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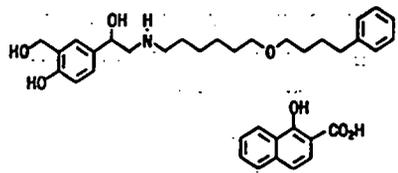
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PRODUCT INFORMATION

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SEREVENT[®]
(salmeterol xinafoate)
Inhalation Aerosol
Bronchodilator Aerosol
For Oral Inhalation Only

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:



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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 two chlorofluorocarbon propellants (trichlorofluoromethane and dichlorodifluoromethane) with 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 of salmeterol base (as salmeterol xinafoate) from the actuator. Each 6.5-g canister provides 60 inhalations and each 13-g canister provides 120 inhalations.

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CLINICAL PHARMACOLOGY:

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

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

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43 mediators of immediate hypersensitivity from cells, especially from mast cells.

44 In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell
45 mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung. Salmeterol
46 inhibits histamine-induced plasma protein extravasation and inhibits platelet activating factor-induced
47 eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In
48 humans, single doses of salmeterol attenuate allergen-induced bronchial hyper-responsiveness.
49 **Pharmacokinetics:** Salmeterol acts locally in the lung; plasma levels therefore do not predict
50 therapeutic effect. Because of the low therapeutic dose, systemic levels of salmeterol are low or
51 undetectable after inhalation of recommended doses (42 mcg twice daily). Following chronic
52 administration of an inhaled dose of 42 mcg twice daily, salmeterol was detected in plasma within 5
53 to 10 minutes in six asthmatic patients; plasma concentrations were very low, with peak
54 concentrations of 150 pg/mL and no accumulation with repeated doses. Larger inhaled doses gave
55 approximately proportionally increased blood levels. In these patients, a second peak concentration
56 of 115 pg/mL occurred at about 45 minutes, probably due to absorption of the swallowed portion of
57 the dose (most of the dose delivered by a metered-dose inhaler is swallowed). Oral administration of
58 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) to two healthy subjects gave peak plasma
59 salmeterol concentrations of about 650 pg/mL at about 45 minutes; the terminal elimination half-life
60 was about 5.5 hours (one volunteer only).

61 Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-
62 naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and excreted
63 independently. Salmeterol base is extensively metabolized by hydroxylation, with subsequent
64 elimination predominantly in the feces. In two healthy subjects who received 1 mg of radiolabeled
65 salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled
66 salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. No significant
67 amount of unchanged salmeterol base was detected in either urine or feces.

68 Salmeterol is 94% to 98% bound to human plasma proteins in vitro over the concentration range
69 of 8 to 7722 ng of base per milliliter, much higher concentrations than those achieved following
70 therapeutic doses of salmeterol.

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

73 The pharmacokinetics of salmeterol base has not been studied in elderly patients nor in
74 patients with hepatic or renal impairment. Since salmeterol is predominantly cleared by hepatic
75 metabolism, liver function impairment may lead to accumulation of salmeterol in plasma. Therefore,
76 patients with hepatic disease should be closely monitored.

77 **Pharmacodynamics:** Inhaled salmeterol, like other beta-adrenergic agonist drugs, can in some
78 patients produce cardiovascular effects (see PRECAUTIONS). The cardiovascular effects (heart
79 rate, blood pressure) associated with salmeterol administration occur with similar frequency, and are
80 of similar type and severity, as those noted following albuterol administration.

81 The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol were
82 studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg resulted in heart
83 rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation
84 aerosol (4 to 10 beats/min). In two double-blind asthma studies, patients receiving either 42 mcg of
85 salmeterol inhalation aerosol twice daily (n = 81) or 180 mcg of albuterol inhalation aerosol four times
86 daily (n = 80) underwent continuous electrocardiographic monitoring during four 24-hour periods; no
87 clinically significant dysrhythmias were noted. Continuous electrocardiographic monitoring was also
88 performed in two double-blind studies in COPD patients (see ADVERSE REACTIONS).

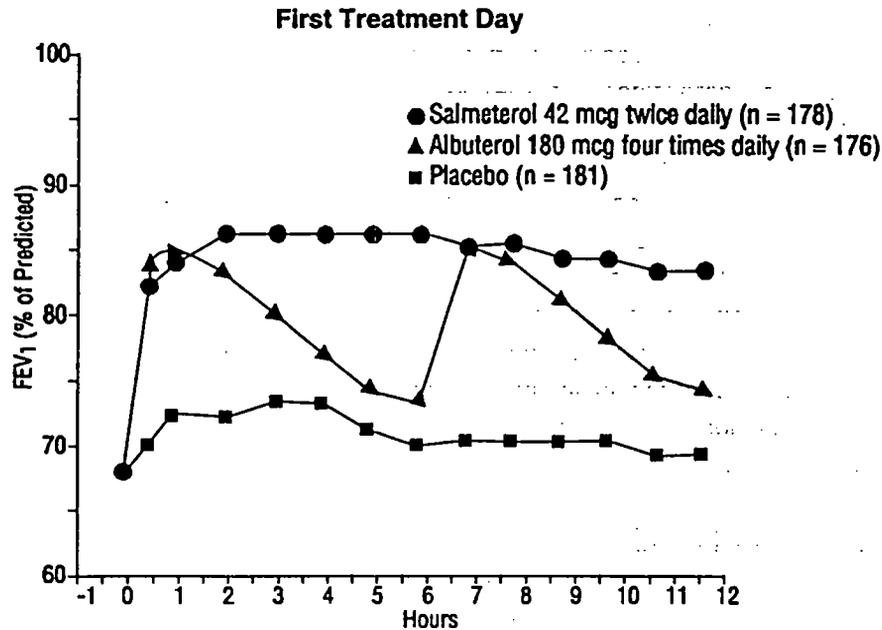
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89 Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of
90 cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-
91 agonists and methylxanthines are administered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

93 **Clinical Trials: Asthma:** In placebo- and albuterol-controlled, single-dose clinical trials with
94 SEREVENT Inhalation Aerosol, the time to onset of effective bronchodilatation (>15% improvement
95 in forced expiratory volume in 1 second [FEV₁]) was 10 to 20 minutes after a 42-mcg dose. Maximum
96 improvement in FEV₁ generally occurred within 180 minutes, and clinically significant improvement
97 continued for 12 hours in most patients.

98 In two large, randomized, double-blind studies, SEREVENT Inhalation Aerosol was compared with
99 albuterol and placebo in patients with mild-to-moderate asthma, including both patients who did and
100 who did not receive concomitant inhaled corticosteroids. The efficacy of SEREVENT Inhalation
101 Aerosol was demonstrated over the 12-week period with no change in effectiveness over this period
102 of time. There were no gender-related differences in safety or efficacy. No development of
103 tachyphylaxis to the bronchodilator effect has been noted in these studies. FEV₁ measurements
104 (percent of predicted) from these two 12-week trials are shown below for both the first and last
105 treatment days.

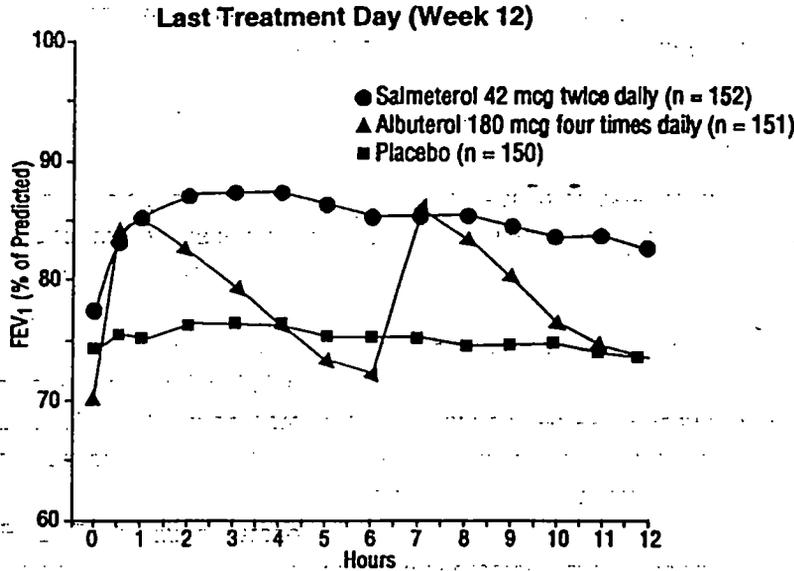
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107 **Figure 1: FEV₁, as Percent of Predicted,
108 From Two Large 12-Week Clinical Trials**



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During daily treatment with SEREVENT Inhalation Aerosol for 12 weeks in patients with asthma, the following treatment effects were seen:

Table 1: Daily Efficacy Measurements in Two Large 12-Week Clinical Trials (Combined Data)

Parameter	Time	Placebo	SEREVENT	Albuterol
No. of randomized subjects		187	184	185
Mean AM peak expiratory flow rate (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%

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*P<0.001 versus albuterol and placebo.

†P<0.05 versus albuterol.

‡P<0.001 versus placebo.

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

Exercise-Induced Bronchospasm: Protection against exercise-induced bronchospasm was examined in three controlled studies. Based on median values, patients who received SEREVENT Inhalation Aerosol had consistently less exercise-induced fall in FEV₁ than patients who received placebo, and they were protected for a longer period of time than patients who received albuterol (see table below). There were, however, some patients who were not protected from exercise-induced bronchospasm after SEREVENT administration and others in whom protection against exercise-induced bronchospasm decreased with continued administration over a period of

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134 4 weeks.

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136 **Table 2: Exercise-Induced Bronchospasm Mean Percentage Fall in Postexercise**

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FEV₁

Clinical Trials/Time After Dose	Treatment		
	Placebo	SEREVENT	Albuterol
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

139 * Statistically superior to placebo ($P \leq 0.05$).

140 † Statistically superior to albuterol ($P \leq 0.05$).

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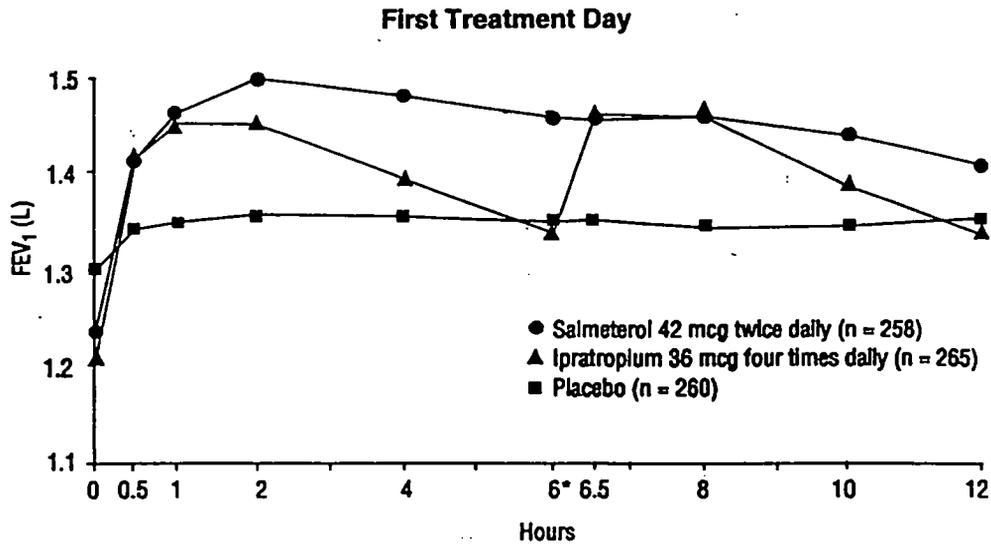
142 **Chronic Obstructive Pulmonary Disease (COPD):** In two large randomized, double-blind
 143 studies, SEREVENT Inhalation Aerosol administered twice daily was compared with placebo and
 144 ipratropium bromide administered four times daily in patients with COPD (emphysema and chronic
 145 bronchitis), including patients who were reversible ($\geq 12\%$ and ≥ 200 mL increase in baseline FEV₁
 146 after albuterol treatment) and nonreversible to albuterol. After a single 42-mcg dose of SEREVENT,
 147 significant improvement in pulmonary function (mean FEV₁ increase of 12% or more) occurred within
 148 30 minutes, reached a peak within 4 hours on average, and persisted for 12 hours with no loss in
 149 effectiveness observed over a 12-week treatment period. Serial 12-hour measurements of FEV₁ from
 150 these two 12-week trials are shown below for both the first and last treatment days.

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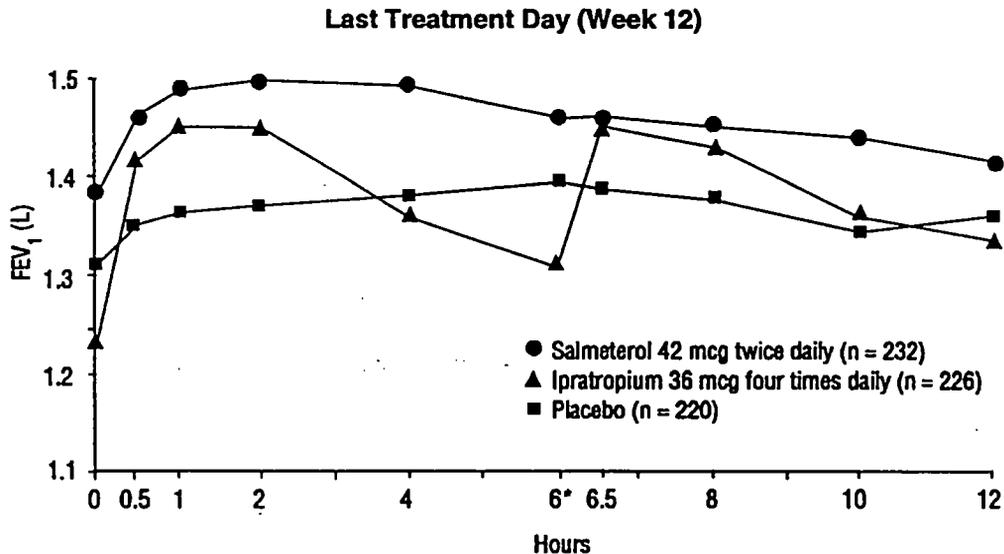
Figure 2: FEV₁ From Two Large 12-Week Clinical Trials

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



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

INDICATIONS AND USAGE:

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

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174 SEREVENT Inhalation Aerosol may be used with or without concurrent inhaled or systemic
175 corticosteroid therapy.

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

178 **COPD:** SEREVENT Inhalation Aerosol is indicated for long-term, twice daily (morning and evening)
179 administration in the maintenance treatment of bronchospasm associated with COPD (including
180 emphysema and chronic bronchitis).

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182 **CONTRAINDICATIONS:** SEREVENT Inhalation Aerosol is contraindicated in patients with a history
183 of hypersensitivity to salmeterol or any of ~~its~~the components.

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185 **WARNINGS:**

186 **IMPORTANT INFORMATION: SEREVENT INHALATION AEROSOL SHOULD NOT BE**
187 **INITIATED IN PATIENTS WITH SIGNIFICANTLY WORSENING OR ACUTELY DETERIORATING**
188 **ASTHMA, WHICH MAY BE A LIFE-THREATENING CONDITION. Serious acute respiratory**
189 **events, including fatalities, have been reported, both in the United States and worldwide,**
190 **when SEREVENT Inhalation Aerosol has been initiated in this situation.**

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

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

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

201 (See **PRECAUTIONS: Information for Patients and the accompanying PATIENT'S**
202 **INSTRUCTIONS FOR USE.**)

203 **1. Do Not Introduce SEREVENT Inhalation Aerosol as a Treatment for Acutely Deteriorating Asthma:**

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

219 **2. Do Not Use SEREVENT Inhalation Aerosol to Treat Acute Symptoms:** An inhaled, short-acting

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

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

229 **3. Watch for Increasing Use of Inhaled, Short-Acting Beta₂-Agonists, Which Is a Marker of**
230 **Deteriorating Asthma:** Asthma may deteriorate acutely over a period of hours or chronically over
231 several days or longer. If the patient's inhaled, short-acting beta₂-agonist becomes less effective or
232 the patient needs more inhalations than usual, this may be a marker of destabilization of asthma. In
233 this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen,
234 giving special consideration to the possible need for corticosteroids. If the patient uses four or more
235 inhalations per day of an inhaled, short-acting beta₂-agonist for 2 or more consecutive days, or if
236 more than one canister (200 inhalations per canister) of inhaled, short-acting beta₂-agonist is used in
237 an 8-week period in conjunction with SEREVENT Inhalation Aerosol, then the patient should consult
238 the physician for reevaluation. **Increasing the daily dosage of SEREVENT Inhalation Aerosol in**
239 **this situation is not appropriate. SEREVENT Inhalation Aerosol should not be used more**
240 **frequently than twice daily (morning and evening) at the recommended dose of two**
241 **inhalations.**

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

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

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

262 **7. Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions may occur after
263 administration of SEREVENT Inhalation Aerosol, as demonstrated by rare cases of urticaria,
264 angioedema, rash, and bronchospasm.

265 **8. Upper Airway Symptoms:** Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and

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266 choking, have been reported rarely in patients receiving SEREVENT Inhalation Aerosol.

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

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278 **PRECAUTIONS:**

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

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

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

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

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

301 **Information for Patients:** See illustrated PATIENT'S INSTRUCTIONS FOR USE Patient's
302 ~~Instructions for Use~~. **SHAKE WELL BEFORE USING.**

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

306 1. Shake well before using.

307 2. The action of SEREVENT Inhalation Aerosol may last up to 12 hours or longer. The
308 recommended dosage (two inhalations twice daily, morning and evening) should not be exceeded.

309 3. SEREVENT Inhalation Aerosol is not meant to relieve acute asthma or COPD symptoms and
310 extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled,
311 short-acting beta₂-agonist such as albuterol (the physician should provide the patient with such

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- 312 medication and instruct the patient in how it should be used).
- 313 4. Patients should not stop SEREVENT therapy for COPD without physician/provider guidance since
- 314 symptoms may recur after discontinuation.
- 315 5. The physician should be notified immediately if any of the following situations occur, which may be
- 316 a sign of seriously worsening asthma.
- 317 • Decreasing effectiveness of inhaled, short-acting beta₂-agonists
- 318 • Need for more inhalations than usual of inhaled, short-acting beta₂-agonists
- 319 • Use of four or more inhalations per day of a short-acting beta₂-agonist for 2 or more days
- 320 consecutively
- 321 • Use of more than one canister of an inhaled, short-acting beta₂-agonist in an 8-week period (i.e.,
- 322 canister with 200 inhalations)
- 323 6. SEREVENT Inhalation Aerosol should not be used as a substitute for oral or inhaled
- 324 corticosteroids. The dosage of these medications should not be changed and they should not be
- 325 stopped without consulting the physician, even if the patient feels better after initiating treatment with
- 326 SEREVENT Inhalation Aerosol.
- 327 7. Patients should be cautioned regarding common adverse cardiovascular effects, such as
- 328 palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 329 8. In patients receiving SEREVENT Inhalation Aerosol, other inhaled medications should be used
- 330 only as directed by the physician.
- 331 9. When using SEREVENT Inhalation Aerosol to prevent exercise-induced bronchospasm, patients
- 332 should take the dose at least 30 to 60 minutes before exercise.
- 333 10. If you are pregnant or nursing, contact your physician about use of SEREVENT Inhalation
- 334 Aerosol.
- 335 11. Effective and safe use of SEREVENT Inhalation Aerosol includes an understanding of the way
- 336 that it should be administered.
- 337 **Drug Interactions: Short-Acting Beta-Agonists:** In the two 3-month, repetitive-dose clinical
- 338 asthma trials (n=184), the mean daily need for additional beta₂-agonist use was 1 to 1½ inhalations
- 339 per day, but some patients used more. Eight percent of patients used at least eight inhalations per
- 340 day at least on one occasion. Six percent used 9 to 12 inhalations at least once. There were 15
- 341 patients (8%) who averaged over four inhalations per day. Four of these used an average of 8 to 11
- 342 inhalations per day. In these 15 patients there was no observed increase in frequency of
- 343 cardiovascular adverse events. The safety of concomitant use of more than eight inhalations per day
- 344 of short-acting beta₂-agonists with SEREVENT Inhalation Aerosol has not been established. In 15
- 345 patients who experienced worsening of asthma while receiving SEREVENT Inhalation Aerosol,
- 346 nebulized albuterol (one dose in most) led to improvement in FEV₁ and no increase in occurrence of
- 347 cardiovascular adverse events.
- 348 **Monoamine Oxidase Inhibitors and Tricyclic Antidepressants:** Salmeterol should be
- 349 administered with extreme caution to patients being treated with monoamine oxidase inhibitors or
- 350 tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of
- 351 salmeterol on the vascular system may be potentiated by these agents.
- 352 **Corticosteroids and Cromoglycate:** In clinical trials, inhaled corticosteroids and/or inhaled
- 353 cromolyn sodium did not alter the safety profile of SEREVENT Inhalation Aerosol when administered
- 354 concurrently.
- 355 **Methylxanthines:** The concurrent use of intravenously or orally administered methylxanthines
- 356 (e.g., aminophylline, theophylline) by patients receiving SEREVENT Inhalation Aerosol has not been
- 357 completely evaluated. In one clinical asthma trial, 87 patients receiving SEREVENT Inhalation

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358 Aerosol 42 mcg twice daily concurrently with a theophylline product had adverse event rates similar to
359 those in 71 patients receiving SEREVENT Inhalation Aerosol without theophylline. Resting heart rates
360 were slightly higher in the patients on theophylline but were little affected by SEREVENT Inhalation
361 Aerosol therapy.

362 Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists,
363 such as SEREVENT Inhalation Aerosol, but may produce severe bronchospasm in asthmatic
364 patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However,
365 under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no
366 acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this
367 setting, cardioselective beta-blockers could be considered, although they should be administered with
368 caution.

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

374 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In an 18-month oral carcinogenicity study
375 in CD-mice, salmeterol xinafoate at oral doses of 1.4 mg/kg and above (approximately nine times
376 the maximum recommended daily inhalation dose in adults based on comparison of the area-under
377 the-plasma-concentration versus time curves [AUCs]) caused dose-related increases in the
378 incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and
379 cysts in the ovaries. The incidence of leiomyosarcomas was not statistically significant. No tumors
380 were seen at 0.2 mg/kg (comparable to the maximum recommended human daily inhalation dose in
381 adults based on comparison of the AUCs).

382 In a 24-month inhalation and oral carcinogenicity study in Sprague Dawley rats, salmeterol caused
383 dose-related increases in the incidence of mesovarian leiomyomas and ovarian cysts at inhalation
384 and oral doses of 0.68 mg/kg per day and above (approximately 55 times the maximum
385 recommended human daily inhalation dose in adults on a mg/m² basis). No tumors were seen at
386 0.21 mg/kg per day (approximately 15 times the maximum recommended human daily inhalation
387 dose in adults on a mg/m² basis). These findings in rodents are similar to those reported previously
388 for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

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

394 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. No teratogenic effects occurred in the rat
395 at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended human daily
396 inhalation dose in adults on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of
397 1 mg/kg and above (approximately 20 times the maximum recommended human daily inhalation
398 dose in adults based on the comparison of the AUCs), salmeterol xinafoate exhibited fetal toxic
399 effects characteristically resulting from beta-adrenoceptor stimulation; these included precocious
400 eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the
401 frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 10
402 times the maximum recommended human daily inhalation dose in adults based on comparison of the
403 AUCs).

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404 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial
405 bones was seen at oral doses of 10 mg/kg (approximately 1600 times the maximum recommended
406 human daily inhalation dose on a mg/m² basis). Extensive use of other beta-agonists has provided no
407 evidence that these class effects in animals are relevant to use in humans. There are no adequate
408 and well-controlled studies with SEREVENT Inhalation Aerosol in pregnant women. SEREVENT
409 Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential
410 risk to the fetus.

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

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

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

423 **Geriatric Use:** Of the total number of patients who received SEREVENT Inhalation Aerosol in all
424 asthma clinical studies, 241 were 65 years of age and older. Geriatric patients (65 years and older)
425 with reversible obstructive airway disease were evaluated in four well-controlled studies of 3 weeks'
426 to 3 months' duration. Two placebo-controlled, crossover studies evaluated twice-daily dosing with
427 salmeterol for 21 to 28 days in 45 patients. An additional 75 geriatric patients were treated with
428 salmeterol for 3 months in two large parallel-group, multicenter studies. These 120 patients
429 experienced increases in AM and PM peak expiratory flow rate and decreases in diurnal variation in
430 peak expiratory flow rate similar to responses seen in the total populations of the two latter studies.
431 The adverse event type and frequency in geriatric patients were not different from those of the total
432 populations studied.

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

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

442
443 **ADVERSE REACTIONS:** Adverse reactions to salmeterol are similar in nature to reactions to other
444 selective beta₂-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity
445 reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache;
446 tremor; nervousness; and paradoxical bronchospasm (see WARNINGS).

447 **Asthma:** Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of
448 SEREVENT Inhalation Aerosol in patients 12 years of age and older with asthma. The following table
449 reports the incidence of adverse events in these two studies.

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Table 3: Adverse Experience Incidence in Two Large 12-Week Asthma Clinical Trials*

Adverse Event Type	Percent of Patients		
	Placebo n = 187	SEREVENT 42 mcg twice daily n = 184	Albuterol 180 mcg four 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

* The only adverse experience classified as serious was one case of upper respiratory tract infection in a patient treated with albuterol.

The table above includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in the SEREVENT Inhalation Aerosol treatment group and were more common in the SEREVENT Inhalation Aerosol group than in the placebo group.

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

Cardiovascular: Tachycardia, palpitations.

Ear, Nose, and Throat: Rhinitis, laryngitis.

Gastrointestinal: Nausea, viral gastroenteritis, nausea and vomiting, diarrhea, abdominal pain.

Hypersensitivity: Urticaria.

Mouth and Teeth: Dental pain.

Musculoskeletal: Pain in joint, back pain, muscle cramp/contraction, myalgia/myositis, muscular soreness.

Neurological: Nervousness, malaise/fatigue.

Respiratory: Tracheitis/bronchitis.

Skin: Rash/skin eruption.

Urogenital: Dysmenorrhea.

In small dose-response studies, tremor, nervousness, and palpitations appeared to be dose

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475 related.
 476 **COPD:** Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of
 477 SEREVENT Inhalation Aerosol in patients with COPD. The following table reports the incidence of
 478 adverse events in these two studies.

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Table 4: Adverse Experience Incidence in Two Large 12-Week COPD Clinical Trials

Adverse Event Type	Percent of Patients		
	Placebo n = 278	SEREVENT 42 mcg twice daily n = 267	Ipratropium 36 mcg four 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

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The table above includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in the SEREVENT Inhalation Aerosol treatment group and were more common in the SEREVENT Inhalation Aerosol group than in the placebo group.

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

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

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

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

Neurological: Insomnia, sinus headache.

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

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

Urogenital: Urinary tract infection.

Electrocardiographic Monitoring in Patients With COPD: Continuous electrocardiographic

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502 (Holter) monitoring was performed on 284 patients in two large COPD clinical trials during five
503 24-hour periods. No cases of sustained ventricular tachycardia were observed. At baseline,
504 non-sustained, asymptomatic ventricular tachycardia was recorded for 7 (7.1%), 8 (9.4%), and 3
505 (3.0%) patients in the placebo, SEREVENT, and ipratropium groups, respectively. During treatment,
506 nonsustained, asymptomatic ventricular tachycardia that represented a clinically significant change
507 from baseline was reported for 11 (11.6%), 15 (18.3%), and 20 (20.8%) patients receiving placebo,
508 SEREVENT, and ipratropium, respectively. Four of these cases of ventricular tachycardia were
509 reported as adverse events (1 placebo, 3 SEREVENT) by one investigator based upon review of
510 Holter data. One case of ventricular tachycardia was observed during ECG evaluation of chest pain
511 (ipratropium) and reported as an adverse event.

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

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

522 **Respiratory:** Rare reports of upper airway symptoms of laryngeal spasm, irritation, or swelling
523 such as stridor or choking.

524 **Cardiovascular:** Hypertension, arrhythmias (including atrial fibrillation, supraventricular
525 tachycardia, extrasystoles).

526

527 **OVERDOSAGE:** The expected signs and symptoms with overdosage are those of excessive
528 beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under
529 ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates
530 up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth,
531 palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with salmeterol may be
532 expected to result in exaggeration of the pharmacologic adverse effects associated with
533 beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle
534 cramps. Overdosage with salmeterol can lead to clinically significant prolongation of the QT_c interval,
535 which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and
536 hyperglycemia.

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

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

543 Cardiac monitoring is recommended in cases of overdosage.

544 No deaths were seen in rats at inhalation doses of 2.9 mg/kg (approximately 240 times the
545 maximum recommended human daily inhalation dose on a mg/m² basis) and in dogs at 0.7 mg/kg
546 (approximately 190 times the maximum recommended human daily inhalation dose on a mg/m²
547 basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6100 times the

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548 maximum recommended human daily inhalation dose on a mg/m² basis) and in rats at 1000 mg/kg
549 (approximately 81 000 times the maximum recommended human daily inhalation dose on a mg/m²
550 basis).

551

552 **DOSAGE AND ADMINISTRATION:** SEREVENT Inhalation Aerosol should be administered by the
553 orally inhaled route only (see PATIENT'S INSTRUCTIONS FOR USE Patient's Instructions for Use). It
554 is recommended to "test spray" SEREVENT Inhalation Aerosol into the air four times before using for
555 the first time and in cases where the aerosol has not been used for a prolonged period of time (i.e.,
556 more than 4 weeks).

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

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

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

569 **COPD:** For maintenance treatment of bronchospasm associated with COPD (including chronic
570 bronchitis and emphysema), the usual dosage for adults is two inhalations (42 mcg) twice daily
571 (morning and evening, approximately 12 hours apart).

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

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

583

584 **HOW SUPPLIED:** SEREVENT Inhalation Aerosol is supplied in 13-g canisters containing 120
585 metered actuations in boxes of one. Each actuation delivers 25 mcg of salmeterol base (as
586 salmeterol xinafoate) from the valve and 21 mcg of salmeterol base (as salmeterol xinafoate) from
587 the actuator. Each canister is supplied with a green plastic actuator with a teal-colored strapcap and
588 patient's instructions (NDC 0173-0464-00). Also available, SEREVENT Inhalation Aerosol Refill (NDC
589 0173-0465-00), a 13-g canister only with patient's instructions.

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591 SEREVENT Inhalation Aerosol is also supplied in a pack that consists of a 6.5-g canister
592 containing 60 metered actuations in boxes of one. Each actuation delivers 25 mcg of salmeterol base
593 (as salmeterol xinafoate) from the valve and 21 mcg of salmeterol base from the actuator (as
salmeterol xinafoate). Each canister is supplied with a green plastic actuator with a teal-colored

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594 strapcap and patient's instructions (NDC 0173-0467-00).

595 For use with SEREVENT Inhalation Aerosol actuator only. The green actuator with SEREVENT
596 Inhalation Aerosol should not be used with other aerosol medications, and actuators from other
597 aerosol medications should not be used with a SEREVENT Inhalation Aerosol canister.

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

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

603 Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store at
604 temperatures above 120°F. Keep out of reach of children. As with most inhaled medications in
605 aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold;
606 for best results, the canister should be at room temperature before use. Shake well before using.
607

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

610
611 **WARNING:** Contains trichlorofluoromethane and dichlorodifluoromethane, substances
612 which harm public health and environment by destroying ozone in the upper atmosphere.
613

614 A notice similar to the above WARNING has been placed in the patient information leaflet of this
615 product pursuant to EPA regulations. The patient's warning states that the patient should consult his
616 or her physician if there are questions about alternatives.
617

618 Rx only

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620
621 **GlaxoWellcome**

622 Glaxo Wellcome Inc.

623 Research Triangle Park, NC 27709

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625 US Patent Nos. 4,992,474; 5,225,445; and 5,380,922

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629 June/March 1998

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