome P450 3A4: Ketoconazole:** In a placebo-controlled,
121 crossover drug interaction study in 20 healthy male and female subjects, coadministration of
122 salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once
123 daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined
124 by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76; 90% CI: 10.66, 23.31)
125 mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma
126 salmeterol concentrations were increased by 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20
127 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-
128 agonist-mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus
129 tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically
130 significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although
131 there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole
132 was associated with more frequent increases in QTc duration compared with salmeterol and
133 placebo administration. Due to the potential increased risk of cardiovascular adverse events, the
134 concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir,
135 atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir,
136 telithromycin) is not recommended.

137 **Erythromycin:** In a repeat-dose study in 13 healthy subjects, concomitant
138 administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol
139 resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with and without erythromycin
140 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;
141 $p < 0.04$), a 5.8-msec increase in QTc interval (95% CI: -6.14, 17.77; $p = 0.34$), and no change in
142 plasma potassium.

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

148 The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied
149 in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as
150 inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as
151 albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and adult
152 patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent continuous
153 electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month

154 of therapy, and no clinically significant dysrhythmias were noted. Also, pediatric patients
155 receiving 50-mcg doses of salmeterol inhalation powder (N = 67) underwent continuous
156 electrocardiographic monitoring during two 12-hour periods after the first dose and after
157 3 months of therapy, and no clinically significant dysrhythmias were noted.

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

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

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

171 **CLINICAL TRIALS**

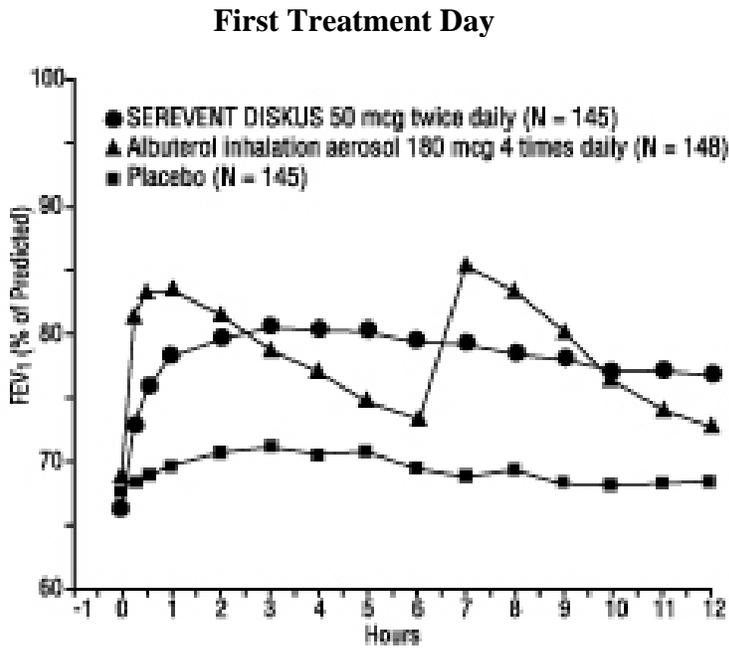
172 **Asthma:** During the initial treatment day in several multiple-dose clinical trials with
173 SEREVENT DISKUS in patients with asthma, the median time to onset of clinically significant
174 bronchodilatation ($\geq 15\%$ improvement in FEV_1) ranged from 30 to 48 minutes after a 50-mcg
175 dose.

176 One hour after a single dose of 50 mcg of SEREVENT DISKUS, the majority of patients had
177 $\geq 15\%$ improvement in FEV_1 . Maximum improvement in FEV_1 generally occurred within
178 180 minutes, and clinically significant improvement continued for 12 hours in most patients.

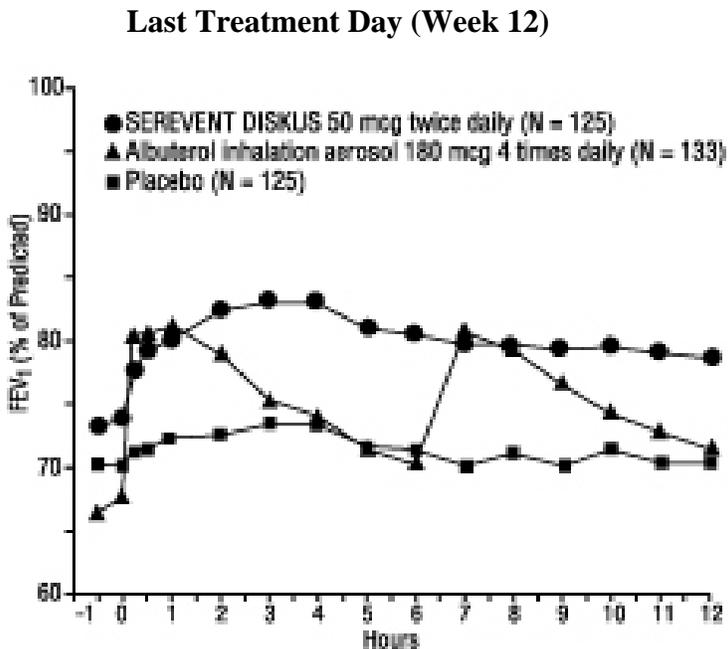
179 In 2 randomized, double-blind studies, SEREVENT DISKUS was compared with albuterol
180 inhalation aerosol and placebo in adolescent and adult patients with mild-to-moderate asthma
181 (protocol defined as 50% to 80% predicted FEV_1 , actual mean of 67.7% at baseline), including
182 patients who did and who did not receive concurrent inhaled corticosteroids. The efficacy of
183 SEREVENT DISKUS was demonstrated over the 12-week period with no change in
184 effectiveness over this time period (see Figure 1). There were no gender- or age-related
185 differences in safety or efficacy. No development of tachyphylaxis to the bronchodilator effect
186 was noted in these studies. FEV_1 measurements (mean change from baseline) from these two 12-
187 week studies are shown in Figure 1 for both the first and last treatment days.
188

189 **Figure 1. Serial 12-Hour FEV₁ From Two 12-Week**
 190 **Clinical Trials in Patients With Asthma**

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 197 Table 1 shows the treatment effects seen during daily treatment with SEREVENT DISKUS
 198 for 12 weeks in adolescent and adult patients with mild-to-moderate asthma.
 199

200 **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 [†]	2.2
Asthma exacerbations		14%	15%	16%

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

202 [†] Statistically superior to placebo (p<0.001).

203

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

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

218 In a randomized, double-blind, controlled study (N = 449), 50 mcg of SEREVENT DISKUS
 219 was administered twice daily to pediatric patients with asthma who did and who did not receive
 220 concurrent inhaled corticosteroids. The efficacy of salmeterol inhalation powder was
 221 demonstrated over the 12-week treatment period with respect to periodic serial peak expiratory
 222 flow (PEF) (36% to 39% postdose increase from baseline) and FEV₁ (32% to 33% postdose
 223 increase from baseline). Salmeterol was effective in demographic subgroup analyses (gender and
 224 age) and was effective when coadministered with other inhaled asthma medications such as
 225 short-acting bronchodilators and inhaled corticosteroids. A second randomized, double-blind,

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

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

234 Two randomized, double-blind, controlled, parallel-group clinical trials (N = 997) enrolled
235 patients (ages 18 to 82 years) with persistent asthma who were previously maintained but not
236 adequately controlled on inhaled corticosteroid therapy. During the 2-week run-in period, all
237 patients were switched to beclomethasone dipropionate 168 mcg twice daily. Patients still not
238 adequately controlled were randomized to either the addition of SEREVENT Inhalation Aerosol
239 42 mcg twice daily or an increase of beclomethasone dipropionate to 336 mcg twice daily. As
240 compared to the doubled dose of beclomethasone dipropionate, the addition of SEREVENT
241 Inhalation Aerosol resulted in statistically significantly greater improvements in pulmonary
242 function and asthma symptoms, and statistically significantly greater reduction in supplemental
243 albuterol use. The percent of patients who experienced asthma exacerbations overall was not
244 different between groups (i.e., 16.2% in the group receiving SEREVENT Inhalation Aerosol
245 versus 17.9% in the higher-dose beclomethasone dipropionate group).

246 Two randomized, double-blind, parallel-group clinical trials (N = 925) enrolled patients (ages
247 12 to 78 years) with persistent asthma who were previously maintained but not adequately
248 controlled on prior therapy. During the 2- to 4-week run-in period, all patients were switched to
249 fluticasone propionate 88 mcg twice daily. Patients still not adequately controlled were
250 randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg twice daily or an
251 increase of fluticasone propionate to 220 mcg twice daily. As compared to the increased (2.5
252 times) dose of fluticasone propionate, the addition of SEREVENT Inhalation Aerosol resulted in
253 statistically significantly greater improvements in pulmonary function and asthma symptoms,
254 and statistically significantly greater reductions in supplemental albuterol use. Fewer patients
255 receiving SEREVENT Inhalation Aerosol experienced asthma exacerbations than those
256 receiving the higher dose of fluticasone propionate (8.8% versus 13.8%).

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

261

262

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 FEV₁</u>				
	<10%	15	29	31	60
	≥10%, <20%	3	6	11	21
	≥20%	34	65	10	19
Mean maximal % fall in FEV ₁ (SE)		-25% (1.8)		-11% (1.9)	
8.5-Hour postdose exercise challenge	<u>% Fall in FEV₁</u>				
	<10%	12	23	26	50
	≥10%, <20%	7	13	12	23
	≥20%	33	63	14	27
Mean maximal % fall in FEV ₁ (SE)		-27% (1.5)		-16% (2.0)	

263

264 In 2 randomized studies in children 4 to 11 years old with asthma and EIB (N = 50), a single
 265 50-mcg dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise,
 266 with protection lasting up to 11.5 hours in repeat testing following this single dose in many
 267 patients.

268 **Salmeterol Multi-center Asthma Research Trial:** The Salmeterol Multi-center Asthma
 269 Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta₂-
 270 agonist-naïve patients with asthma (average age of 39 years, 71% Caucasian, 18% African
 271 American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol)
 272 42 mcg twice daily over 28 weeks compared to placebo when added to usual asthma therapy.

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

279 Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death
 280 occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo
 281 (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also,
 282 asthma-related death occurred at a higher rate in patients treated with salmeterol than those
 283 treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the
 284 relative risks of asthma-related death were similar in Caucasians and African Americans, the
 285 estimate of excess deaths in patients treated with salmeterol was greater in African Americans
 286 because there was a higher overall rate of asthma-related death in African American patients (see

287 Table 3).

288 Post-hoc analyses in pediatric patients 12 to 18 years of age were also performed. Pediatric
289 patients accounted for approximately 12% of patients in each treatment arm. Respiratory related
290 death or life threatening experience occurred at a similar rate in the salmeterol group 0.12%
291 (2/1653) and the placebo group (0.12%) (2/1622) [relative risk 1.0, 95% CI 0.1-7.2]. All cause
292 hospitalization, however, was increased in the salmeterol group (2%) (35/1653) vs. the placebo
293 group (<1%) (16/1622) [relative risk 2.1, 95% CI 1.1-3.7].

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

297
298 **Table 3: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research**
299 **Trial (SMART)**

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

300 ^{*} Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to
301 study treatment to account for early withdrawal of patients from the study.

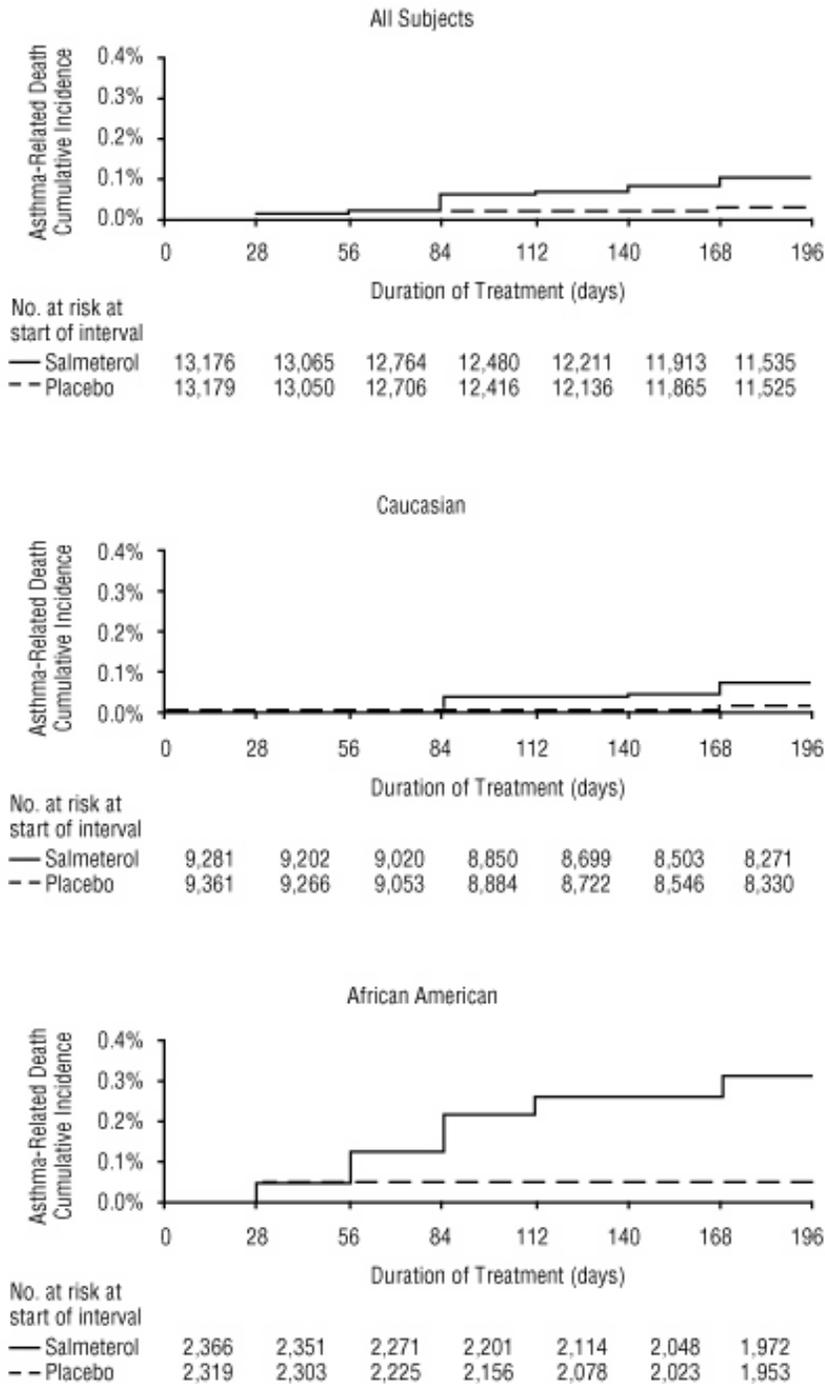
302 [†] Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the
303 rate in the placebo group. The relative risk indicates how many more times likely an
304 asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week
305 treatment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

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

310 [§] The Total Population includes the following ethnic origins listed on the case report form:
311 Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population
312 includes those patients whose ethnic origin was not reported. The results for Caucasian and

313 African American subpopulations are shown above. No asthma-related deaths occurred in the
314 Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149),
315 or “Other” (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death
316 occurred in the placebo group in the subpopulation whose ethnic origin was not reported
317 (salmeterol n = 130, placebo n = 127).
318

319 **Figure 2. Cumulative Incidence of Asthma-Related Deaths**
 320 **in the 28-Week Salmeterol Multi-center Asthma Research**
 321 **Trial (SMART), by Duration of Treatment**
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 325 **Chronic Obstructive Pulmonary Disease:** In 2 clinical trials evaluating twice-daily

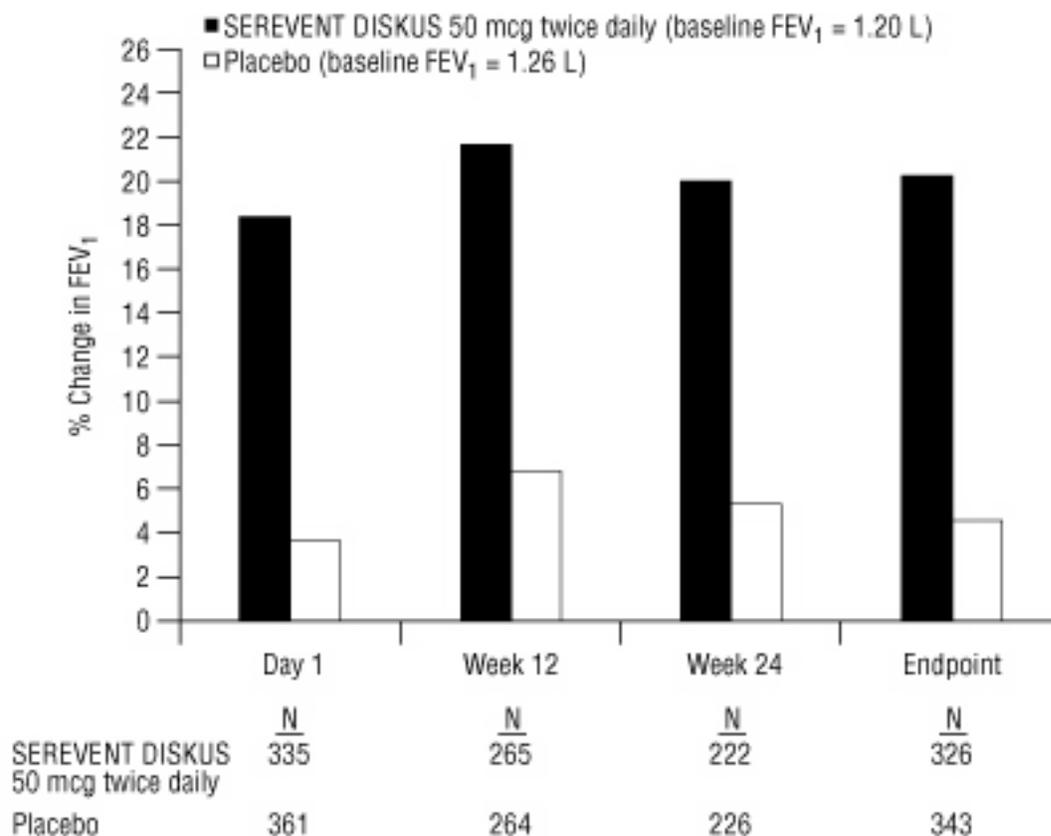
326 treatment with SEREVENT DISKUS 50 mcg (N = 336) compared to placebo (N = 366) in
 327 patients with chronic bronchitis with airflow limitation, with or without emphysema,
 328 improvements in pulmonary function endpoints were greater with salmeterol 50 mcg than with
 329 placebo. Treatment with SEREVENT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

333 Figure 3 displays the integrated 2-hour postdose FEV₁ results from the 2 clinical trials. The
 334 percent change in FEV₁ refers to the change from baseline, defined as the predose value on
 335 Treatment Day 1. To account for patient withdrawals during the study, Endpoint (last evaluable
 336 FEV₁) data are provided. Patients receiving SEREVENT DISKUS 50 mcg had significantly
 337 greater improvements in 2-hour postdose FEV₁ at Endpoint (216 mL, 20%) compared to placebo
 338 (43 mL, 5%). Improvement was apparent on the first day of treatment and maintained throughout
 339 the 24 weeks of treatment.

340

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

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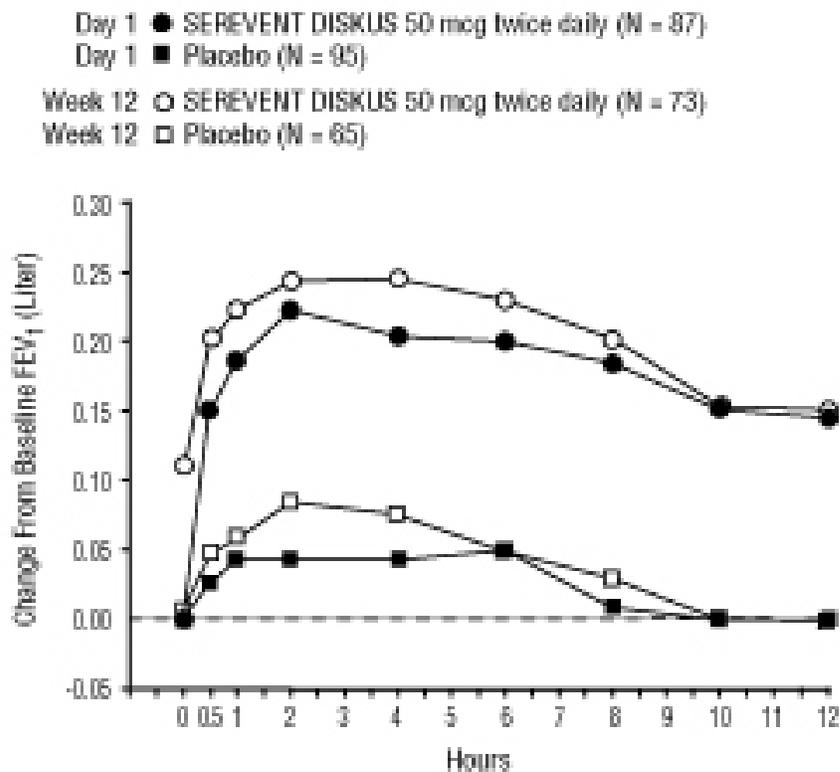


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345 **Onset of Action and Duration of Effect:** The onset of action and duration of effect of

346 SEREVENT DISKUS were evaluated in a subset of patients (n = 87) from 1 of the 2 clinical
 347 trials discussed above. Following the first 50-mcg dose, significant improvement in pulmonary
 348 function (mean FEV₁ increase of 12% or more and at least 200 mL) occurred at 2 hours. The
 349 mean time to peak bronchodilator effect was 4.75 hours. As seen in Figure 4, evidence of
 350 bronchodilatation was seen throughout the 12-hour period. Figure 4 also demonstrates that the
 351 bronchodilating effect after 12 weeks of treatment was similar to that observed after the first
 352 dose. The mean time to peak bronchodilator effect after 12 weeks of treatment was 3.27 hours.
 353

354 **Figure 4. Serial 12-Hour FEV₁ on the First Day and at Week 12**
 355 **of Treatment**



356

357 **INDICATIONS AND USAGE**

358 **Asthma:** SEREVENT DISKUS is indicated for the treatment of asthma and in the prevention of
 359 bronchospasm only as concomitant therapy with a long-term asthma control medication, such as
 360 an inhaled corticosteroid, in patients 4 years of age and older with reversible obstructive airway
 361 disease, including patients with symptoms of nocturnal asthma. Long-acting beta₂-adrenergic
 362 agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of
 363 asthma-related death (see WARNINGS). Use of SEREVENT DISKUS for the treatment of
 364 asthma without concomitant use of a long-term asthma control medication, such as an inhaled
 365 corticosteroid is contraindicated (see CONTRAINDICATIONS). Use SEREVENT DISKUS

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

373 **Pediatric and Adolescent Patients**

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

383 **Exercise Induced Bronchospasm:** SEREVENT DISKUS is also indicated for prevention
384 of exercise induced bronchospasm in patients 4 years of age and older. Use of SEREVENT
385 DISKUS as a single agent for the prevention of exercise induced bronchospasm may be
386 clinically indicated in patients who do not have persistent asthma. In patients with persistent
387 asthma, use of SEREVENT DISKUS for the prevention of exercise induced bronchospasm may
388 be clinically indicated, but the treatment of asthma should include a long-term asthma control
389 medication, such as an inhaled corticosteroid.

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

393 **CONTRAINDICATIONS**

394 **Because of the risk of asthma-related death and hospitalization, use of SEREVENT**
395 **DISKUS for the treatment of asthma without concomitant use of a long-term asthma**
396 **control medication, such as an inhaled corticosteroid is contraindicated (see Warnings --**
397 **Asthma Related Death).** SEREVENT DISKUS is contraindicated in patients with a history of
398 hypersensitivity to salmeterol or any other component of the drug product (see DESCRIPTION
399 and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site Specific*).

400 **WARNINGS**

401 **Asthma Related Death**

402 **Long-acting beta₂-adrenergic agonists, such as salmeterol, the active ingredient in**
403 **SEREVENT DISKUS, increase the risk of asthma-related death. Currently available data**
404 **are inadequate to determine whether concurrent use of inhaled corticosteroids or other**

405 long-term asthma control drugs mitigates the increased risk of asthma-related death from
406 LABA.

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

417 ***Pediatric and Adolescent Patients***

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

427 ***SMART and SNS***

428 A large 28-week, placebo-controlled US study comparing the safety of salmeterol (SEREVENT
429 Inhalation Aerosol) with placebo, each added to usual asthma therapy, showed an increase in
430 asthma-related deaths in patients receiving salmeterol (see CLINICAL TRIALS: Asthma:
431 *Salmeterol Multi-center Asthma Research Trial*). Given the similar basic mechanisms of action
432 of beta₂-agonists, the findings seen in the SMART study are considered a class effect.

433 A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide
434 Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate
435 of asthma-related death was numerically, though not statistically significantly, greater in patients
436 with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol
437 (180 mcg 4 times daily) added to usual asthma therapy.

438 The SNS and SMART studies enrolled patients with asthma. No studies have been
439 conducted that were adequate to determine whether the rate of death in patients with
440 COPD is increased by long-acting beta₂-adrenergic agonists.

- 441 • **It is important to watch for signs of worsening asthma**, such as increasing use of
442 inhaled, short-acting beta₂-agonists or a significant decrease in PEF or lung function.
443 Such findings require immediate evaluation. Patients should be advised to seek
444 immediate medical attention should their condition deteriorate.

- 445 • **SEREVENT DISKUS should not be used to treat acute symptoms.** It is crucial to
446 inform patients of this and prescribe an inhaled, short-acting beta₂-agonist for this
447 purpose and to warn them that increasing inhaled beta₂-agonist use is a signal of
448 deteriorating asthma that requires prompt consultation with a physician.
- 449 • **SEREVENT DISKUS should not be initiated in patients with significantly worsening or**
450 **acutely deteriorating asthma, which may be a life-threatening condition.** Serious acute
451 respiratory events, including fatalities, have been reported both in the United States
452 and worldwide when SEREVENT has been initiated in this situation. Although it is not
453 possible from these reports to determine whether SEREVENT contributed to these
454 adverse events or simply failed to relieve the deteriorating asthma, the use of
455 SEREVENT DISKUS in this setting is inappropriate.
- 456 • **SEREVENT DISKUS is not a substitute for inhaled or oral corticosteroids.**
457 **Corticosteroids should not be stopped or reduced when SEREVENT DISKUS is**
458 **initiated.**

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

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

- 462 1. **SEREVENT DISKUS should not be used as a treatment for acutely deteriorating asthma.**
463 SEREVENT DISKUS should not be introduced in acutely deteriorating asthma, which is
464 a potentially life-threatening condition. There are no data demonstrating that SEREVENT
465 DISKUS provides greater efficacy than or additional efficacy to inhaled, short-acting
466 beta₂-agonists in patients with worsening asthma. Serious acute respiratory events,
467 including fatalities, have been reported both in the United States and worldwide in
468 patients receiving SEREVENT. In most cases, these have occurred in patients with severe
469 asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary
470 function, intubation, mechanical ventilation, frequent hospitalizations, or previous
471 life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has
472 been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for
473 inhaled, short-acting beta₂-agonists; increasing need for systemic corticosteroids;
474 significant increase in symptoms; recent emergency room visits; sudden or progressive
475 deterioration in pulmonary function). However, they have occurred in a few patients with
476 less severe asthma as well. It was not possible from these reports to determine whether
477 SEREVENT contributed to these events.
- 478 2. **SEREVENT DISKUS should not be used to treat acute symptoms.** An inhaled,
479 short-acting beta₂-agonist, not SEREVENT DISKUS, should be used to relieve acute
480 asthma or COPD symptoms. When prescribing SEREVENT DISKUS, the physician
481 must also provide the patient with an inhaled, short-acting beta₂-agonist (e.g., albuterol)
482 for treatment of symptoms that occur acutely, despite regular twice-daily (morning and
483 evening) use of SEREVENT DISKUS.

484 When beginning treatment with SEREVENT DISKUS, patients who have been taking

485 inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be
486 instructed to discontinue the regular use of these drugs and use them only for symptomatic
487 relief of acute asthma or COPD symptoms (see PRECAUTIONS: Information for Patients).

488 3. Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma
489 or COPD. The physician and patient should be alert to such changes. The patient's
490 condition may deteriorate acutely over a period of hours or chronically over several days
491 or longer. If the patient's inhaled, short-acting beta₂-agonist becomes less effective, the
492 patient needs more inhalations than usual, or the patient develops a significant decrease in
493 PEF or lung function, these may be markers of destabilization of their disease. In this
494 setting, the patient requires immediate reevaluation with reassessment of the treatment
495 regimen, giving special consideration to the possible need for corticosteroids. If the
496 patient uses 4 or more inhalations per day of an inhaled, short-acting beta₂-agonist for 2
497 or more consecutive days, or if more than 1 canister (200 inhalations per canister) of
498 inhaled, short-acting beta₂-agonist is used in an 8-week period in conjunction with
499 SEREVENT DISKUS, then the patient should consult the physician for reevaluation.
500 **Increasing the daily dosage of SEREVENT DISKUS in this situation is not**
501 **appropriate. SEREVENT DISKUS should not be used more frequently than twice**
502 **daily (morning and evening) at the recommended dose of 1 inhalation.**

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

506 5. SEREVENT DISKUS is not a substitute for oral or inhaled corticosteroids. There are no
507 data demonstrating that SEREVENT DISKUS has a clinical anti-inflammatory effect and
508 could be expected to take the place of corticosteroids. When initiating SEREVENT
509 DISKUS in patients receiving oral or inhaled corticosteroids for treatment of asthma,
510 patients should be continued on a suitable dose of corticosteroids to maintain clinical
511 stability even if they feel better as a result of initiating SEREVENT DISKUS. Any
512 change in corticosteroid dosage should be made ONLY after clinical evaluation (see
513 PRECAUTIONS: Information for Patients).

514 6. The recommended dosage should not be exceeded. As with other inhaled
515 beta₂-adrenergic drugs, SEREVENT DISKUS should not be used more often or at higher
516 doses than recommended. Fatalities have been reported in association with excessive use
517 of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to
518 20 times the recommended dose) have been associated with clinically significant
519 prolongation of the QTc interval, which has the potential for producing ventricular
520 arrhythmias.

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

- 525 SEREVENT DISKUS should be discontinued immediately; and alternative therapy
526 should be instituted.
- 527 8. Immediate hypersensitivity reactions. Immediate hypersensitivity reactions may occur
528 after administration of SEREVENT DISKUS, as demonstrated by cases of urticaria,
529 angioedema, rash, and bronchospasm.
- 530 9. Upper airway symptoms. Symptoms of laryngeal spasm, irritation, or swelling, such as
531 stridor and choking, have been reported in patients receiving SEREVENT DISKUS.
- 532 10. Cardiovascular disorders. SEREVENT DISKUS, like all sympathomimetic amines,
533 should be used with caution in patients with cardiovascular disorders, especially coronary
534 insufficiency, cardiac arrhythmias, and hypertension. SEREVENT DISKUS, like all
535 other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect
536 in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although
537 such effects are uncommon after administration of SEREVENT DISKUS at
538 recommended doses, if they occur, the drug may need to be discontinued. In addition,
539 beta-agonists have been reported to produce ECG changes, such as flattening of the
540 T wave, prolongation of the QTc interval, and ST segment depression. The clinical
541 significance of these findings is unknown.
- 542 11. Potential drug interactions. Because of the potential for drug interactions and the
543 potential for increased risk of cardiovascular adverse events, the concomitant use of
544 SEREVENT DISKUS with strong CYP 3A4 inhibitors (e.g., ketoconazole, ritonavir,
545 atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir,
546 telithromycin) is not recommended (see CLINICAL PHARMACOLOGY:
547 Pharmacokinetics: *Drug Interactions*).

548 PRECAUTIONS

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

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

561 **Metabolic Effects:** Doses of the related beta₂-adrenoceptor agonist albuterol, when
562 administered intravenously, have been reported to aggravate preexisting diabetes mellitus and
563 ketoacidosis. Beta-adrenergic agonist medications may produce significant hypokalemia in some

564 patients, possibly through intracellular shunting, which has the potential to produce adverse
565 cardiovascular effects. The decrease in serum potassium is usually transient, not requiring
566 supplementation.

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

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

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

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

- 579 1. **Patients should be informed that salmeterol increases the risk of asthma-related death**
580 **and may increase the risk of asthma-related hospitalizations in pediatric and adolescent**
581 **patients. Patients should be informed that SEREVENT DISKUS should not be the only**
582 **therapy for the treatment of asthma and must only be used as additional therapy when**
583 **long-term asthma control medications (e.g., inhaled corticosteroids) do not adequately**
584 **control asthma symptoms. Patients should be informed that when SEREVENT**
585 **DISKUS is added to their treatment regimen they must continue to use their long-term**
586 **asthma control medication.**
- 587 2. SEREVENT DISKUS is not meant to relieve acute asthma or COPD symptoms and extra
588 doses should not be used for that purpose. Acute symptoms should be treated with an
589 inhaled, short-acting bronchodilator (the physician should provide the patient with such
590 medication and instruct the patient in how it should be used).
- 591 3. The physician should be notified immediately if any of the following signs of seriously
592 worsening asthma or COPD occur:
 - 593 • decreasing effectiveness of inhaled, short-acting beta₂-agonists;
 - 594 • need for more inhalations than usual of inhaled, short-acting beta₂-agonists;
 - 595 • significant decrease in PEF or lung function as outlined by the physician;
 - 596 • use of 4 or more inhalations per day of a short-acting beta₂-agonist for 2 or more days
597 consecutively;
 - 598 • use of more than 1 canister (200 inhalations per canister) of an inhaled, short-acting
599 beta₂-agonist in an 8-week period.
- 600 4. Patients should not stop therapy with SEREVENT DISKUS for asthma or COPD without
601 physician/provider guidance since symptoms may worsen after discontinuation.
- 602 5. SEREVENT DISKUS should not be used as a substitute for oral or inhaled corticosteroids.
603 The dosage of these medications should not be changed and they should not be stopped

604 without consulting the physician, even if the patient feels better after initiating treatment with
605 SEREVENT DISKUS.

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

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

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

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

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

615 11. When used for the treatment of EIB, 1 inhalation of SEREVENT DISKUS should be taken
616 30 minutes before exercise.

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

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

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

622 • Never exhale into the DISKUS.

623 • Never attempt to take the DISKUS apart.

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

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

626 • Always keep the DISKUS in a dry place.

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

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

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

636 **Drug Interactions: Inhibitors of Cytochrome P450 3A4:** In a drug interaction study in
637 20 healthy subjects, coadministration of salmeterol (50 mcg twice daily) and ketoconazole
638 (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC
639 increased 16-fold and C_{max} increased 1.4-fold). Three (3) subjects were withdrawn due to
640 beta₂-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia).
641 Although there was no statistical effect on the mean QTc, coadministration of salmeterol and
642 ketoconazole was associated with more frequent increases in QTc duration compared with
643 salmeterol and placebo administration. Due to the potential increased risk of cardiovascular

644 adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g.,
645 ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone,
646 nelfinavir, saquinavir, telithromycin) is not recommended.

647 **Short-Acting Beta₂-Agonists:** In two 12-week, repetitive-dose adolescent and adult
648 clinical trials in patients with asthma (N = 149), the mean daily need for additional beta₂-agonist
649 in patients using SEREVENT DISKUS was approximately 1½ inhalations/day. Twenty-six
650 percent (26%) of the patients in these trials used between 8 and 24 inhalations of short-acting
651 beta-agonist per day on 1 or more occasions. Nine percent (9%) of the patients in these trials
652 averaged over 4 inhalations/day over the course of the 12-week trials. No increase in frequency
653 of cardiovascular events was observed among the 3 patients who averaged 8 to 11
654 inhalations/day; however, the safety of concomitant use of more than 8 inhalations/day of
655 short-acting beta₂-agonist with SEREVENT DISKUS has not been established. In 29 patients
656 who experienced worsening of asthma while receiving SEREVENT DISKUS during these trials,
657 albuterol therapy administered via either nebulizer or inhalation aerosol (1 dose in most cases)
658 led to improvement in FEV₁ and no increase in occurrence of cardiovascular adverse events.

659 In 2 clinical trials in patients with COPD, the mean daily need for additional beta₂-agonist for
660 patients using SEREVENT DISKUS was approximately 4 inhalations/day. Twenty-four percent
661 (24%) of the patients using SEREVENT DISKUS in these trials averaged 6 or more inhalations
662 of albuterol per day over the course of the 24-week trials. No increase in frequency of
663 cardiovascular events was observed among patients who averaged 6 or more inhalations per day.

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

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

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

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

683 **Beta-Adrenergic Receptor Blocking Agents:** Beta-blockers not only block the

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

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

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

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

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

718 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. No teratogenic effects occurred in
719 rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily
720 inhalation dose in adults on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of
721 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in
722 adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects
723 characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid

724 openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the
725 frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately
726 20 times the maximum recommended daily inhalation dose in adults based on comparison of the
727 AUCs).

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

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

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

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

748 **Pediatric Use:** Available data from controlled clinical trials suggest that LABA increase the
749 risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and
750 adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a
751 fixed-dose combination product containing both an inhaled corticosteroid and LABA should
752 ordinarily be used to ensure adherence with both drugs (see INDICATIONS AND USAGE and
753 WARNINGS).

754 The safety and efficacy of SEREVENT DISKUS in adolescents (12 years and older) has been
755 established based on adequate and well-controlled trials conducted in adults and adolescents (see
756 CLINICAL TRIALS). A large 28-week, placebo-controlled US study, comparing salmeterol
757 (SEREVENT Inhalation Aerosol) and placebo, added to usual asthma therapy, showed an
758 increase in asthma-related deaths in patients receiving salmeterol (see CLINICAL TRIALS:
759 Asthma: *Salmeterol Multi-center Asthma Research Trial*). Post-hoc analyses in pediatric patients
760 12 to 18 years of age were also performed. Pediatric patients accounted for approximately 12%
761 of patients in each treatment arm. Respiratory related death or life threatening experience
762 occurred at a similar rate in the salmeterol group 0.12% (2/1653) and the placebo group (0.12%)
763 (2/1622) [relative risk 1.0, 95% CI 0.1-7.2]. All cause hospitalization, however, was increased in

764 the salmeterol group (2%) (35/1653) vs. the placebo group (<1%) (16/1622) [relative risk 2.1,
765 95% CI 1.1-3.7].

766 The safety and efficacy of SEREVENT DISKUS has been evaluated in over 2,500 patients
767 aged 4 to 11 years with asthma, 346 of whom were administered SEREVENT DISKUS for
768 1 year. Based on available data, no adjustment of dosage of SEREVENT DISKUS in pediatric
769 patients is warranted for either asthma or EIB (see DOSAGE AND ADMINISTRATION).

770 In 2 randomized, double-blind, controlled clinical trials of 12 weeks' duration, SEREVENT
771 DISKUS 50 mcg was administered to 211 pediatric patients with asthma who did and who did
772 not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was
773 demonstrated over the 12-week treatment period with respect to PEF and FEV₁. SEREVENT
774 DISKUS was effective in demographic subgroups (gender and age) of the population.

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

778 **Geriatric Use:** Of the total number of adolescent and adult patients with asthma who received
779 SEREVENT DISKUS in chronic dosing clinical trials, 209 were 65 years of age and older. Of
780 the total number of patients with COPD who received SEREVENT DISKUS in chronic dosing
781 clinical trials, 167 were 65 years of age or older and 45 were 75 years of age or older. No
782 apparent differences in the safety of SEREVENT DISKUS were observed when geriatric patients
783 were compared with younger patients in clinical trials. As with other beta₂-agonists, however,
784 special caution should be observed when using SEREVENT DISKUS in geriatric patients who
785 have concomitant cardiovascular disease that could be adversely affected by this class of drug.
786 Data from the trials in patients with COPD suggested a greater effect on FEV₁ of SEREVENT
787 DISKUS in the <65 years age-group, as compared with the ≥65 years age-group. However,
788 based on available data, no adjustment of dosage of SEREVENT DISKUS in geriatric patients is
789 warranted.

790 **ADVERSE REACTIONS**

791 **LABA, including salmeterol, the active ingredient in SEREVENT DISKUS, increase the**
792 **risk of asthma-related death. Data from a large, 28-week, placebo-controlled US study that**
793 **compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to**
794 **usual asthma therapy showed an increase in asthma-related deaths in patients receiving**
795 **salmeterol. Available data from controlled clinical trials suggest that LABA increase the**
796 **risk of asthma-related hospitalization in pediatric and adolescent patients. (see**
797 **WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research***
798 ***Trial*).**

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

802

803 **Table 4. Adverse Event Incidence in Two 12-Week Adolescent and Adult Clinical Trials in**
 804 **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

805
 806 Table 4 includes all events (whether considered drug-related or nondrug-related by the
 807 investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT
 808 DISKUS and were more common than in the placebo group.

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

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

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

816 **Gastrointestinal:** Nausea.

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

818 **Musculoskeletal:** Pain in joint.

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

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

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

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

827

828 **Table 5. Adverse Event Incidence in Two 12-Week Pediatric Clinical Trials in Patients**
 829 **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

830
 831 The following events were reported at an incidence of 1% to 2% (3 to 4 patients) in the
 832 salmeterol group and with a higher incidence than in the albuterol and placebo groups:
 833 gastrointestinal signs and symptoms, lower respiratory signs and symptoms, photodermatitis, and
 834 arthralgia and articular rheumatism.

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

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

843

844 **Table 6. Adverse Events With $\geq 3\%$ Incidence in US Controlled Clinical Trials With**
 845 **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

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

850
 851 Other events occurring in the group receiving SEREVENT DISKUS that occurred at a
 852 frequency of 1% to <3% and were more common than in the placebo group were as follows:

853 **Endocrine and Metabolic:** Hyperglycemia.

854 **Eye:** Keratitis and conjunctivitis.

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

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

858 **Musculoskeletal:** Arthralgia and articular rheumatism; muscle pain; bone and skeletal pain;

859 musculoskeletal inflammation; muscle stiffness, tightness, and rigidity.

860 **Neurology:** Migraines.

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

862 **Psychiatry:** Anxiety.

863 **Skin:** Skin rashes.

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

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

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

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

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

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

885 **OVERDOSAGE**

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

897 As with all sympathomimetic medications, cardiac arrest and even death may be associated

898 with abuse of SEREVENT DISKUS.

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

904 No deaths were seen in rats at an inhalation dose of 2.9 mg/kg (approximately 240 times the
905 maximum recommended daily inhalation dose in adults and approximately 110 times the
906 maximum recommended daily inhalation dose in children on a mg/m² basis) and in dogs at an
907 inhalation dose of 0.7 mg/kg (approximately 190 times the maximum recommended daily
908 inhalation dose in adults and approximately 90 times the maximum recommended daily
909 inhalation dose in children on a mg/m² basis). By the oral route, no deaths occurred in mice at
910 150 mg/kg (approximately 6,100 times the maximum recommended daily inhalation dose in
911 adults and approximately 2,900 times the maximum recommended daily inhalation dose in
912 children on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 81,000 times the maximum
913 recommended daily inhalation dose in adults and approximately 38,000 times the maximum
914 recommended daily inhalation dose in children on a mg/m² basis).

915 **DOSAGE AND ADMINISTRATION**

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

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

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

933 **Pediatric Patients and Adolescent Patients**

934 Available data from controlled clinical trials suggest that LABA increase the risk of asthma-
935 related hospitalization in pediatric and adolescent patients. For patients with asthma less than 18
936 years of age who require addition of a LABA to an inhaled corticosteroid, a fixed-dose

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

943 For bronchodilatation and prevention of symptoms of asthma, including the symptoms of
944 nocturnal asthma, the usual dosage for adults and children 4 years of age and older is 1 inhalation
945 (50 mcg) twice daily (morning and evening, approximately 12 hours apart). If a previously
946 effective dosage regimen fails to provide the usual response, medical advice should be sought
947 immediately as this is often a sign of destabilization of asthma. Under these circumstances, the
948 therapeutic regimen should be reevaluated. If symptoms arise in the period between doses, an
949 inhaled, short-acting beta₂-agonist should be taken for immediate relief.

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

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

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

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

960 **Prevention of Exercise-Induced Bronchospasm:** Use of SEREVENT DISKUS as a
961 single agent for the prevention of exercise induced bronchospasm may be clinically indicated in
962 patients who do not have persistent asthma. In patients with persistent asthma, use of
963 SEREVENT DISKUS for the prevention of exercise induced bronchospasm may be clinically
964 indicated, but the treatment of asthma should include a long-term asthma control medication,
965 such as an inhaled corticosteroid. One inhalation of SEREVENT DISKUS at least 30 minutes
966 before exercise has been shown to protect patients against EIB. When used intermittently as
967 needed for prevention of EIB, this protection may last up to 9 hours in adolescents and adults and
968 up to 12 hours in patients 4 to 11 years of age. Additional doses of SEREVENT should not be
969 used for 12 hours after the administration of this drug. Patients who are receiving SEREVENT
970 DISKUS twice daily should not use additional SEREVENT for prevention of EIB.

971 HOW SUPPLIED

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

975 SEREVENT DISKUS is also supplied in an institutional pack of 1 disposable teal green unit

976 containing 28 blisters. The drug product is packaged within a teal green, plastic-coated,
977 moisture-protective foil pouch (NDC 0173-0520-00).

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

983
984



985
986 GlaxoSmithKline
987 Research Triangle Park, NC 27709

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MEDICATION GUIDE

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

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998
999
1000
1001

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

1002 **What is the most important information I should know about SEREVENT DISKUS?**

1003 **SEREVENT DISKUS can cause serious side effects, including:**

1004 **1. People with asthma who take long-acting beta₂-adrenergic agonist (LABA) medicines**
1005 **such as salmeterol (SEREVENT DISKUS), have an increased risk of death from**
1006 **asthma problems.**

- 1007 • Call your healthcare provider if breathing problems worsen over time while using
1008 SEREVENT DISKUS. You may need a different treatment.
- 1009 • Get emergency medical care if:
 - 1010 • breathing problems worsen quickly, and
 - 1011 • you use your rescue inhaler medicine, but it does not relieve your breathing problems.

1012 2. **Do not use SEREVENT DISKUS as your only asthma medicine. SEREVENT DISKUS**
1013 **must only be used with a long-term asthma-control medicine, such as an inhaled**
1014 **corticosteroid.**

1015 3. When your asthma is well controlled, your healthcare provider may tell you to stop taking
1016 SEREVENT DISKUS. Your healthcare provider will decide if you can stop SEREVENT
1017 DISKUS without loss of asthma control. You will continue taking your long-term asthma-
1018 control medicine, such as an inhaled corticosteroid.

1019 4. Children and adolescents who take LABA medicines may have an increased risk of being
1020 hospitalized for asthma problems.

1021

1022 **What is SEREVENT DISKUS?**

1023 • SEREVENT DISKUS is a LABA medicine. LABA medicines help the muscles around the
1024 airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of
1025 breath. These symptoms can happen when the muscles around the airways tighten. This
1026 makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death
1027 if not treated right away.

1028 • SEREVENT DISKUS is used for asthma, exercise-induced bronchospasm (EIB), and chronic
1029 obstructive pulmonary disease (COPD) as follows:

1030 **Asthma:**

1031 SEREVENT DISKUS is used in adults and children aged 4 years and older, with a long-term
1032 asthma control medicine, such as an inhaled corticosteroid:

- 1033 • to control symptoms of asthma, and
- 1034 • to prevent symptoms such as wheezing.

1035 LABA medicines, such as SEREVENT DISKUS, increase the risk of death from asthma
1036 problems. SEREVENT DISKUS is not for adults and children with asthma who are well
1037 controlled with a long-term asthma-control medicine, such as a low to medium dose of an
1038 inhaled corticosteroid medicine.

1039 **Exercise-Induced Bronchospasm:**

1040 SEREVENT DISKUS is used to prevent wheezing caused by exercise in adults and children
1041 aged 4 years and older.

- 1042 • If you have EIB only, your healthcare provider may prescribe only SEREVENT DISKUS
1043 for your condition.

- 1044 • If you have EIB and asthma, your healthcare provider should also prescribe an asthma
1045 control medicine, such as an inhaled corticosteroid.

1046 **Chronic Obstructive Pulmonary Disease:**

1047 SEREVENT DISKUS is used long term, 2 times each day (morning and evening) to control
1048 symptoms of COPD and prevent wheezing in adults with COPD.

1049

1050 **Who should not use SEREVENT DISKUS?**

1051 **Do not take SEREVENT DISKUS:**

- 1052 • to treat your asthma without an asthma medicine known as an inhaled corticosteroid
- 1053 • if you are allergic to salmeterol or any of the ingredients in SEREVENT DISKUS. Ask your
1054 healthcare provider if you are not sure. See the end of this Medication Guide for a complete
1055 list of ingredients in SEREVENT DISKUS.

1056

1057 **What should I tell my healthcare provider before using SEREVENT DISKUS?**

1058 Tell your healthcare provider about all of your health conditions, including if you:

- 1059 • have heart problems
- 1060 • have high blood pressure
- 1061 • have seizures
- 1062 • have thyroid problems
- 1063 • have diabetes
- 1064 • have liver problems
- 1065 • are pregnant or planning to become pregnant. It is not known if SEREVENT DISKUS may
1066 harm your unborn baby.
- 1067 • are breastfeeding. It is not known if SEREVENT DISKUS passes into your milk and if it can
1068 harm your baby.
- 1069 • are allergic to SEREVENT DISKUS, any other medicines, or food products. See the end of
1070 this Medication Guide for a complete list of ingredients in SEREVENT DISKUS.

1071

1072 Tell your healthcare provider about all the medicines you take including prescription and
1073 non-prescription medicines, vitamins, and herbal supplements. SEREVENT DISKUS and certain
1074 other medicines, especially those used to treat infections, may interact with each other. This may
1075 cause serious side effects.

1076

1077 Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist
1078 each time you get a new medicine.

1079

1080 **How do I use SEREVENT DISKUS?**

1081 See the step-by-step instructions for using the SEREVENT DISKUS at the end of this
1082 Medication Guide. Do not use SEREVENT DISKUS unless your healthcare provider has taught
1083 you and you understand everything. Ask your healthcare provider or pharmacist if you have any
1084 questions.

- 1085 • Children should use SEREVENT 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:**

- 1122 • **See “What is the most important information I should know about SEREVENT**
1123 **DISKUS?”**
- 1124 • **serious allergic reactions.** Call your healthcare provider or get emergency medical care if
1125 you get any of the following symptoms of a serious allergic reaction:
- 1126 • rash
1127 • hives
1128 • swelling of the face, mouth, and tongue
1129 • breathing problems.
- 1130 • **sudden breathing problems immediately after inhaling your medicine**
- 1131 • **effects on heart**
- 1132 • increased blood pressure
1133 • a fast and irregular heartbeat
1134 • chest pain
- 1135 • **effects on nervous system**
- 1136 • tremor
1137 • nervousness
- 1138 • **changes in blood (sugar, potassium)**
1139
- 1140 **Common side effects of SEREVENT DISKUS include:**
- 1141 **Asthma in adults and children:**
- 1142 • headache
1143 • nasal congestion
1144 • bronchitis
1145 • throat irritation
1146 • runny nose
1147 • flu
1148
- 1149 **Chronic obstructive pulmonary disease:**
- 1150 • headache
1151 • musculoskeletal pain
1152 • throat irritation
1153 • cough
1154 • respiratory infection
1155
- 1156 Tell your healthcare provider about any side effect that bothers you or that does not go away.
- 1157 These are not all the side effects with SEREVENT DISKUS. Ask your healthcare provider or
1158 pharmacist for more information.

1159 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-
1160 800-FDA-1088.

1161

1162 **How do I store SEREVENT DISKUS?**

- 1163 • Store SEREVENT DISKUS at room temperature between 68°F to 77° F (20°C to 25° C).
1164 Keep in a dry place away from heat and sunlight.
- 1165 • Safely discard SEREVENT DISKUS 6 weeks after you remove it from the foil pouch, or
1166 after the dose indicator reads “0”, whichever comes first.
- 1167 • Keep SEREVENT DISKUS and all medicines out of the reach of children.

1168

1169 **General Information about SEREVENT DISKUS**

1170 Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not
1171 use SEREVENT DISKUS for a condition for which it was not prescribed. Do not give your
1172 SEREVENT DISKUS to other people, even if they have the same condition that you have. It
1173 may harm them.

1174 This Medication Guide summarizes the most important information about SEREVENT
1175 DISKUS. If you would like more information, talk with your healthcare provider or pharmacist.
1176 You can ask your healthcare provider or pharmacist for information about SEREVENT DISKUS
1177 that was written for healthcare professionals. You can also contact the company that makes
1178 SEREVENT DISKUS (toll free) at 1-888-825-5249 or at www.serevent.com.

1179

1180 **What are the ingredients in SEREVENT DISKUS?**

1181 Active ingredient: salmeterol xinafoate

1182 Inactive ingredient: lactose (contains milk proteins)

1183

1184 **Instructions for Using SEREVENT DISKUS**

1185 Follow the instructions below for using your SEREVENT DISKUS. **You will breathe in**
1186 **(inhale) the medicine from the DISKUS.** If you have any questions, ask your healthcare
1187 provider or pharmacist.



1188
 1189 Take the SEREVENT DISKUS out of the box and foil pouch. Write the **“Pouch opened”** and
 1190 **“Use by”** dates on the label on top of the DISKUS. **The “Use by” date is 6 weeks from date of**
 1191 **opening the pouch.**

- 1192
- 1193 • The DISKUS will be in the closed position when the pouch is opened.
- 1194
- 1195 • The **dose indicator** on the top of the DISKUS tells you how many doses are left. The
- 1196 dose indicator number will decrease each time you use the DISKUS. After you have used
- 1197 55 doses from the DISKUS, the numbers 5 to 0 will appear in **red** to warn you that there
- 1198 are only a few doses left (*see Figure 1*).
- 1199



1200
 1201
 1202
 1203 Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.

- 1204
- 1205 **1. OPEN**

1206 Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**. Push
1207 your thumb away from you as far as it will go until the mouthpiece appears and snaps into
1208 position (*see Figure 2*).
1209



1210
1211 Figure 2

1212
1213 **2. CLICK**

1214 Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the **lever**
1215 away from you as far as it will go until it **clicks** (*see Figure 3*). The DISKUS is now ready to
1216 use.
1217



1218
1219 Figure 3

1220
1221 Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a
1222 decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the**
1223 **DISKUS is ready:**

- 1224
- **Do not close the DISKUS.**

- 1225 • Do not tilt the DISKUS.
- 1226 • Do not play with the lever.
- 1227 • Do not move the lever more than once.

1228
1229 **3. INHALE**

1230 Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the
1231 DISKUS level and away from your mouth (*see Figure 4*). **Remember, never breathe out**
1232 **into the DISKUS mouthpiece.**

1233



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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.



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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.

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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

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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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Month Year

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