

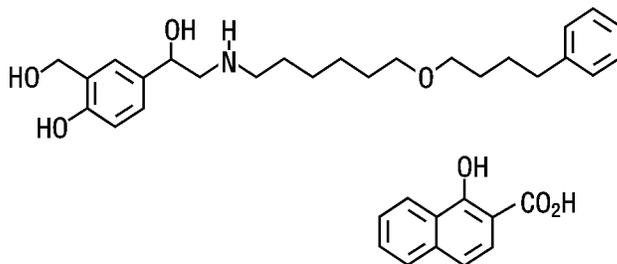
SEREVENT[®]
(salmeterol xinafoate)
Inhalation Aerosol

Bronchodilator Aerosol
For Oral Inhalation Only

WARNING: 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 a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks) versus those on placebo (3 of 13,179) (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).

DESCRIPTION

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



The molecular weight of salmeterol xinafoate is 603.8, and the empirical formula is C₂₅H₃₇NO₄•C₁₁H₈O₃. Salmeterol xinafoate is a white to off-white powder. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

SEREVENT Inhalation Aerosol is a pressurized, metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of salmeterol xinafoate in a mixture of 2 chlorofluorocarbon propellants (trichlorofluoromethane and dichlorodifluoromethane) with soya lecithin. 36.25 mcg of salmeterol xinafoate is equivalent to 25 mcg of salmeterol base. Each actuation delivers 25 mcg of salmeterol base (as salmeterol xinafoate) from the valve and 21 mcg

33 of salmeterol base (as salmeterol xinafoate) from the actuator. Each 6.5-g canister provides
34 60 inhalations and each 13-g canister provides 120 inhalations.

35

36 **CLINICAL PHARMACOLOGY**

37 **Mechanism of Action:** Salmeterol is a long-acting beta₂-adrenergic agonist. In vitro studies
38 and in vivo pharmacologic studies demonstrate that salmeterol is selective for
39 beta₂-adrenoceptors compared with isoproterenol, which has approximately equal agonist
40 activity on beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least 50 times
41 more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the
42 predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the
43 predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart
44 comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these is not yet
45 established, but they raise the possibility that even highly selective beta₂-agonists may have
46 cardiac effects.

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

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

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

62 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low or
63 undetectable after inhalation of recommended doses (42 mcg of salmeterol inhalation aerosol
64 twice daily). Following chronic administration of an inhaled dose of 42 mcg twice daily,
65 salmeterol was detected in plasma within 5 to 10 minutes in 6 patients with asthma; plasma
66 concentrations were very low, with peak concentrations of 150 pg/mL and no accumulation with
67 repeated doses. Larger inhaled doses gave approximately proportionally increased blood levels.
68 In these patients, a second peak concentration of 115 pg/mL occurred at about 45 minutes,
69 probably due to absorption of the swallowed portion of the dose (most of the dose delivered by a
70 metered-dose inhaler is swallowed).

71 **Distribution:** Binding of salmeterol to human plasma proteins averages 96% in vitro over
72 the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher than those
73 achieved following therapeutic doses of salmeterol.

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

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

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

83 **Special Populations:** The pharmacokinetics of salmeterol base has not been studied in
84 elderly patients or in patients with hepatic or renal impairment. Since salmeterol is
85 predominantly cleared by hepatic metabolism, liver function impairment may lead to
86 accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely
87 monitored.

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

93 The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied
94 in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as
95 inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as
96 albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). In 2 double-blind asthma
97 studies, patients receiving either 42 mcg of salmeterol inhalation aerosol twice daily (N = 81) or
98 180 mcg of albuterol inhalation aerosol 4 times daily (N = 80) underwent continuous
99 electrocardiographic monitoring during four 24-hour periods; no clinically significant
100 dysrhythmias were noted. Continuous electrocardiographic monitoring was also performed in 2
101 double-blind studies in patients with chronic obstructive pulmonary disease (COPD) (see
102 ADVERSE REACTIONS).

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

107 **CLINICAL TRIALS**

108 **Asthma:** In placebo- and albuterol-controlled, single-dose clinical trials with SEREVENT
109 Inhalation Aerosol, the time to onset of effective bronchodilatation (>15% improvement in
110

111 forced expiratory volume in 1 second [FEV₁]) was 10 to 20 minutes after a 42-mcg dose.
112 Maximum improvement in FEV₁ generally occurred within 180 minutes, and clinically
113 significant improvement continued for 12 hours in most patients.

114 In 2 large, randomized, double-blind studies, SEREVENT Inhalation Aerosol was compared
115 with albuterol and placebo in patients with mild-to-moderate asthma, including both patients
116 who did and who did not receive concomitant inhaled corticosteroids. The efficacy of
117 SEREVENT Inhalation Aerosol was demonstrated over the 12-week period with no change in
118 effectiveness over this period of time. There were no gender-related differences in safety or
119 efficacy. No development of tachyphylaxis to the bronchodilator effect has been noted in these
120 studies. FEV₁ measurements (percent of predicted) from these two 12-week trials are shown in
121 Figure 1 for both the first and last treatment days.

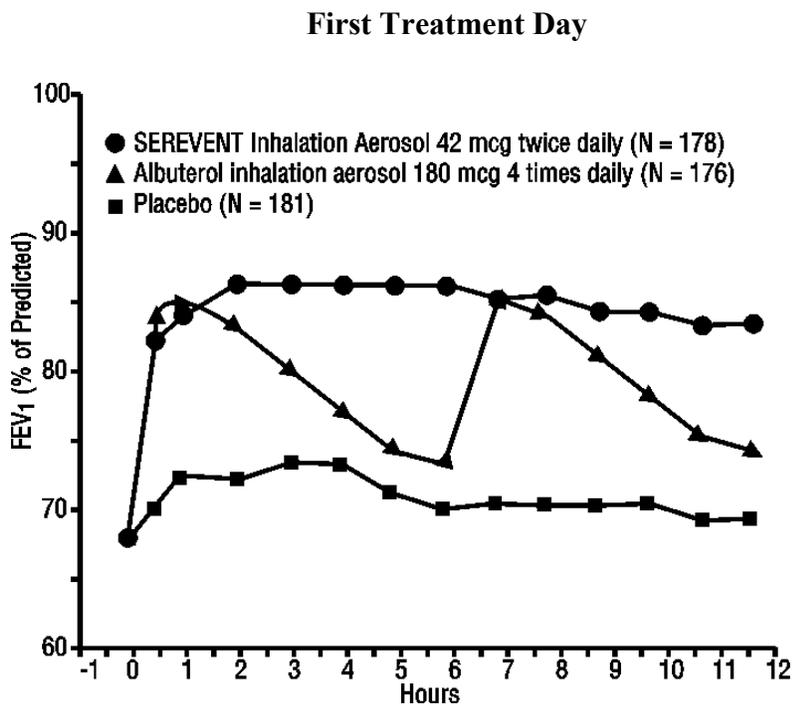
122

123 **Figure 1. FEV₁, as Percent of Predicted, From 2 Large**
124 **12-Week Clinical Trials**

125

126

127

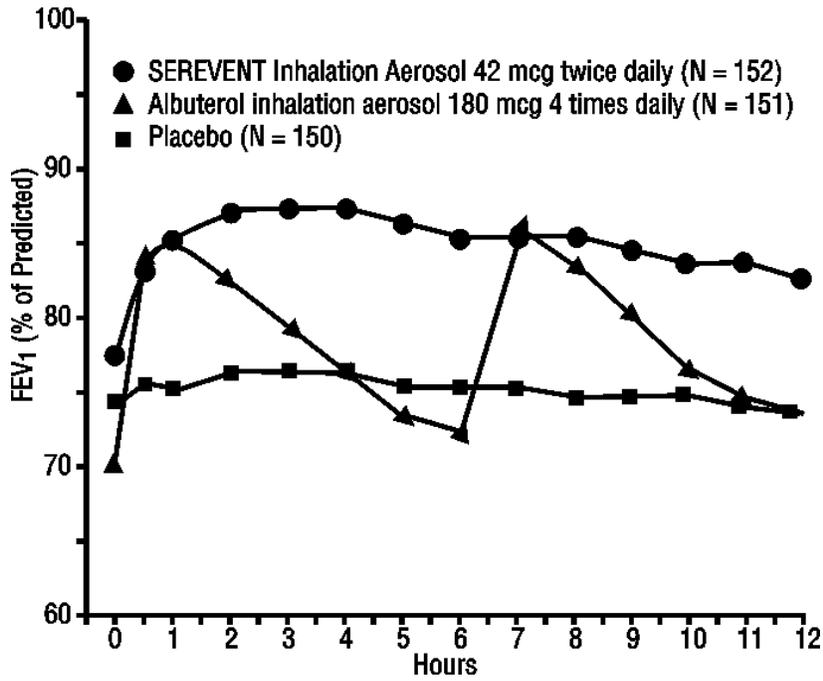


128

129

130
131

Last Treatment Day (Week 12)



132
133
134
135
136

Table 1 shows the treatment effects seen during daily treatment with SEREVENT Inhalation Aerosol for 12 weeks in patients with asthma.

137 **Table 1. Daily Efficacy Measurements in 2 Large 12-Week Clinical Trials (Combined**
 138 **Data)**

Parameter	Time	Placebo	SEREVENT Inhalation Aerosol	Albuterol Inhalation Aerosol
No. of randomized subjects		187	184	185
Mean AM peak expiratory flow (L/min)	baseline	412	409	398
	12 weeks	414	438*	390
Mean % days with no asthma symptoms	baseline	11	11	14
	12 weeks	17	35*	24
Mean % nights with no awakenings	baseline	67	67	65
	12 weeks	74	87*	74
Rescue medications (mean no. of inhalations per day)	baseline	4.4	4.1	4.0
	12 weeks	3.3	1.3 ^{†‡}	1.9
Asthma exacerbations		17%	11%	14%

139 *p<0.001 versus albuterol and placebo.

140 †p<0.05 versus albuterol.

141 ‡p<0.001 versus placebo.

142

143 Safe usage with maintenance of efficacy for periods up to 1 year has been documented.

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

150 Two randomized, double-blind, parallel-group clinical trials (N = 997) enrolled patients (ages
 151 18 to 82 years) with persistent asthma who were previously maintained but not adequately
 152 controlled on inhaled corticosteroid therapy. During the 2-week run-in period, all patients were
 153 switched to beclomethasone dipropionate 168 mcg twice daily. Patients still not adequately
 154 controlled were randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg
 155 twice daily or an increase of beclomethasone dipropionate to 336 mcg twice daily. As compared
 156 to the doubled dose of beclomethasone dipropionate, the addition of salmeterol resulted in
 157 statistically significantly greater improvements in pulmonary function and asthma symptoms,
 158 and statistically significantly greater reduction in supplemental albuterol use. The percent of
 159 patients who experienced asthma exacerbations overall was not different between groups (i.e.,
 160 16.2% in the salmeterol group versus 17.9% in the higher-dose beclomethasone dipropionate
 161 group).

162 Two randomized, double-blind, parallel-group clinical trials (N = 925) enrolled patients (ages
163 12 to 78 years) with persistent asthma who were previously maintained but not adequately
164 controlled on prior therapy. During the 2- to 4-week run-in period, all patients were switched to
165 fluticasone propionate 88 mcg twice daily. Patients still not adequately controlled were
166 randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg twice daily or an
167 increase of fluticasone propionate to 220 mcg twice daily. As compared to the increased
168 (2.5 times) dose of fluticasone propionate, the addition of salmeterol resulted in statistically
169 significantly greater improvements in pulmonary function and asthma symptoms, and
170 statistically significantly greater reduction in supplemental albuterol use. Fewer patients
171 receiving salmeterol experienced asthma exacerbations than those receiving the higher dose of
172 fluticasone propionate (8.8% versus 13.8%).

173 **Salmeterol Multi-center Asthma Research Trial:** The Salmeterol Multi-center
174 Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled
175 long-acting beta₂-agonist-naïve patients with asthma (average age of 39 years, 71% Caucasian,
176 18% African American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation
177 Aerosol, 42 mcg twice daily over 28 weeks) compared to placebo when added to usual asthma
178 therapy. The primary endpoint was the combined number of respiratory-related deaths or
179 respiratory-related life-threatening experiences (intubation and mechanical ventilation).
180 Secondary endpoints included combined asthma-related deaths or life-threatening experiences
181 and asthma-related deaths. A planned interim analysis was conducted when approximately half
182 of the intended number of patients had been enrolled (N = 26,355).

183 Due to the low rate of primary events in the study, the findings of the planned interim analysis
184 were not conclusive. However, analyses of secondary endpoints suggested that patients receiving
185 salmeterol may be at increased risk for some of these events compared to patients receiving
186 placebo. The analysis for the total population showed a relative risk of 1.40 (95% CI 0.91, 2.14)
187 for the primary endpoint in the salmeterol group relative to the placebo group (50 out of 13,176
188 vs. 36 out of 13,179, respectively). In the total population, a higher number of asthma-related
189 deaths (13 vs. 3, RR 4.37, 95% CI 1.25, 15.34) and combined asthma-related deaths or life-
190 threatening experiences (37 vs. 22, RR 1.71, 95% CI 1.01, 2.89) occurred in patients treated with
191 salmeterol than those treated with placebo. The analysis of the African American subgroup
192 showed a relative risk of 4.10 (95% CI 1.54, 10.90) for the primary endpoint in patients treated
193 with salmeterol relative to those treated with placebo (20 out of 2,366 vs. 5 out of 2,319,
194 respectively). In African Americans, a higher number of asthma-related deaths (7 vs. 1, RR 7.26,
195 95% CI 0.89, 58.94) and combined asthma-related deaths or life-threatening experiences (19 vs.
196 4, RR 4.92, 95% CI 1.68, 14.45) occurred in patients treated with salmeterol than those treated
197 with placebo. Analysis of the Caucasian population showed a relative risk of 1.05 (95% CI 0.62,
198 1.76) for the primary endpoint for those treated with salmeterol relative to those treated with
199 placebo (29 out of 9,281 vs. 28 out of 9,361, respectively). In Caucasians, a higher number of
200 asthma-related deaths (6 vs. 1, RR 5.82, 95% CI 0.70, 48.37) occurred in patients treated with
201 salmeterol than in patients treated with placebo. In Caucasians, the relative risk was 1.08 (17 vs.

202 16, 95% CI 0.55, 2.14) for combined asthma-related deaths or life-threatening experiences in
 203 patients treated with salmeterol relative to placebo. The numbers of patients from other ethnic
 204 groups were too small to draw any conclusions in these populations. Even though SMART did
 205 not reach predetermined stopping criteria for the total population, the study was stopped due to
 206 the findings in African American patients and difficulties in enrollment.

207 **Exercise-Induced Bronchospasm:** Protection against exercise-induced bronchospasm
 208 (EIB) was examined in 3 controlled studies. Based on median values, patients who received
 209 SEREVENT Inhalation Aerosol had consistently less exercise-induced fall in FEV₁ than patients
 210 who received placebo, and they were protected for a longer period of time than patients who
 211 received albuterol (see Table 2). There were, however, some patients who were not protected
 212 from EIB after SEREVENT administration and others in whom protection against EIB decreased
 213 with continued administration over a period of 4 weeks.

214

215 **Table 2. Exercise-Induced Bronchospasm Mean Percentage Fall in Postexercise FEV₁**

Clinical Trials/Time After Dose	Treatment		
	Placebo	SEREVENT Inhalation Aerosol	Albuterol Inhalation Aerosol
Study A: 1st Dose			
6 hours	37	9*	
12 hours	27	16*	
Study A: 4th Week			
6 hours	30	19	
12 hours	24	12	
Study B:			
1 hour	37	0*	2*
6 hours	37	5*†	27
12 hours	34	6*†	33
Study C:			
0.5 hour	43	16*	8*
2.5 hours	33	12*†	30
4.5 hours	--	12†	36
6.0 hours	--	19†	41

216 *Statistically superior to placebo (p≤0.05).

217 †Statistically superior to albuterol (p≤0.05).

218

219 **Chronic Obstructive Pulmonary Disease:** In 2 large randomized, double-blind studies,
 220 SEREVENT Inhalation Aerosol administered twice daily was compared with placebo and
 221 ipratropium bromide inhalation aerosol administered 4 times daily in patients with COPD

222 (emphysema and chronic bronchitis), including patients who were reversible ($\geq 12\%$ and
 223 ≥ 200 mL increase in baseline FEV₁ after albuterol treatment) and nonreversible to albuterol.
 224 After a single 42-mcg dose of SEREVENT, significant improvement in pulmonary function
 225 (mean FEV₁ increase of 12% or more) occurred within 30 minutes, reached a peak within
 226 4 hours on average, and persisted for 12 hours with no loss in effectiveness observed over a
 227 12-week treatment period. Figure 2 displays serial 12-hour measurements of FEV₁ from these
 228 two 12-week trials for both the first and last treatment days.

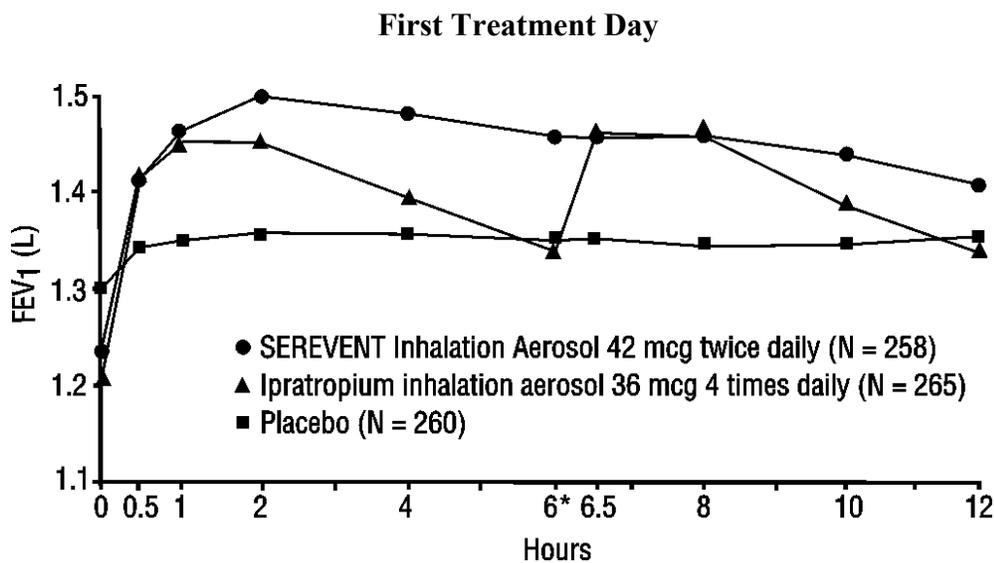
229

230 **Figure 2. FEV₁ From 2 Large 12-Week Clinical Trials**

231

232

233



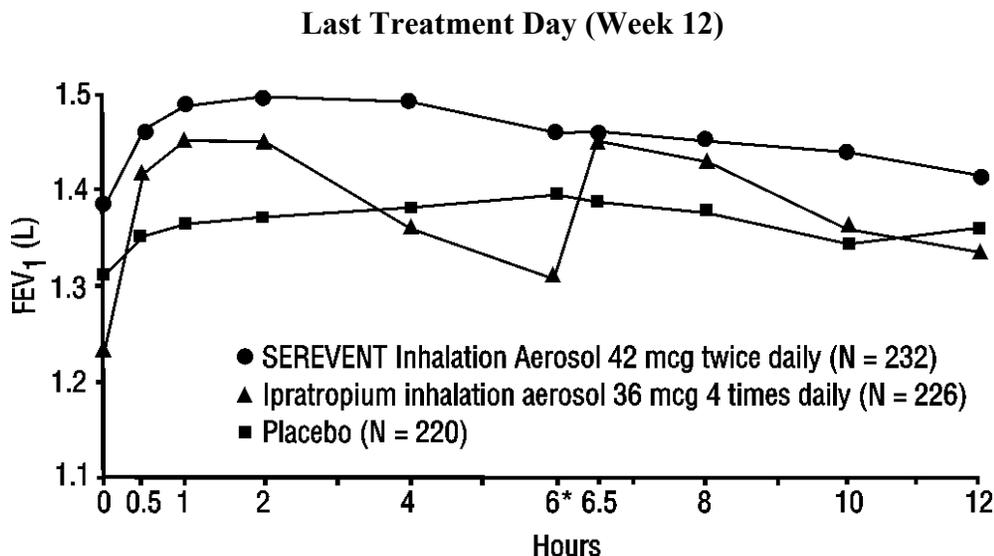
234

235

236 * Ipratropium inhalation aerosol (or matching placebo) administered immediately
 237 following hour 6 assessment.

238

239
240



241
242

* Ipratropium inhalation aerosol (or matching placebo) administered immediately following hour 6 assessment.

245

INDICATIONS AND USAGE

247 **Asthma:** SEREVENT Inhalation Aerosol is indicated for long-term, twice-daily (morning and
248 evening) administration in the maintenance treatment of asthma and in the prevention of
249 bronchospasm in patients 12 years of age and older with reversible obstructive airway disease,
250 including patients with symptoms of nocturnal asthma, who require regular treatment with
251 inhaled, short-acting beta₂-agonists. It should not be used in patients whose asthma can be
252 managed by occasional use of inhaled, short-acting beta₂-agonists.

253 SEREVENT Inhalation Aerosol may be used alone or in combination with inhaled or
254 systemic corticosteroid therapy.

255 SEREVENT Inhalation Aerosol is also indicated for prevention of exercise-induced
256 bronchospasm in patients 12 years of age and older.

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

260

CONTRAINDICATIONS

262 SEREVENT Inhalation Aerosol is contraindicated in patients with a history of
263 hypersensitivity to salmeterol or any other component of the drug product (see DESCRIPTION).

264

WARNINGS

266 DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS
267 STOPPED EARLY SUGGEST THAT SALMETEROL MAY BE ASSOCIATED WITH RARE
268 SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. Data from this study,

269 called the Salmeterol Multi-center Asthma Research Trial (SMART), further suggest that the risk
270 might be greater in African American patients. These results led to stopping the study
271 prematurely (see CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research*
272 *Trial*). The data from the SMART study are not adequate to determine whether concurrent use of
273 inhaled corticosteroids provides protection from this risk. Given the similar basic mechanisms of
274 action of beta₂-agonists, it is possible that the findings seen in the SMART study may be
275 consistent with a class effect.

276 Findings similar to the SMART study findings were reported in a prior 16-week clinical study
277 performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the
278 SNS study, the incidence of asthma-related death was numerically, though not statistically,
279 greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol
280 (180 mcg 4 times daily) added to usual asthma therapy.

281 **SEREVENT INHALATION AEROSOL SHOULD NOT BE INITIATED IN**
282 **PATIENTS WITH SIGNIFICANTLY WORSENING OR ACUTELY DETERIORATING**
283 **ASTHMA, WHICH MAY BE A LIFE-THREATENING CONDITION. Serious acute**
284 **respiratory events, including fatalities, have been reported, both in the United States and**
285 **worldwide, when SEREVENT Inhalation Aerosol has been initiated in this situation.**

286 **Although it is not possible from these reports to determine whether SEREVENT**
287 **Inhalation Aerosol contributed to these adverse events or simply failed to relieve the**
288 **deteriorating asthma, the use of SEREVENT Inhalation Aerosol in this setting is**
289 **inappropriate.**

290 **SEREVENT INHALATION AEROSOL SHOULD NOT BE USED TO TREAT**
291 **ACUTE SYMPTOMS. It is crucial to inform patients of this and prescribe an inhaled,**
292 **short-acting beta₂-agonist for this purpose as well as warn them that increasing inhaled**
293 **beta₂-agonist use is a signal of deteriorating asthma.**

294 **SEREVENT INHALATION AEROSOL IS NOT A SUBSTITUTE FOR INHALED OR**
295 **ORAL CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced when**
296 **SEREVENT Inhalation Aerosol is initiated.**

297 **(See PRECAUTIONS: Information for Patients and the PATIENT'S INSTRUCTIONS**
298 **FOR USE accompanying the product.)**

299 1. Do Not Introduce SEREVENT Inhalation Aerosol as a Treatment for Acutely Deteriorating
300 Asthma: SEREVENT Inhalation Aerosol is intended for the maintenance treatment of asthma
301 (see INDICATIONS AND USAGE) and should not be introduced in acutely deteriorating
302 asthma, which is a potentially life-threatening condition. There are no data demonstrating that
303 SEREVENT Inhalation Aerosol provides greater efficacy than or additional efficacy to inhaled,
304 short-acting beta₂-agonists in patients with worsening asthma. Serious acute respiratory events,
305 including fatalities, have been reported both in the United States and worldwide in patients
306 receiving SEREVENT Inhalation Aerosol. In most cases, these have occurred in patients with
307 severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary
308 function, intubation, mechanical ventilation, frequent hospitalizations, or previous

309 life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been
310 acutely deteriorating (e.g., unresponsive to usual medications; increasing need for inhaled,
311 short-acting beta₂-agonists; increasing need for systemic corticosteroids; significant increase in
312 symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary
313 function). However, they have occurred in a few patients with less severe asthma as well. It was
314 not possible from these reports to determine whether SEREVENT Inhalation Aerosol
315 contributed to these events or simply failed to relieve the deteriorating asthma.

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

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

326 3. Watch for Increasing Use of Inhaled, Short-Acting Beta₂-Agonists, Which Is a Marker of
327 Deteriorating Asthma: Asthma may deteriorate acutely over a period of hours or chronically
328 over several days or longer. If the patient's inhaled, short-acting beta₂-agonist becomes less
329 effective or the patient needs more inhalations than usual, this may be a marker of
330 destabilization of asthma. In this setting, the patient requires immediate reevaluation with
331 reassessment of the treatment regimen, giving special consideration to the possible need for
332 corticosteroids. If the patient uses 4 or more inhalations per day of an inhaled, short-acting
333 beta₂-agonist for 2 or more consecutive days, or if more than 1 canister (200 inhalations per
334 canister) of inhaled, short-acting beta₂-agonist is used in an 8-week period in conjunction with
335 SEREVENT Inhalation Aerosol, then the patient should consult the physician for reevaluation.
336 **Increasing the daily dosage of SEREVENT Inhalation Aerosol in this situation is not**
337 **appropriate. SEREVENT Inhalation Aerosol should not be used more frequently than**
338 **twice daily (morning and evening) at the recommended dose of 2 inhalations.**

339 4. Do Not Use SEREVENT Inhalation Aerosol as a Substitute for Oral or Inhaled
340 Corticosteroids: The use of beta-adrenergic agonist bronchodilators alone may not be adequate
341 to control asthma in many patients. Early consideration should be given to adding
342 anti-inflammatory agents, e.g., corticosteroids. There are no data demonstrating that
343 SEREVENT Inhalation Aerosol has a clinical anti-inflammatory effect and could be expected to
344 take the place of corticosteroids. Patients who already require oral or inhaled corticosteroids for
345 treatment of asthma should be continued on this type of treatment even if they feel better as a
346 result of initiating SEREVENT Inhalation Aerosol. Any change in corticosteroid dosage should
347 be made ONLY after clinical evaluation (see PRECAUTIONS: Information for Patients).

348 5. Do Not Exceed Recommended Dosage: As with other inhaled beta₂-adrenergic drugs,
349 SEREVENT Inhalation Aerosol should not be used more often or at higher doses than
350 recommended. Fatalities have been reported in association with excessive use of inhaled
351 sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the
352 recommended dose) have been associated with clinically significant prolongation of the QTc
353 interval, which has the potential for producing ventricular arrhythmias.

354 6. Paradoxical Bronchospasm: SEREVENT Inhalation Aerosol can produce paradoxical
355 bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs,
356 SEREVENT Inhalation Aerosol should be discontinued immediately and alternative therapy
357 instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled
358 formulations, frequently occurs with the first use of a new canister or vial.

359 7. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after
360 administration of SEREVENT Inhalation Aerosol, as demonstrated by rare cases of urticaria,
361 angioedema, rash, and bronchospasm.

362 8. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as
363 stridor and choking, have been reported rarely in patients receiving SEREVENT Inhalation
364 Aerosol.

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

375

376 **PRECAUTIONS**

377 **General:** 1. Use With Spacer or Other Devices: The safety and effectiveness of SEREVENT
378 Inhalation Aerosol when used with a spacer or other devices have not been adequately studied.

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

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

390 3. Metabolic Effects: Doses of the related beta₂-adrenoceptor agonist albuterol, when
391 administered intravenously, have been reported to aggravate preexisting diabetes mellitus and
392 ketoacidosis. No effects on glucose have been seen with SEREVENT Inhalation Aerosol at
393 recommended doses. Beta-adrenergic agonist medications may produce significant hypokalemia
394 in some patients, possibly through intracellular shunting, which has the potential to produce
395 adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

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

399 **Information for Patients:** See illustrated PATIENT'S INSTRUCTIONS FOR USE. **SHAKE**
400 **WELL BEFORE USING.**

401 It is important that patients understand how to use SEREVENT Inhalation Aerosol
402 appropriately and how it should be used in relation to other asthma or COPD medications they
403 are taking. Patients should be given the following information:

- 404 1. Shake well before using.
- 405 2. The action of SEREVENT Inhalation Aerosol may last up to 12 hours or longer. The
406 recommended dosage (2 inhalations twice daily, morning and evening) should not be exceeded.
- 407 3. SEREVENT Inhalation Aerosol is not meant to relieve acute asthma or COPD symptoms
408 and extra doses should not be used for that purpose. Acute symptoms should be treated with an
409 inhaled, short-acting beta₂-agonist such as albuterol (the physician should provide the patient
410 with such medication and instruct the patient in how it should be used).
- 411 4. Patients should not stop SEREVENT therapy for asthma or COPD without
412 physician/provider guidance since symptoms may recur after discontinuation.
- 413 5. The physician should be notified immediately if any of the following situations occur, which
414 may be a sign of seriously worsening asthma.
 - 415 • Decreasing effectiveness of inhaled, short-acting beta₂-agonists
 - 416 • Need for more inhalations than usual of inhaled, short-acting beta₂-agonists
 - 417 • Use of 4 or more inhalations per day of a short-acting beta₂-agonist for 2 or more days
418 consecutively
 - 419 • Use of more than one 200-inhalation canister of an inhaled, short-acting beta₂-agonist
420 (e.g., albuterol) in an 8-week period
- 421 6. SEREVENT Inhalation Aerosol should not be used as a substitute for oral or inhaled
422 corticosteroids. The dosage of these medications should not be changed and they should not be
423 stopped without consulting the physician, even if the patient feels better after initiating treatment
424 with SEREVENT Inhalation Aerosol.
- 425 7. Patients should be cautioned regarding common adverse cardiovascular effects, such as
426 palpitations, chest pain, rapid heart rate, tremor, or nervousness.

427 8. In patients receiving SEREVENT Inhalation Aerosol, other inhaled medications should be
428 used only as directed by the physician.

429 9. When using SEREVENT Inhalation Aerosol to prevent exercise-induced bronchospasm,
430 patients should take the dose at least 30 to 60 minutes before exercise.

431 10. Patients who are pregnant or nursing should contact the physician about the use of
432 SEREVENT Inhalation Aerosol.

433 11. Effective and safe use of SEREVENT Inhalation Aerosol includes an understanding of the
434 way that it should be administered.

435 **Drug Interactions: Short-Acting Beta₂-Agonists:** In the two 3-month, repetitive-dose
436 clinical asthma trials (N = 184), the mean daily need for additional beta₂-agonist use was 1 to 1½
437 inhalations/day, but some patients used more. Eight percent (8%) of patients used at least 8
438 inhalations/day at least on 1 occasion. Six percent (6%) used 9 to 12 inhalations at least once.
439 There were 15 patients (8%) who averaged over 4 inhalations/day. Four (4) of these used an
440 average of 8 to 11 inhalations/day. In these 15 patients there was no observed increase in
441 frequency of cardiovascular adverse events. The safety of concomitant use of more than 8
442 inhalations/day of short-acting beta₂-agonists with SEREVENT Inhalation Aerosol has not been
443 established. In 15 patients who experienced worsening of asthma while receiving SEREVENT
444 Inhalation Aerosol, nebulized albuterol (1 dose in most) led to improvement in FEV₁ and no
445 increase in occurrence of cardiovascular adverse events.

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

450 **Corticosteroids and Cromoglycate:** In clinical trials, inhaled corticosteroids and/or
451 inhaled cromolyn sodium did not alter the safety profile of SEREVENT Inhalation Aerosol when
452 administered concurrently.

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

460 Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists,
461 such as SEREVENT Inhalation Aerosol, but may also produce severe bronchospasm in patients
462 with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers.
463 However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may
464 be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with
465 asthma. In this setting, cardioselective beta-blockers could be considered, although they should
466 be administered with caution.

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

472 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In an 18-month oral
473 carcinogenicity study in CD-mice, salmeterol xinafoate at oral doses of 1.4 mg/kg and above
474 (approximately 9 times the maximum recommended daily inhalation dose in adults based on
475 comparison of the areas under the plasma concentration versus time curves [AUCs]) caused
476 dose-related increases in the incidence of smooth muscle hyperplasia, cystic glandular
477 hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of
478 leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg
479 (comparable to the maximum recommended human daily inhalation dose in adults based on
480 comparison of the AUCs).

481 In a 24-month inhalation and oral carcinogenicity study in Sprague Dawley rats, salmeterol
482 caused dose-related increases in the incidence of mesovarian leiomyomas and ovarian cysts at
483 inhalation and oral doses of 0.68 mg/kg/day and above (approximately 55 times the maximum
484 recommended human daily inhalation dose in adults on a mg/m² basis). No tumors were seen at
485 0.21 mg/kg/day (approximately 15 times the maximum recommended human daily inhalation
486 dose in adults on a mg/m² basis). These findings in rodents are similar to those reported
487 previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use
488 is unknown.

489 Salmeterol xinafoate produced no detectable or reproducible increases in microbial and
490 mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human
491 lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in male
492 and female rats treated orally with salmeterol xinafoate at doses up to 2 mg/kg (approximately
493 160 times the maximum recommended human daily inhalation dose in adults on a mg/m² basis).

494 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. No teratogenic effects occurred in
495 the rat at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended human
496 daily inhalation dose in adults on a mg/m² basis). In pregnant Dutch rabbits administered oral
497 doses of 1 mg/kg and above (approximately 20 times the maximum recommended human daily
498 inhalation dose in adults based on the comparison of the AUCs), salmeterol xinafoate exhibited
499 fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation; these included
500 precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed
501 ossification of the frontal cranial bones. No significant effects occurred at an oral dose of
502 0.6 mg/kg (approximately 10 times the maximum recommended human daily inhalation dose in
503 adults based on comparison of the AUCs).

504 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal
505 cranial bones was seen at oral doses of 10 mg/kg (approximately 1,600 times the maximum
506 recommended human daily inhalation dose on a mg/m² basis). Extensive use of other

507 beta-agonists has provided no evidence that these class effects in animals are relevant to use in
508 humans. There are no adequate and well-controlled studies with SEREVENT Inhalation Aerosol
509 in pregnant women. SEREVENT Inhalation Aerosol should be used during pregnancy only if the
510 potential benefit justifies the potential risk to the fetus.

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

516 **Nursing Mothers:** Plasma levels of salmeterol after inhaled therapeutic doses are very low. In
517 rats, salmeterol xinafoate is excreted in milk. However, since there is no experience with use of
518 SEREVENT Inhalation Aerosol by nursing mothers, a decision should be made whether to
519 discontinue nursing or to discontinue the drug, taking into account the importance of the drug to
520 the mother. Caution should be exercised when salmeterol xinafoate is administered to a nursing
521 woman.

522 **Pediatric Use:** The safety and effectiveness of SEREVENT Inhalation Aerosol in children
523 younger than 12 years of age have not been established.

524 **Geriatric Use:** Of the total number of patients who received SEREVENT Inhalation Aerosol in
525 all asthma clinical studies, 241 were 65 years of age and older. Geriatric patients (65 years and
526 older) with reversible obstructive airway disease were evaluated in 4 well-controlled studies of 3
527 weeks' to 3 months' duration. Two placebo-controlled, crossover studies evaluated twice-daily
528 dosing with salmeterol for 21 to 28 days in 45 patients. An additional 75 geriatric patients were
529 treated with salmeterol for 3 months in 2 large parallel-group, multicenter studies. These 120
530 patients experienced increases in AM and PM PEF and decreases in diurnal variation in PEF
531 similar to responses seen in the total populations of the 2 latter studies. The adverse event type
532 and frequency in geriatric patients were not different from those of the total populations studied.

533 In 2 large, randomized, double-blind, placebo-controlled 3-month studies involving patients
534 with COPD, 133 patients using SEREVENT Inhalation Aerosol were 65 years and older. These
535 patients experienced similar improvements in FEV₁ as observed for patients younger than 65.

536 No apparent differences in the efficacy and safety of SEREVENT Inhalation Aerosol were
537 observed when geriatric patients were compared with younger patients in asthma and COPD
538 clinical trials. As with other beta₂-agonists, however, special caution should be observed when
539 using SEREVENT Inhalation Aerosol in geriatric patients who have concomitant cardiovascular
540 disease that could be adversely affected by this class of drug. Based on available data, no
541 adjustment of salmeterol dosage in geriatric patients is warranted.

542

543 **ADVERSE REACTIONS**

544 Adverse reactions to salmeterol are similar in nature to reactions to other selective
545 beta₂-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions,

546 including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor;
 547 nervousness; and paradoxical bronchospasm (see WARNINGS).

548 **Asthma:** Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of
 549 SEREVENT Inhalation Aerosol in patients 12 years of age and older with asthma. Table 3
 550 reports the incidence of adverse events in these 2 studies.

551

552 **Table 3. Adverse Event Incidence in 2 Large 12-Week Clinical Trials in Patients With**
 553 **Asthma***

	Percent of Patients		
	Placebo (N = 187)	SEREVENT Inhalation Aerosol 42 mcg Twice Daily (N = 184)	Albuterol Inhalation Aerosol 180 mcg 4 Times Daily (N = 185)
Ear, nose, and throat			
Upper respiratory tract infection	13	14	16*
Nasopharyngitis	12	14	11
Disease of nasal cavity/sinus	4	6	1
Sinus headache	2	4	<1
Gastrointestinal			
Stomachache	0	4	0
Neurological			
Headache	23	28	27
Tremor	2	4	3
Respiratory			
Cough	6	7	3
Lower respiratory infection	2	4	2

554 * The only adverse event classified as serious was 1 case of upper respiratory tract infection in a
 555 patient treated with albuterol.

556

557 Table 3 includes all events (whether considered drug-related or nondrug-related by the
 558 investigator) that occurred at a rate of over 3% in the group treated with SEREVENT Inhalation
 559 Aerosol and were more common in the group treated with SEREVENT Inhalation Aerosol than
 560 in the placebo group.

561 Pharyngitis, allergic rhinitis, dizziness/giddiness, and influenza occurred at 3% or more but
 562 were equally common on placebo. Other events occurring in the group treated with SEREVENT
 563 Inhalation Aerosol at a frequency of 1% to 3% were as follows:

564 **Cardiovascular:** Tachycardia, palpitations.
565 **Ear, Nose, and Throat:** Rhinitis, laryngitis.
566 **Gastrointestinal:** Nausea, viral gastroenteritis, nausea and vomiting, diarrhea, abdominal
567 pain.
568 **Hypersensitivity:** Urticaria.
569 **Mouth and Teeth:** Dental pain.
570 **Musculoskeletal:** Pain in joint, back pain, muscle cramp/contraction, myalgia/myositis,
571 muscular soreness.
572 **Neurological:** Nervousness, malaise/fatigue.
573 **Respiratory:** Tracheitis/bronchitis.
574 **Skin:** Rash/skin eruption.
575 **Urogenital:** Dysmenorrhea.
576 Data from small dose-response studies show an apparent dose relationship for tremor,
577 nervousness, and palpitations.
578 In clinical trials evaluating concurrent therapy of salmeterol with inhaled corticosteroids,
579 adverse events were consistent with those previously reported for salmeterol, or might otherwise
580 be expected with the use of inhaled corticosteroids.
581 **Chronic Obstructive Pulmonary Disease:** Two multicenter, 12-week, controlled studies
582 have evaluated twice-daily doses of SEREVENT Inhalation Aerosol in patients with COPD.
583 Table 4 reports the incidence of adverse events in these 2 studies.
584

585 **Table 4. Adverse Event Incidence in 2 Large 12-Week COPD Clinical Trials in Patients**
 586 **With Chronic Obstructive Pulmonary Disease**

Adverse Event	Percent of Patients		
	Placebo (N = 278)	SEREVENT Inhalation Aerosol 42 mcg Twice Daily (N = 267)	Ipratropium Inhalation Aerosol 36 mcg 4 Times Daily (N = 271)
Ear, nose, and throat			
Upper respiratory tract infection	7	9	9
Sore throat	3	8	6
Nasal sinus infection	1	4	2
Gastrointestinal			
Diarrhea	3	5	4
Musculoskeletal			
Back pain	3	4	3
Neurological			
Headache	10	12	8
Respiratory			
Chest congestion	3	4	3

587
 588 Table 4 includes all events (whether considered drug-related or nondrug-related by the
 589 investigator) that occurred at a rate of over 3% in the group treated with SEREVENT Inhalation
 590 Aerosol and were more common in the group treated with SEREVENT Inhalation Aerosol than
 591 in the placebo group.

592 Common cold, rhinorrhea, bronchitis, cough, exacerbation of chest congestion, chest pain, and
 593 dizziness occurred at 3% or more but were equally common on placebo. Other events occurring
 594 in the group treated with SEREVENT Inhalation Aerosol at a frequency of 1% to 3% were as
 595 follows:

596 **Ear, Nose, and Throat:** Cold symptoms, earache, epistaxis, nasal congestion, nasal sinus
 597 congestion, sneezing.

598 **Gastrointestinal:** Nausea, dyspepsia, gastric pain, gastric upset, abdominal pain,
 599 constipation, heartburn, oral candidiasis, xerostomia, vomiting, surgical removal of tooth.

600 **Musculoskeletal:** Leg cramps, myalgia, neck pain, pain in arm, shoulder pain, muscle
 601 injury of neck.

602 **Neurological:** Insomnia, sinus headache.

603 **Non-Site Specific:** Fatigue, fever, pain in body, discomfort in chest.

604 **Respiratory:** Acute bronchitis, dyspnea, influenza, lower respiratory tract infection,
605 pneumonia, respiratory tract infection, shortness of breath, wheezing.

606 **Urogenital:** Urinary tract infection.

607 **Electrocardiographic Monitoring in Patients With Chronic Obstructive**
608 **Pulmonary Disease:** Continuous electrocardiographic (Holter) monitoring was performed on
609 284 patients in 2 large COPD clinical trials during five 24-hour periods. No cases of sustained
610 ventricular tachycardia were observed. At baseline, non-sustained, asymptomatic ventricular
611 tachycardia was recorded for 7 (7.1%), 8 (9.4%), and 3 (3.0%) patients in the placebo,
612 SEREVENT, and ipratropium groups, respectively. During treatment, nonsustained,
613 asymptomatic ventricular tachycardia that represented a clinically significant change from
614 baseline was reported for 11 (11.6%), 15 (18.3%), and 20 (20.8%) patients receiving placebo,
615 SEREVENT, and ipratropium, respectively. Four of these cases of ventricular tachycardia were
616 reported as adverse events (1 placebo, 3 SEREVENT) by 1 investigator based upon review of
617 Holter data. One case of ventricular tachycardia was observed during ECG evaluation of chest
618 pain (ipratropium) and reported as an adverse event.

619 **Observed During Clinical Practice:** In extensive US and worldwide postmarketing
620 experience, serious exacerbations of asthma, including some that have been fatal, have been
621 reported. In most cases, these have occurred in patients with severe asthma and/or in some
622 patients in whom asthma has been acutely deteriorating (see WARNINGS no. 1), but they have
623 occurred in a few patients with less severe asthma as well. It was not possible from these reports
624 to determine whether SEREVENT Inhalation Aerosol contributed to these events or simply
625 failed to relieve the deteriorating asthma.

626 The following events have also been identified during postapproval use of SEREVENT in
627 clinical practice. Because they are reported voluntarily from a population of unknown size,
628 estimates of frequency cannot be made. These events have been chosen for inclusion due to a
629 combination of their seriousness, frequency of reporting, or potential causal connection to
630 SEREVENT.

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

633 **Cardiovascular:** Hypertension, arrhythmias (including atrial fibrillation, supraventricular
634 tachycardia, extrasystoles).

635

636 **OVERDOSAGE**

637 The expected signs and symptoms with overdosage are those of excessive beta-adrenergic
638 stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE
639 REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to
640 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth,
641 palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with SEREVENT
642 Inhalation Aerosol may be expected to result in exaggeration of the pharmacologic adverse
643 effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia,

644 tremor, headache, and muscle cramps. Overdosage with SEREVENT Inhalation Aerosol can lead
645 to clinically significant prolongation of the QTc interval, which can produce ventricular
646 arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

647 As with all sympathomimetic aerosol medications, cardiac arrest and even death may be
648 associated with abuse of SEREVENT Inhalation Aerosol.

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

654 No deaths were seen in rats at inhalation doses of 2.9 mg/kg (approximately 240 times the
655 maximum recommended human daily inhalation dose on a mg/m² basis) and in dogs at
656 0.7 mg/kg (approximately 190 times the maximum recommended human daily inhalation dose
657 on a mg/m² basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately
658 6,100 times the maximum recommended human daily inhalation dose on a mg/m² basis) and in
659 rats at 1,000 mg/kg (approximately 81,000 times the maximum recommended human daily
660 inhalation dose on a mg/m² basis).

661

662 **DOSAGE AND ADMINISTRATION**

663 SEREVENT Inhalation Aerosol should be administered by the orally inhaled route only (see
664 PATIENT'S INSTRUCTIONS FOR USE). It is recommended to "test spray" SEREVENT
665 Inhalation Aerosol into the air 4 times before using for the first time and in cases where the
666 aerosol has not been used for a prolonged period of time (i.e., more than 4 weeks).

667 **Asthma:** For maintenance of bronchodilatation and prevention of symptoms of asthma,
668 including the symptoms of nocturnal asthma, the usual dosage for patients 12 years of age and
669 older is 2 inhalations (42 mcg) twice daily (morning and evening, approximately 12 hours apart).
670 Adverse effects are more likely to occur with higher doses of salmeterol, and more frequent
671 administration or administration of a larger number of inhalations is not recommended.

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

674 If a previously effective dosage regimen fails to provide the usual response, medical advice
675 should be sought immediately as this is often a sign of destabilization of asthma. Under these
676 circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options,
677 such as inhaled or systemic corticosteroids, should be considered. If symptoms arise in the period
678 between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

679 **Chronic Obstructive Pulmonary Disease:** For maintenance treatment of bronchospasm
680 associated with COPD (including chronic bronchitis and emphysema), the usual dosage for
681 adults is 2 inhalations (42 mcg) twice daily (morning and evening, approximately 12 hours
682 apart).

683 **Prevention of Exercise-Induced Bronchospasm:** Two inhalations at least 30 to
684 60 minutes before exercise have been shown to protect against EIB in many patients for up to
685 12 hours. Additional doses of SEREVENT Inhalation Aerosol should not be used for 12 hours
686 after the administration of this drug. Patients who are receiving SEREVENT Inhalation Aerosol
687 twice daily (morning and evening) should not use additional SEREVENT Inhalation Aerosol for
688 prevention of EIB. If this dose is not effective, other appropriate therapy for EIB should be
689 considered.

690 **Geriatric Use:** In studies where geriatric patients (65 years of age or older, see
691 PRECAUTIONS) have been treated with SEREVENT Inhalation Aerosol, efficacy and safety of
692 42 mcg given twice daily (morning and evening) did not differ from that in younger patients.
693 Consequently, no dosage adjustment is recommended.

694

695 **HOW SUPPLIED**

696 SEREVENT Inhalation Aerosol is supplied in 13-g canisters containing 120 metered
697 actuations in boxes of 1. Each actuation delivers 25 mcg of salmeterol base (as salmeterol
698 xinafoate) from the valve and 21 mcg of salmeterol base (as salmeterol xinafoate) from the
699 actuator. Each canister is supplied with a green plastic actuator with a teal strapcap and patient's
700 instructions (NDC 0173-0464-00). Also available, SEREVENT Inhalation Aerosol Refill (NDC
701 0173-0465-00), a 13-g canister only with patient's instructions.

702 SEREVENT Inhalation Aerosol is also supplied in institutional packs that consist of a 6.5-g
703 canister containing 60 metered actuations in boxes of 1. Each actuation delivers 25 mcg of
704 salmeterol base (as salmeterol xinafoate) from the valve and 21 mcg of salmeterol base from the
705 actuator (as salmeterol xinafoate). Each canister is supplied with a green plastic actuator with a
706 teal strapcap and patient's instructions (NDC 0173-0467-00).

707 For use with SEREVENT Inhalation Aerosol actuator only. The green actuator with
708 SEREVENT Inhalation Aerosol should not be used with other aerosol medications, and actuators
709 from other aerosol medications should not be used with a SEREVENT Inhalation Aerosol
710 canister.

711 The correct amount of medication in each inhalation cannot be assured after 120 actuations
712 from the 13-g canister or 60 actuations from the 6.5-g canister even though the canister is not
713 completely empty. The canister should be discarded when the labeled number of actuations has
714 been used.

715 Store between 15° and 30°C (59° and 86°F). Store canister with nozzle end down. Protect from
716 freezing temperatures and direct sunlight.

717 Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store
718 at temperatures above 120°F. Keep out of reach of children. As with most inhaled medications in
719 aerosol canisters, the therapeutic effect of this medication may decrease when the canister is
720 cold; for best results, the canister should be at room temperature before use. Shake well before
721 using.

722

723 **Note:** The indented statement below is required by the Federal government’s Clean Air Act for
724 all products containing or manufactured with chlorofluorocarbons (CFCs).

725
726 **WARNING:** Contains trichlorofluoromethane and dichlorodifluoromethane,
727 substances that harm public health and environment by destroying ozone in the upper
728 atmosphere.

729
730 A notice similar to the above WARNING has been placed in the patient information leaflet of
731 this product pursuant to EPA regulations. The patient’s warning states that the patient should
732 consult his or her physician if there are questions about alternatives.

733
734



735
736 GlaxoSmithKline
737 Research Triangle Park, NC 27709

738
739 ©Year, GlaxoSmithKline. All rights reserved.

740
741 Month Year RL-

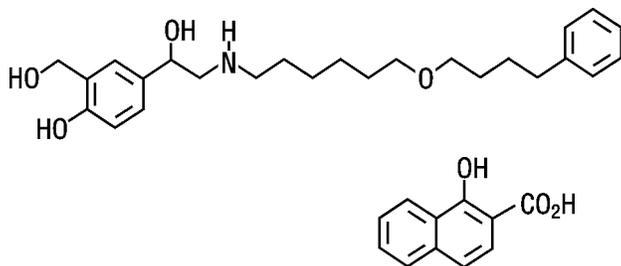
SEREVENT[®] DISKUS[®]
(salmeterol xinafoate inhalation powder)

FOR ORAL INHALATION ONLY

WARNING: 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 a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks) versus those on placebo (3 of 13,179) (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).

DESCRIPTION

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



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

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

33 Under standardized in vitro test conditions, SEREVENT DISKUS delivers 47 mcg when
34 tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and
35 severely compromised lung function (mean forced expiratory volume in 1 second [FEV₁] 20% to
36 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS was 82.4 L/min (range,
37 46.1 to 115.3 L/min).

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

40

41 **CLINICAL PHARMACOLOGY**

42 **Mechanism of Action:** Salmeterol is a selective, long-acting beta₂-adrenergic agonist. In vitro
43 studies and in vivo pharmacologic studies demonstrate that salmeterol is selective for
44 beta₂-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity
45 on beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more
46 selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the
47 predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the
48 predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart
49 comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors
50 has not been established, but they raise the possibility that even highly selective beta₂-agonists
51 may have cardiac effects.

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

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

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

67 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low or
68 undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder
69 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol
70 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in
71 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of
72 167 pg/mL at 20 minutes and no accumulation with repeated doses.

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

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

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

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

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

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

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

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

109 No effect of treatment with salmeterol 50 mcg was observed on pulse rate and systolic and
110 diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial vital
111 sign measurements after the first dose (N = 91) and after 12 weeks of therapy (N = 74). Median

112 changes from baseline in pulse rate and systolic and diastolic blood pressure were similar for
113 patients receiving either salmeterol or placebo (see ADVERSE REACTIONS).

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

118

119 **CLINICAL TRIALS**

120 **Asthma:** During the initial treatment day in several multiple-dose clinical trials with
121 SEREVENT DISKUS in patients with asthma, the median time to onset of clinically significant
122 bronchodilatation ($\geq 15\%$ improvement in FEV₁) ranged from 30 to 48 minutes after a 50-mcg
123 dose.

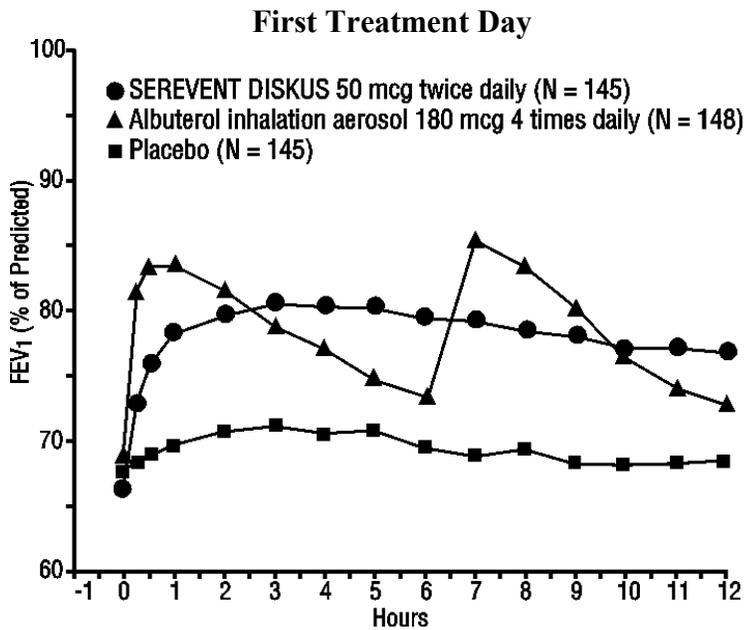
124 One hour after a single dose of 50 mcg of SEREVENT DISKUS, the majority of patients had
125 $\geq 15\%$ improvement in FEV₁. Maximum improvement in FEV₁ generally occurred within
126 180 minutes, and clinically significant improvement continued for 12 hours in most patients.

127 In 2 randomized, double-blind studies, SEREVENT DISKUS was compared with albuterol
128 inhalation aerosol and placebo in adolescent and adult patients with mild-to-moderate asthma
129 (protocol defined as 50% to 80% predicted FEV₁, actual mean of 67.7% at baseline), including
130 patients who did and who did not receive concurrent inhaled corticosteroids. The efficacy of
131 SEREVENT DISKUS was demonstrated over the 12-week period with no change in
132 effectiveness over this time period (see Figure 1). There were no gender- or age-related
133 differences in safety or efficacy. No development of tachyphylaxis to the bronchodilator effect
134 was noted in these studies. FEV₁ measurements (mean change from baseline) from these two
135 12-week studies are shown in Figure 1 for both the first and last treatment days.

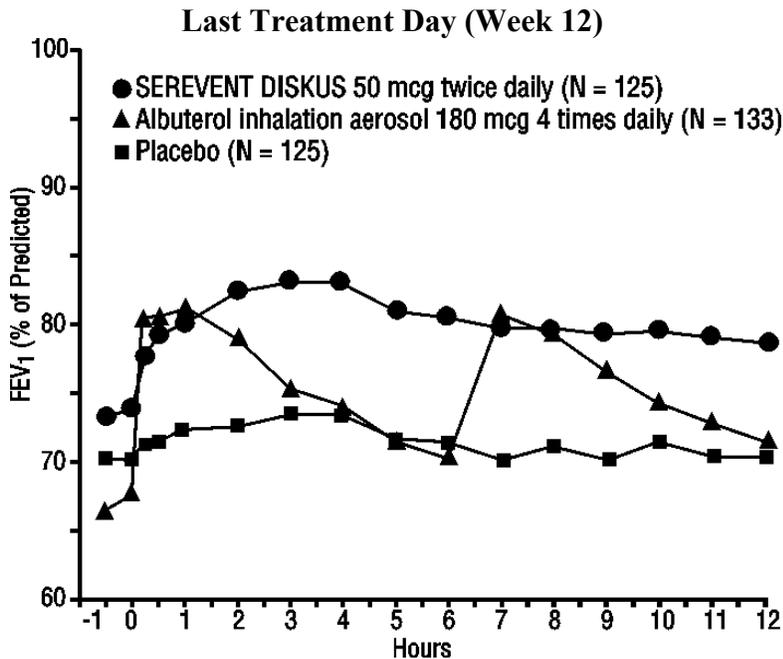
136

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

139
 140



141
 142
 143



144
 145
 146
 147
 148

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

149 **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%

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

151 †Statistically superior to placebo (p<0.001).

152
153 Safe usage with maintenance of efficacy for periods up to 1 year has been documented.

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

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

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

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

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

195 Two randomized, double-blind, parallel-group clinical trials (N = 925) enrolled patients (ages
196 12 to 78 years) with persistent asthma who were previously maintained but not adequately
197 controlled on prior therapy. During the 2- to 4-week run-in period, all patients were switched to
198 fluticasone propionate 88 mcg twice daily. Patients still not adequately controlled were
199 randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg twice daily or an
200 increase of fluticasone propionate to 220 mcg twice daily. As compared to the increased (2.5
201 times) dose of fluticasone propionate, the addition of SEREVENT Inhalation Aerosol resulted in
202 statistically significantly greater improvements in pulmonary function and asthma symptoms, and
203 statistically significantly greater reductions in supplemental albuterol use. Fewer patients
204 receiving SEREVENT Inhalation Aerosol experienced asthma exacerbations than those receiving
205 the higher dose of fluticasone propionate (8.8% versus 13.8%).

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

210

211 **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)	

212
 213 In 2 randomized studies in children 4 to 11 years old with asthma and EIB (N = 50), a single
 214 50-mcg dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise,
 215 with protection lasting up to 11.5 hours in repeat testing following this single dose in many
 216 patients.

217 **Salmeterol Multi-center Asthma Research Trial:** The Salmeterol Multi-center Asthma
 218 Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting
 219 beta₂-agonist-naïve patients with asthma (average age of 39 years, 71% Caucasian, 18% African
 220 American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol, 42
 221 mcg twice daily over 28 weeks) compared to placebo when added to usual asthma therapy. The
 222 primary endpoint was the combined number of respiratory-related deaths or respiratory-related
 223 life-threatening experiences (intubation and mechanical ventilation). Secondary endpoints
 224 included combined asthma-related deaths or life-threatening experiences and asthma-related
 225 deaths. A planned interim analysis was conducted when approximately half of the intended
 226 number of patients had been enrolled (N = 26,355).

227 Due to the low rate of primary events in the study, the findings of the planned interim analysis
 228 were not conclusive. However, analyses of secondary endpoints suggested that patients receiving
 229 salmeterol may be at increased risk for some of these events compared to patients receiving
 230 placebo. The analysis for the total population showed a relative risk of 1.40 (95% CI 0.91, 2.14)
 231 for the primary endpoint in the salmeterol group relative to the placebo group (50 out of 13,176
 232 vs. 36 out of 13,179, respectively). In the total population, a higher number of asthma-related
 233 deaths (13 vs. 3, RR 4.37, 95% CI 1.25, 15.34) and combined asthma-related deaths or life-

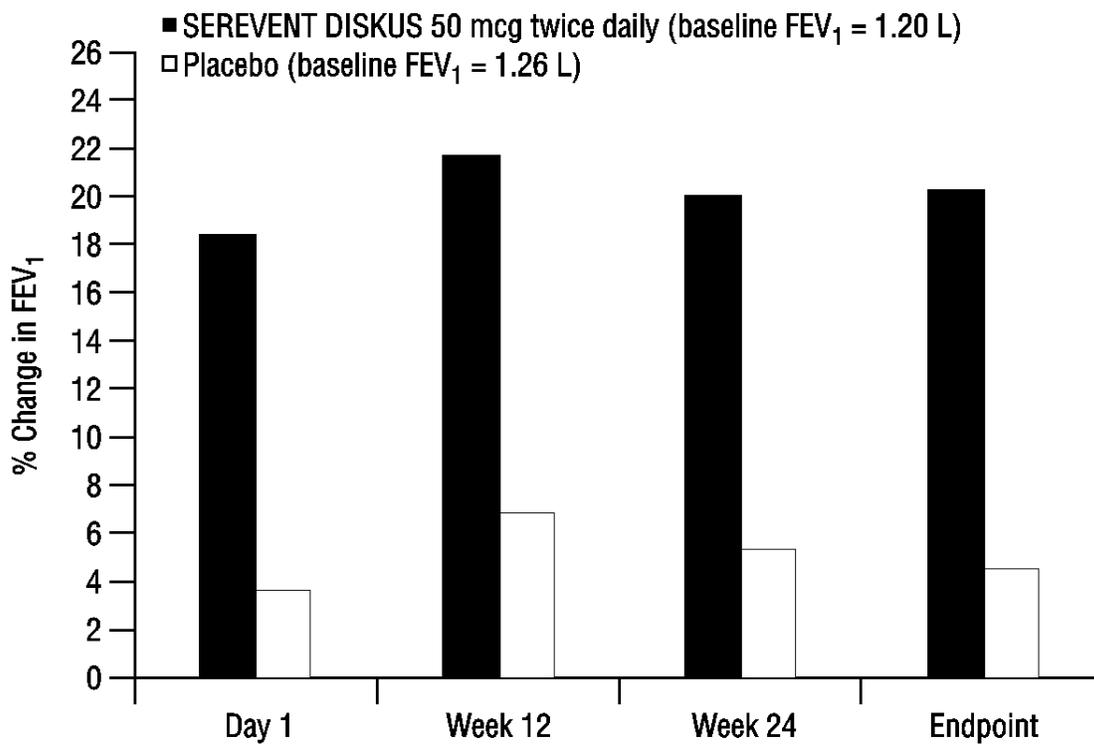
234 threatening experiences (37 vs. 22, RR 1.71, 95% CI 1.01, 2.89) occurred in patients treated with
235 salmeterol than those treated with placebo. The analysis of the African American subgroup
236 showed a relative risk of 4.10 (95% CI 1.54, 10.90) for the primary endpoint in patients treated
237 with salmeterol relative to those treated with placebo (20 out of 2,366 vs. 5 out of 2,319,
238 respectively). In African Americans, a higher number of asthma-related deaths (7 vs. 1, RR 7.26,
239 95% CI 0.89, 58.94) and combined asthma-related deaths or life-threatening experiences (19 vs.
240 4, RR 4.92, 95% CI 1.68, 14.45) occurred in patients treated with salmeterol than those treated
241 with placebo. Analysis of the Caucasian population showed a relative risk of 1.05 (95% CI 0.62,
242 1.76) for the primary endpoint for those treated with salmeterol relative to those treated with
243 placebo (29 out of 9,281 vs. 28 out of 9,361, respectively). In Caucasians, a higher number of
244 asthma-related deaths (6 vs. 1, RR 5.82, 95% CI 0.70, 48.37) occurred in patients treated with
245 salmeterol than in patients treated with placebo. In Caucasians, the relative risk was 1.08 (17 vs.
246 16, 95% CI 0.55, 2.14) for combined asthma-related deaths or life-threatening experiences in
247 patients treated with salmeterol relative to placebo. The numbers of patients from other ethnic
248 groups were too small to draw any conclusions in these populations. Even though SMART did
249 not reach predetermined stopping criteria for the total population, the study was stopped due to
250 the findings in African American patients and difficulties in enrollment.

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

259 Figure 2 displays the integrated 2-hour postdose FEV₁ results from the 2 clinical trials. The
260 percent change in FEV₁ refers to the change from baseline, defined as the predose value on
261 Treatment Day 1. To account for patient withdrawals during the study, Endpoint (last evaluable
262 FEV₁) data are provided. Patients receiving SEREVENT DISKUS 50 mcg had significantly
263 greater improvements in 2-hour postdose FEV₁ at Endpoint (216 mL, 20%) compared to placebo
264 (43 mL, 5%). Improvement was apparent on the first day of treatment and maintained throughout
265 the 24 weeks of treatment.

266

267 **Figure 2. Mean Percent Change From Baseline in Postdose FEV₁ Integrated Data From 2**
 268 **Trials of Patients With Chronic Bronchitis and Airflow Limitation**
 269

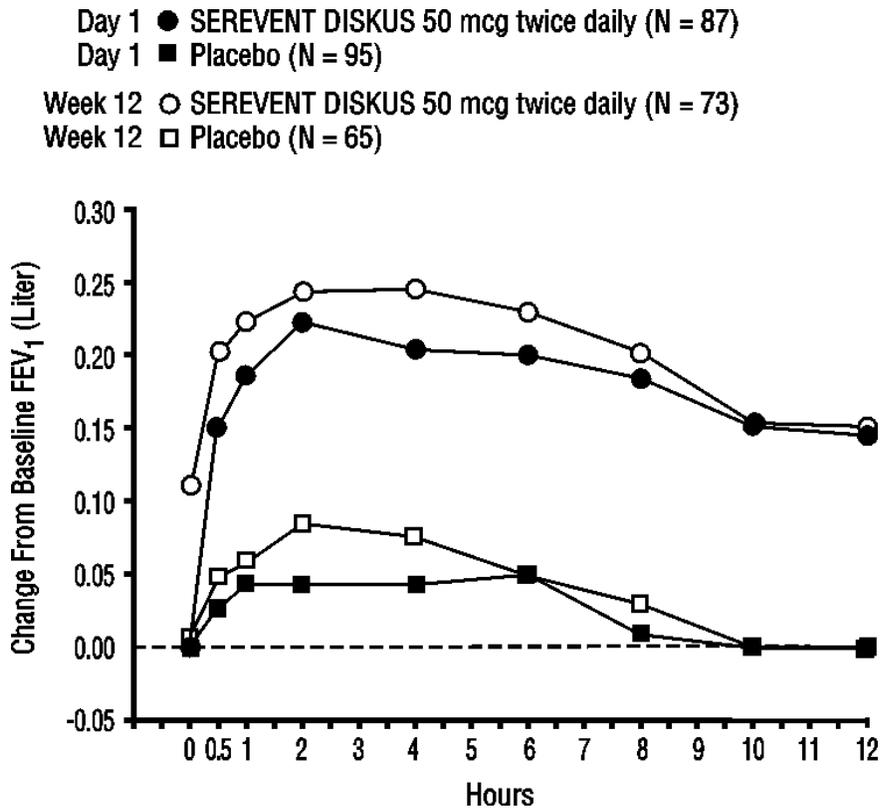


	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
SEREVENT DISKUS 50 mcg twice daily	335	265	222	326
Placebo	361	264	226	343

270
 271
 272 **Onset of Action and Duration of Effect:** The onset of action and duration of effect of
 273 SEREVENT DISKUS were evaluated in a subset of patients (n = 87) from 1 of the 2 clinical
 274 trials discussed above. Following the first 50-mcg dose, significant improvement in pulmonary
 275 function (mean FEV₁ increase of 12% or more and at least 200 mL) occurred at 2 hours. The
 276 mean time to peak bronchodilator effect was 4.75 hours. As seen in Figure 3, evidence of
 277 bronchodilatation was seen throughout the 12-hour period. Figure 3 also demonstrates that the
 278 bronchodilating effect after 12 weeks of treatment was similar to that observed after the first
 279 dose. The mean time to peak bronchodilator effect after 12 weeks of treatment was 3.27 hours.
 280

281 **Figure 3. Serial 12-Hour FEV₁ on the First Day and at Week**
 282 **12 of Treatment**

283



284

285

286 **INDICATIONS AND USAGE**

287 **Asthma:** SEREVENT DISKUS is indicated for long-term, twice-daily (morning and evening)
 288 administration in the maintenance treatment of asthma and in the prevention of bronchospasm in
 289 patients 4 years of age and older with reversible obstructive airway disease, including patients
 290 with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting
 291 beta₂-agonists. It is not indicated for patients whose asthma can be managed by occasional use of
 292 inhaled, short-acting beta₂-agonists.

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

295 SEREVENT DISKUS may be used alone or in combination with inhaled or systemic
 296 corticosteroid therapy.

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

300

301 **CONTRAINDICATIONS**

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

305

306 **WARNINGS**

307 DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS
308 STOPPED EARLY SUGGEST THAT SALMETEROL MAY BE ASSOCIATED WITH RARE
309 SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. Data from this study,
310 called the Salmeterol Multi-center Asthma Research Trial (SMART), further suggest that the risk
311 might be greater in African American patients. These results led to stopping the study
312 prematurely (see CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).
313 The data from the SMART study are not adequate to determine whether concurrent use of
314 inhaled corticosteroids provides protection from this risk. Given the similar basic mechanisms of
315 action of beta₂-agonists, it is possible that the findings seen in the SMART study may be
316 consistent with a class effect.

317 Findings similar to the SMART study findings were reported in a prior 16-week clinical study
318 performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the
319 SNS study, the incidence of asthma-related death was numerically, though not statistically,
320 greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol
321 (180 mcg 4 times daily) added to usual asthma therapy.

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

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

330 **SEREVENT DISKUS SHOULD NOT BE USED TO TREAT ACUTE SYMPTOMS. It**
331 **is crucial to inform patients of this and prescribe an inhaled, short-acting beta₂-agonist for**
332 **this purpose as well as warn them that increasing inhaled beta₂-agonist use is a signal of**
333 **deteriorating asthma.**

334 **SEREVENT DISKUS IS NOT A SUBSTITUTE FOR INHALED OR ORAL**
335 **CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced when**
336 **SEREVENT DISKUS is initiated.**

337 **(See PRECAUTIONS: Information for Patients and the Patient's Instructions for Use**
338 **accompanying the product.)**

339 1. Do Not Introduce SEREVENT DISKUS as a Treatment for Acutely Deteriorating Asthma:
340 SEREVENT DISKUS is intended for the maintenance treatment of asthma (see INDICATIONS
341 AND USAGE) and should not be introduced in acutely deteriorating asthma, which is a

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

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

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

365 3. Watch for Increasing Use of Inhaled, Short-Acting Beta₂-Agonists, Which Is a Marker of
366 Deteriorating Asthma or COPD: The patient's condition may deteriorate acutely over a period of
367 hours or chronically over several days or longer. If the patient's inhaled, short-acting
368 beta₂-agonist becomes less effective, the patient needs more inhalations than usual, or the patient
369 develops a significant decrease in PEF or lung function, these may be markers of destabilization
370 of their disease. In this setting, the patient requires immediate reevaluation with reassessment of
371 the treatment regimen, giving special consideration to the possible need for corticosteroids. If the
372 patient uses 4 or more inhalations per day of an inhaled, short-acting beta₂-agonist for 2 or more
373 consecutive days, or if more than 1 canister (200 inhalations per canister) of inhaled, short-acting
374 beta₂-agonist is used in an 8-week period in conjunction with SEREVENT DISKUS, then the
375 patient should consult the physician for reevaluation. **Increasing the daily dosage of**
376 **SEREVENT DISKUS in this situation is not appropriate. SEREVENT DISKUS should not**
377 **be used more frequently than twice daily (morning and evening) at the recommended dose**
378 **of 1 inhalation.**

379 4. Do Not Use SEREVENT DISKUS as a Substitute for Oral or Inhaled Corticosteroids: The use
380 of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many
381 patients. Early consideration should be given to adding anti-inflammatory agents, e.g.,

382 corticosteroids. There are no data demonstrating that SEREVENT DISKUS has a clinical
383 anti-inflammatory effect and could be expected to take the place of corticosteroids. Patients who
384 already require oral or inhaled corticosteroids for treatment of asthma should be continued on a
385 suitable dose to maintain clinical stability even if they feel better as a result of initiating
386 SEREVENT DISKUS. Any change in corticosteroid dosage should be made ONLY after clinical
387 evaluation (see PRECAUTIONS: Information for Patients).

388 5. Do Not Exceed Recommended Dosage: As with other inhaled beta₂-adrenergic drugs,
389 SEREVENT DISKUS should not be used more often or at higher doses than recommended.
390 Fatalities have been reported in association with excessive use of inhaled sympathomimetic
391 drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have
392 been associated with clinically significant prolongation of the QTc interval, which has the
393 potential for producing ventricular arrhythmias.

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

399 7. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after
400 administration of SEREVENT DISKUS, as demonstrated by cases of urticaria, angioedema, rash,
401 and bronchospasm.

402 8. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as stridor
403 and choking, have been reported in patients receiving SEREVENT DISKUS.

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

413

414 **PRECAUTIONS**

415 **General:** 1. Cardiovascular and Other Effects: No effect on the cardiovascular system is usually
416 seen after the administration of inhaled salmeterol at recommended doses, but the cardiovascular
417 and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood
418 pressure, heart rate, excitement) can occur after use of salmeterol and may require
419 discontinuation of SEREVENT DISKUS. SEREVENT DISKUS, like all sympathomimetic
420 amines, should be used with caution in patients with cardiovascular disorders, especially
421 coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive

422 disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic
423 amines.

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

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

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

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

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

- 443 1. The action of SEREVENT DISKUS may last up to 12 hours or longer. The recommended
444 dosage (1 inhalation twice daily, morning and evening) should not be exceeded.
- 445 2. Most patients are able to taste or feel a dose delivered from SEREVENT DISKUS.
446 However, whether or not patients are able to sense delivery of a dose, you should instruct
447 them not to exceed the recommended dose of 1 inhalation twice daily, morning and evening.
448 You should instruct them to contact you or the pharmacist if they have questions.
- 449 3. SEREVENT DISKUS is not meant to relieve acute asthma or COPD symptoms and extra
450 doses should not be used for that purpose. Acute symptoms should be treated with an
451 inhaled, short-acting bronchodilator (the physician should provide the patient with such
452 medication and instruct the patient in how it should be used).
- 453 4. Patients should not stop therapy with SEREVENT DISKUS for asthma or COPD without
454 physician/provider guidance since symptoms may worsen after discontinuation.
- 455 5. • When used for the treatment of EIB, 1 inhalation of SEREVENT DISKUS should be taken
456 30 minutes before exercise.
457 • Additional doses of SEREVENT should not be used for 12 hours.
458 • Patients who are receiving SEREVENT DISKUS twice daily should not use additional
459 SEREVENT for prevention of EIB.
- 460 6. The physician should be notified immediately if any of the following situations occur, which
461 may be a sign of seriously worsening asthma or COPD:

- 462 • Decreasing effectiveness of inhaled, short-acting beta₂-agonists
- 463 • Need for more inhalations than usual of inhaled, short-acting beta₂-agonists
- 464 • Significant decrease in PEF or lung function as outlined by the physician
- 465 • Use of 4 or more inhalations per day of a short-acting beta₂-agonist for 2 or more days
- 466 consecutively
- 467 • Use of more than 1 canister (200 inhalations per canister) of an inhaled, short-acting
- 468 beta₂-agonist in an 8-week period.
- 469 7. SEREVENT DISKUS should not be used as a substitute for oral or inhaled corticosteroids.
- 470 The dosage of these medications should not be changed and they should not be stopped
- 471 without consulting the physician, even if the patient feels better after initiating treatment
- 472 with SEREVENT DISKUS.
- 473 8. Patients should be cautioned regarding adverse effects associated with beta₂-agonists, such
- 474 as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 475 9. When patients are prescribed SEREVENT DISKUS, other medications for asthma and
- 476 COPD should be used only as directed by the physician.
- 477 10. SEREVENT DISKUS should not be used with a spacer device.
- 478 11. Patients who are pregnant or nursing should contact the physician about the use of
- 479 SEREVENT DISKUS.
- 480 12. Effective and safe use of SEREVENT DISKUS includes an understanding of the way that it
- 481 should be used:
- 482 • Never exhale into the DISKUS.
- 483 • Never attempt to take the DISKUS apart.
- 484 • Always activate and use the DISKUS in a level, horizontal position.
- 485 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
- 486 • Always keep the DISKUS in a dry place.
- 487 • Discard **6 weeks** after removal from the moisture-protective foil overwrap pouch or after
- 488 all blisters have been used (when the dose indicator reads “0”), whichever comes first.
- 489 13. For the proper use of SEREVENT DISKUS and to attain maximum benefit, the patient
- 490 should read and follow carefully the Patient's Instructions for Use accompanying the
- 491 product.

492 **Drug Interactions: Short-Acting Beta₂-Agonists:** In two 12-week, repetitive-dose
493 adolescent and adult clinical trials in patients with asthma (N = 149), the mean daily need for
494 additional beta₂-agonist in patients using SEREVENT DISKUS was approximately 1½
495 inhalations/day. Twenty-six percent (26%) of the patients in these trials used between 8 and
496 24 inhalations of short-acting beta-agonist per day on 1 or more occasions. Nine percent (9%) of
497 the patients in these trials averaged over 4 inhalations/day over the course of the 12-week trials.
498 No increase in frequency of cardiovascular events was observed among the 3 patients who
499 averaged 8 to 11 inhalations/day; however, the safety of concomitant use of more than
500 8 inhalations/day of short-acting beta₂-agonist with SEREVENT DISKUS has not been
501 established. In 29 patients who experienced worsening of asthma while receiving SEREVENT

502 DISKUS during these trials, albuterol therapy administered via either nebulizer or inhalation
503 aerosol (1 dose in most cases) led to improvement in FEV₁ and no increase in occurrence of
504 cardiovascular adverse events.

505 In 2 clinical trials in patients with COPD, the mean daily need for additional beta₂-agonist for
506 patients using SEREVENT DISKUS was approximately 4 inhalations/day. Twenty-four percent
507 (24%) of the patients using SEREVENT DISKUS in these trials averaged 6 or more inhalations
508 of albuterol per day over the course of the 24-week trials. No increase in frequency of
509 cardiovascular events was observed among patients who averaged 6 or more inhalations per day.

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

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

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

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

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

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

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

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

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

564 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. No teratogenic effects occurred in
565 rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily
566 inhalation dose in adults on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of
567 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in
568 adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects
569 characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid
570 openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the
571 frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately
572 20 times the maximum recommended daily inhalation dose in adults based on comparison of the
573 AUCs).

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

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

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

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

594 **Pediatric Use:** The safety and efficacy of SEREVENT DISKUS has been evaluated in over
595 2,500 patients aged 4 to 11 years with asthma, 346 of whom were administered SEREVENT
596 DISKUS for 1 year. Based on available data, no adjustment of dosage of SEREVENT DISKUS
597 in pediatric patients is warranted for either asthma or EIB (see DOSAGE AND
598 ADMINISTRATION).

599 In 2 randomized, double-blind, controlled clinical trials of 12 weeks' duration, SEREVENT
600 DISKUS 50-mcg was administered to 211 pediatric patients with asthma who did and who did
601 not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was
602 demonstrated over the 12-week treatment period with respect to PEF and FEV₁. SEREVENT
603 DISKUS was effective in demographic subgroups (gender and age) of the population.
604 SEREVENT DISKUS was effective when coadministered with other inhaled asthma
605 medications, such as short-acting bronchodilators and inhaled corticosteroids. SEREVENT
606 DISKUS was well tolerated in the pediatric population, and there were no safety issues identified
607 specific to the administration of SEREVENT DISKUS to pediatric patients.

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

611 **Geriatric Use:** Of the total number of adolescent and adult patients with asthma who received
612 SEREVENT DISKUS in chronic dosing clinical trials, 209 were 65 years of age and older. Of
613 the total number of patients with COPD who received SEREVENT DISKUS in chronic dosing
614 clinical trials, 167 were 65 years of age or older and 45 were 75 years of age or older. No
615 apparent differences in the safety of SEREVENT DISKUS were observed when geriatric patients
616 were compared with younger patients in clinical trials. As with other beta₂-agonists, however,
617 special caution should be observed when using SEREVENT DISKUS in geriatric patients who
618 have concomitant cardiovascular disease that could be adversely affected by this class of drug.
619 Data from the trials in patients with COPD suggested a greater effect on FEV₁ of SEREVENT
620 DISKUS in the <65 years age-group, as compared with the ≥65 years age-group. However, based

621 on available data, no adjustment of dosage of SEREVENT DISKUS in geriatric patients is
622 warranted.

623

624 **ADVERSE REACTIONS**

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

629 **Asthma:** Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of
630 SEREVENT DISKUS in patients 12 years of age and older with asthma. Table 3 reports the
631 incidence of adverse events in these 2 studies.

632

633 **Table 3. Adverse Event Incidence in Two 12-Week Adolescent and Adult Clinical Trials in**
634 **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

635

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

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

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

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

646 **Gastrointestinal:** Nausea.

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

648 **Musculoskeletal:** Pain in joint.

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

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

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

652 Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of
653 SEREVENT DISKUS in patients aged 4 to 11 years with asthma. Table 4 includes all events
654 (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of
655 3% or greater in the group receiving SEREVENT DISKUS and were more common than in the
656 placebo group.

657

658 **Table 4. Adverse Event Incidence in Two 12-Week Pediatric Clinical Trials**
659 **in Patients 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

660

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

665 In clinical trials evaluating concurrent therapy of salmeterol with inhaled corticosteroids,
666 adverse events were consistent with those previously reported for salmeterol, or might otherwise
667 be expected with the use of inhaled corticosteroids.

668 **Chronic Obstructive Pulmonary Disease:** Two multicenter, 24-week, controlled studies
669 have evaluated twice-daily doses of SEREVENT DISKUS in patients with COPD. For
670 presentation (Table 5), the placebo data from a third trial, identical in design, patient entrance

671 criteria, and overall conduct but comparing fluticasone propionate with placebo, were integrated
 672 with the placebo data from these 2 studies (total N = 341 for salmeterol and 576 for placebo).

673

674 **Table 5. Adverse Events With $\geq 3\%$ Incidence in US Controlled Clinical Trials With**
 675 **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

676 *Table 5 includes all events (whether considered drug-related or nondrug-related by the
 677 investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT
 678 DISKUS and were more common in the group receiving SEREVENT DISKUS than in the
 679 placebo group.

680

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

683 **Endocrine and Metabolic:** Hyperglycemia.

684 **Eye:** Keratitis and conjunctivitis.

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

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

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

690 **Neurology:** Migraines.

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

692 **Psychiatry:** Anxiety.

693 **Skin:** Skin rashes.

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

699 In extensive US and worldwide postmarketing experience with salmeterol, serious
700 exacerbations of asthma, including some that have been fatal, have been reported. In most cases,
701 these have occurred in patients with severe asthma and/or in some patients in whom asthma has
702 been acutely deteriorating (see WARNINGS no. 1), but they have also occurred in a few patients
703 with less severe asthma. It was not possible from these reports to determine whether salmeterol
704 contributed to these events or simply failed to relieve the deteriorating asthma.

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

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

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

711

712 **OVERDOSAGE**

713 The expected signs and symptoms with overdosage of SEREVENT DISKUS are those of
714 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and
715 symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or
716 hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache,
717 tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.
718 Overdosage with SEREVENT DISKUS may be expected to result in exaggeration of the
719 pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia
720 and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with SEREVENT
721 DISKUS can lead to clinically significant prolongation of the QTc interval, which can produce
722 ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

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

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

730 No deaths were seen in rats at an inhalation dose of 2.9 mg/kg (approximately 240 times the
731 maximum recommended daily inhalation dose in adults and approximately 110 times the
732 maximum recommended daily inhalation dose in children on a mg/m² basis) and in dogs at an
733 inhalation dose of 0.7 mg/kg (approximately 190 times the maximum recommended daily
734 inhalation dose in adults and approximately 90 times the maximum recommended daily
735 inhalation dose in children on a mg/m² basis). By the oral route, no deaths occurred in mice at
736 150 mg/kg (approximately 6,100 times the maximum recommended daily inhalation dose in
737 adults and approximately 2,900 times the maximum recommended daily inhalation dose in
738 children on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 81,000 times the maximum
739 recommended daily inhalation dose in adults and approximately 38,000 times the maximum
740 recommended daily inhalation dose in children on a mg/m² basis).

741

742 **DOSAGE AND ADMINISTRATION**

743 SEREVENT DISKUS should be administered by the orally inhaled route only (see Patient's
744 Instructions for Use). The patient must not exhale into the DISKUS and the DISKUS should only
745 be activated and used in a level, horizontal position.

746 **Asthma:** For maintenance of bronchodilatation and prevention of symptoms of asthma,
747 including the symptoms of nocturnal asthma, the usual dosage for adults and children 4 years of
748 age and older is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours
749 apart). If a previously effective dosage regimen fails to provide the usual response, medical
750 advice should be sought immediately as this is often a sign of destabilization of asthma. Under
751 these circumstances, the therapeutic regimen should be reevaluated and additional therapeutic
752 options, such as inhaled or systemic corticosteroids, should be considered. If symptoms arise in
753 the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate
754 relief.

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

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

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

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

765 **Prevention of Exercise-Induced Bronchospasm:** One inhalation of SEREVENT
766 DISKUS at least 30 minutes before exercise has been shown to protect patients against EIB.
767 When used intermittently as needed for prevention of EIB, this protection may last up to 9 hours
768 in adolescents and adults and up to 12 hours in patients 4 to 11 years of age. Additional doses of
769 SEREVENT should not be used for 12 hours after the administration of this drug. Patients who
770 are receiving SEREVENT DISKUS twice daily should not use additional SEREVENT for
771 prevention of EIB. If regular, twice-daily dosing is not effective in preventing EIB, other
772 appropriate therapy for EIB should be considered.
773

774 **HOW SUPPLIED**

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

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

781 **Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place**
782 **away from direct heat or sunlight. Keep out of reach of children. SEREVENT DISKUS**
783 **should be discarded 6 weeks after removal from the moisture-protective foil overwrap**
784 **pouch or after all blisters have been used (when the dose indicator reads “0”), whichever**
785 **comes first. The DISKUS is not reusable. Do not attempt to take the DISKUS apart.**
786
787



788
789 GlaxoSmithKline
790 Research Triangle Park, NC 27709
791

792 ©Year, GlaxoSmithKline. All rights reserved.
793

794 Month Year

RL-