

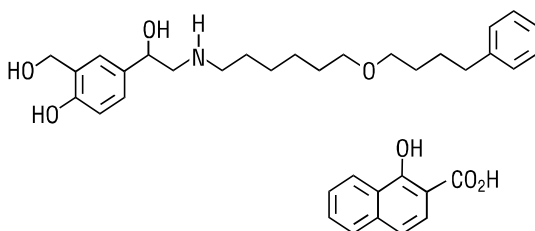
PRESCRIBING INFORMATION

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

FOR ORAL INHALATION ONLY

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. After a blister containing medication is opened by activating the DISKUS, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

61 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low or
62 undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder
63 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol
64 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in
65 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of
66 167 pg/mL at 20 minutes and no accumulation with repeated doses.

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

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

73 **Elimination:** In 2 healthy subjects who received 1 mg of radiolabeled salmeterol (as
74 salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was

75 eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination
76 half-life was about 5.5 hours (1 volunteer only).

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

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

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

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

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

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

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

112

113 **CLINICAL TRIALS**

114 **Asthma:** During the initial treatment day in several multiple-dose clinical trials with salmeterol
115 inhalation powder in patients with asthma, the median time to onset of clinically significant
116 bronchodilatation ($\geq 15\%$ improvement in FEV₁) ranged from 30 to 48 minutes after a 50-mcg
117 dose.

118 One hour after a single dose of 50 mcg of salmeterol inhalation powder, the majority of
119 patients had $\geq 15\%$ improvement in FEV₁. Maximum improvement in FEV₁ generally occurred
120 within 180 minutes, and clinically significant improvement continued for 12 hours in most
121 patients.

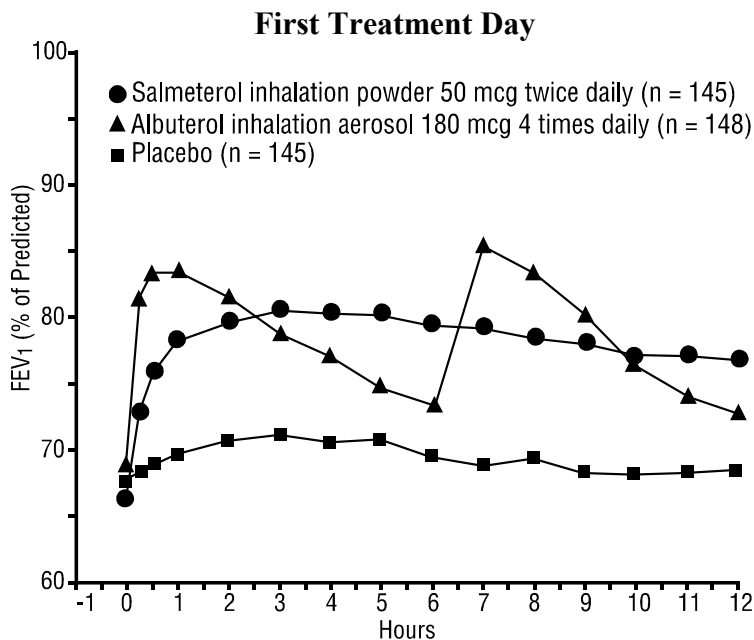
122 In 2 randomized, double-blind studies, salmeterol inhalation powder was compared with
123 albuterol inhalation aerosol and placebo in adolescent and adult patients with mild-to-moderate
124 asthma (protocol defined as 50% to 80% predicted FEV₁, actual mean of 67.7% at baseline),
125 including patients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

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132 **Figure 1. Serial 12-Hour FEV₁ From 2 12-Week Clinical**
133 **Trials in Patients with Asthma**

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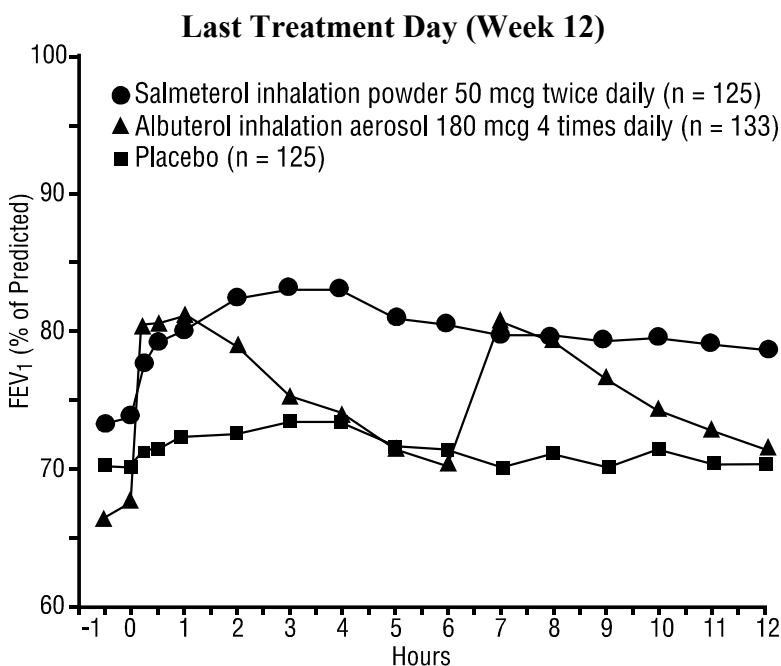
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141 During daily treatment with salmeterol inhalation powder for 12 weeks in adolescent and adult
142 patients with mild-to-moderate asthma, the following treatment effects were seen:

143

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

Parameter	Time	Placebo	Salmeterol Inhalation Powder	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%

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

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

147

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

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

163 In a randomized, double-blind, controlled study (n = 449), 50 mcg of salmeterol inhalation
164 powder, via the DISKUS, was administered twice daily to pediatric patients with asthma who did
165 and who did not receive concurrent inhaled corticosteroids. The efficacy of salmeterol inhalation
166 powder was demonstrated over the 12-week treatment period with respect to periodic serial peak
167 expiratory flow (PEF) (36% to 39% postdose increase from baseline) and FEV₁ (32% to 33%
168 postdose increase from baseline). Salmeterol was effective in demographic subgroup analyses
169 (gender and age) and was effective when coadministered with other inhaled asthma medications
170 such as short-acting bronchodilators and inhaled corticosteroids. A second randomized,
171 double-blind, placebo-controlled study (n = 207) with 50 mcg of salmeterol inhalation powder
172 via an alternate device supported the findings of the trial with the DISKUS.

173 **Effects in Patients With Asthma on Concomitant Inhaled Corticosteroids:** In 4 clinical
174 trials in adult and adolescent patients with asthma (n = 1922), the effect of adding salmeterol to
175 inhaled corticosteroid therapy was evaluated. The studies utilized the inhalation aerosol
176 formulation of salmeterol xinafoate for a treatment period of 6 months. They compared the
177 addition of salmeterol therapy to an increase (at least doubling) of the inhaled corticosteroid
178 dose.

179 Two randomized, double-blind, controlled, parallel-group clinical trials (n = 997) enrolled
180 patients (ages 18 to 82 years) with persistent asthma who were previously maintained but not
181 adequately controlled on inhaled corticosteroid therapy. During the 2-week run-in period all
182 patients were switched to beclomethasone dipropionate 168 mcg twice daily. Patients still not
183 adequately controlled were randomized to either the addition of salmeterol inhalation aerosol
184 42 mcg twice daily or an increase of beclomethasone dipropionate to 336 mcg twice daily. As
185 compared to the doubled dose of beclomethasone dipropionate, the addition of salmeterol
186 resulted in statistically significantly greater improvements in pulmonary function and asthma
187 symptoms, and statistically significantly greater reduction in supplemental albuterol use. The
188 percent of patients who experienced asthma exacerbations overall was not different between

189 groups (i.e., 16.2% in the salmeterol group versus 17.9% in the higher dose beclomethasone
190 dipropionate group).

191 Two randomized, double-blind, parallel-group clinical trials (n = 925) enrolled patients (ages
192 12 to 78 years) with persistent asthma who were previously maintained but not adequately
193 controlled on prior therapy. During the 2- to 4-week run-in period, all patients were switched to
194 fluticasone propionate 88 mcg twice daily. Patients still not adequately controlled were
195 randomized to either the addition of salmeterol inhalation aerosol 42 mcg twice daily or an
196 increase of fluticasone propionate to 220 mcg twice daily. As compared to the increased (2.5
197 times) dose of fluticasone propionate, the addition of salmeterol resulted in statistically
198 significantly greater improvements in pulmonary function and asthma symptoms, and statistically
199 significantly greater reductions in supplemental albuterol use. Fewer patients receiving
200 salmeterol experienced asthma exacerbations than those receiving the higher dose of fluticasone
201 propionate (8.8% versus 13.8%)

202 In 2 randomized, single-dose, crossover studies in adolescents and adults with
203 exercise-induced bronchospasm (EIB) (n = 53), 50 mcg of salmeterol inhalation powder
204 prevented EIB when dosed 30 minutes prior to exercise. For many patients, this protective effect
205 against EIB was still apparent up to 8.5 hours following a single dose.

206

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

		Placebo (n = 52)		Salmeterol Inhalation Powder (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)	

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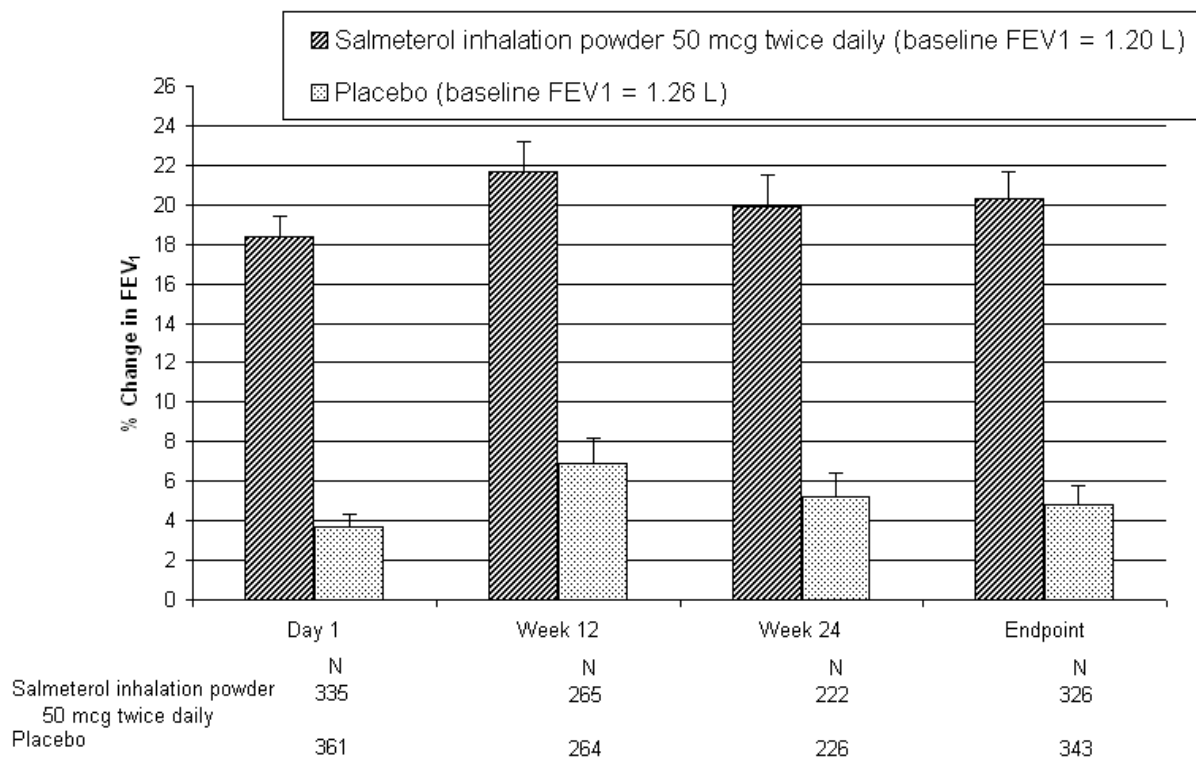
209 In 2 randomized studies in children 4 to 11 years old with asthma and EIB (n = 50), a single
210 50-mcg dose of salmeterol inhalation powder prevented EIB when dosed 30 minutes prior to
211 exercise, with protection lasting up to 11.5 hours in repeat testing following this single dose in
212 many patients.

213 **Chronic Obstructive Pulmonary Disease (COPD):** In 2 clinical trials evaluating
 214 twice-daily treatment with salmeterol inhalation powder 50 mcg (n = 336) compared to placebo
 215 (n = 366) in patients with chronic bronchitis with airflow limitation, with or without emphysema,
 216 improvements in pulmonary function endpoints were greater with salmeterol 50 mcg than with
 217 placebo. Treatment with salmeterol did not result in significant improvements in secondary
 218 endpoints assessing COPD symptoms in either clinical trial. Both trials were randomized,
 219 double-blind, parallel-group studies of 24 weeks' duration and were identical in design, patient
 220 entrance criteria, and overall conduct.

221 Figure 2 displays the integrated 2-hour postdose FEV₁ results from the 2 clinical trials. The
 222 percent change in FEV₁ refers to the change from baseline, defined as the predose value on
 223 Treatment Day 1. To account for patient withdrawals during the study, Endpoint (last evaluable
 224 FEV₁) data are provided. Patients receiving salmeterol 50 mcg had significantly greater
 225 improvements in 2-hour postdose FEV₁ at Endpoint (216 mL, 20%) compared to placebo
 226 (43 mL, 5%). Improvement was apparent on the first day of treatment and maintained throughout
 227 the 24 weeks of treatment.

228

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



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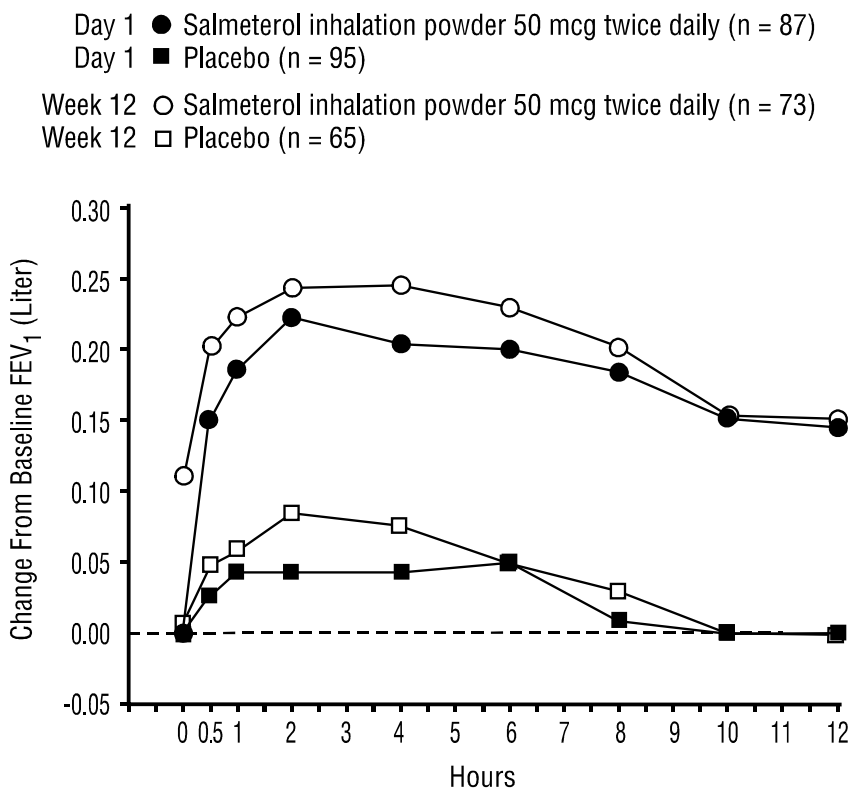
233 **Onset of Action and Duration of Effect:** The onset of action and duration of effect of
 234 salmeterol were evaluated in a subset of patients (n = 87) from 1 of the 2 clinical trials discussed

235 above. Following the first 50-mcg dose, significant improvement in pulmonary function (mean
236 FEV₁ increase of 12% or more and at least 200 mL) occurred at 2 hours. The mean time to peak
237 bronchodilator effect was 4.75 hours. As seen in Figure 3, evidence of bronchodilatation was
238 seen throughout the 12-hour period. Figure 3 also demonstrates that the bronchodilating effect
239 after 12 weeks of treatment was similar to that observed after the first dose. The mean time to
240 peak bronchodilator effect after 12 weeks of treatment was 3.27 hours.

241

242 **Figure 3. Serial 12-Hour FEV₁ on the First Day and at Week**
243 **12 of Treatment**

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245

246

247 INDICATIONS AND USAGE

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

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

256 SEREVENT DISKUS may be used alone or in combination with inhaled or systemic
257 corticosteroid therapy.

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

261

262 **CONTRAINDICATIONS**

263 SEREVENT DISKUS is contraindicated in patients with a history of hypersensitivity to
264 salmeterol or any other component of the drug product.

265

266 **WARNINGS**

267 **IMPORTANT INFORMATION: SEREVENT DISKUS SHOULD NOT BE INITIATED IN**
268 **PATIENTS WITH SIGNIFICANTLY WORSENING OR ACUTELY DETERIORATING**
269 **ASTHMA, WHICH MAY BE A LIFE-THREATENING CONDITION. Serious acute**
270 **respiratory events, including fatalities, have been reported both in the United States and**
271 **worldwide when SEREVENT has been initiated in this situation.**

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

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

279 **SEREVENT DISKUS IS NOT A SUBSTITUTE FOR INHALED OR ORAL**
280 **CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced when**
281 **SEREVENT DISKUS is initiated.**

282 **(See PRECAUTIONS: Information for Patients and the accompanying Patient's**
283 **Instructions for Use.)**

284 **1. Do Not Introduce SEREVENT DISKUS as a Treatment for Acutely Deteriorating Asthma:**
285 SEREVENT DISKUS is intended for the maintenance treatment of asthma (see INDICATIONS
286 AND USAGE) and should not be introduced in acutely deteriorating asthma, which is a
287 potentially life-threatening condition. There are no data demonstrating that SEREVENT
288 DISKUS provides greater efficacy than or additional efficacy to inhaled, short-acting
289 beta₂-agonists in patients with worsening asthma. Serious acute respiratory events, including
290 fatalities, have been reported both in the United States and worldwide in patients receiving
291 SEREVENT. In most cases, these have occurred in patients with severe asthma (e.g., patients
292 with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical
293 ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations)
294 and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to
295 usual medications; increasing need for inhaled, short-acting beta₂-agonists; increasing need for
296 systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden
297 or progressive deterioration in pulmonary function). However, they have occurred in a few

298 patients with less severe asthma as well. It was not possible from these reports to determine
299 whether SEREVENT contributed to these events or simply failed to relieve the deteriorating
300 asthma.

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

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

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

324 4. Do Not Use SEREVENT DISKUS as a Substitute for Oral or Inhaled Corticosteroids: The use
325 of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many
326 patients. Early consideration should be given to adding anti-inflammatory agents, e.g.,
327 corticosteroids. There are no data demonstrating that SEREVENT DISKUS has a clinical
328 anti-inflammatory effect and could be expected to take the place of corticosteroids. Patients who
329 already require oral or inhaled corticosteroids for treatment of asthma should be continued on a
330 suitable dose to maintain clinical stability even if they feel better as a result of initiating
331 SEREVENT DISKUS. Any change in corticosteroid dosage should be made ONLY after clinical
332 evaluation (see PRECAUTIONS: Information for Patients).

333 5. Do Not Exceed Recommended Dosage: As with other inhaled beta₂-adrenergic drugs,
334 SEREVENT DISKUS should not be used more often or at higher doses than recommended.
335 Fatalities have been reported in association with excessive use of inhaled sympathomimetic
336 drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have

337 been associated with clinically significant prolongation of the QTc interval, which has the
338 potential for producing ventricular arrhythmias.

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

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

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

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

358

359 **PRECAUTIONS**

360 **General:** 1. Cardiovascular and Other Effects: No effect on the cardiovascular system is usually
361 seen after the administration of inhaled salmeterol at recommended doses, but the cardiovascular
362 and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood
363 pressure, heart rate, excitement) can occur after use of salmeterol and may require
364 discontinuation of the drug. Salmeterol, like all sympathomimetic amines, should be used with
365 caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac
366 arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in
367 patients who are unusually responsive to sympathomimetic amines.

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

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

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

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

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

- 386 1. The action of SEREVENT DISKUS may last up to 12 hours or longer. The recommended
387 dosage (1 inhalation twice daily, morning and evening) should not be exceeded.
- 388 2. SEREVENT DISKUS is not meant to relieve acute asthma or COPD symptoms and extra
389 doses should not be used for that purpose. Acute symptoms should be treated with an inhaled,
390 short-acting bronchodilator (the physician should provide the patient with such medication and
391 instruct the patient in how it should be used).
- 392 3. Patients should not stop therapy with SEREVENT DISKUS without physician/provider
393 guidance since symptoms may worsen after discontinuation.
- 394 4. • When used for the treatment of EIB, 1 inhalation of SEREVENT DISKUS should be taken
395 30 minutes before exercise.
396 • Additional doses of SEREVENT should not be used for 12 hours.
397 • Patients who are receiving SEREVENT DISKUS twice daily should not use additional
398 SEREVENT for prevention of EIB.
- 399 5. The physician should be notified immediately if any of the following situations occur, which
400 may be a sign of seriously worsening asthma or COPD:
 - 401 • decreasing effectiveness of inhaled, short-acting beta₂-agonists,
 - 402 • need for more inhalations than usual of inhaled, short-acting beta₂-agonists,
 - 403 • significant decrease in PEF or lung function as outlined by the physician,
 - 404 • use of 4 or more inhalations per day of a short-acting beta₂-agonist for 2 or more days
405 consecutively,
 - 406 • use of more than 1 canister (200 inhalations per canister) of an inhaled, short-acting
407 beta₂-agonist in an 8-week period.
- 408 6. SEREVENT DISKUS should not be used as a substitute for oral or inhaled corticosteroids.
409 The dosage of these medications should not be changed and they should not be stopped without
410 consulting the physician, even if the patient feels better after initiating treatment with
411 SEREVENT DISKUS.
- 412 7. Patients should be cautioned regarding adverse effects associated with beta₂-agonists, such as
413 palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 414 8. When patients are prescribed SEREVENT DISKUS, other medications for asthma and COPD
415 should be used only as directed by the physician.
- 416 9. SEREVENT DISKUS should not be used with a spacer device.

417 10. If you are pregnant or nursing, contact your physician about the use of SEREVENT DISKUS.
418 11. Effective and safe use of SEREVENT DISKUS includes an understanding of the way that it
419 should be used:

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

427 12. For the proper use of SEREVENT DISKUS and to attain maximum benefit, the patient
428 should read and follow carefully the Patient's Instructions for Use accompanying the product.

429 **Drug Interactions: Short-Acting Beta-Agonists:** In the two 12-week, repetitive-dose
430 adolescent and adult clinical trials in patients with asthma (n = 149), the mean daily need for
431 additional beta₂-agonist in patients using salmeterol inhalation powder was approximately 1½
432 inhalations/day. Twenty-six percent (26%) of the patients in these trials used between 8 and
433 24 inhalations of short-acting beta-agonist per day on 1 or more occasions. Nine percent (9%) of
434 the patients in these trials averaged over 4 inhalations/day over the course of the 12-week trials.
435 No increase in frequency of cardiovascular events was observed among the 3 patients who
436 averaged 8 to 11 inhalations per day; however, the safety of concomitant use of more than
437 8 inhalations per day of short-acting beta₂-agonist with salmeterol inhalation powder has not
438 been established. In 29 patients who experienced worsening of asthma while receiving salmeterol
439 inhalation powder during these trials, albuterol therapy administered via either nebulizer or
440 inhalation aerosol (1 dose in most cases) led to improvement in FEV₁ and no increase in
441 occurrence of cardiovascular adverse events.

442 In 2 clinical trials in patients with COPD, the mean daily need for additional beta₂-agonist for
443 patients using salmeterol inhalation powder was approximately 4 inhalations/day. Twenty-four
444 percent (24%) of the patients using salmeterol inhalation powder in these trials averaged 6 or
445 more inhalations of albuterol per day over the course of the 24-week trials. No increase in
446 frequency of cardiovascular events was observed among patients who averaged 6 or more
447 inhalations per day.

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

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

454 **Methylxanthines:** The concurrent use of intravenously or orally administered
455 methylxanthines (e.g., aminophylline, theophylline) by patients receiving salmeterol has not been
456 completely evaluated. In 1 clinical asthma trial, 87 patients receiving SEREVENT Inhalation

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

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

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

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

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

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

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

501 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. No teratogenic effects occurred in
502 rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily
503 inhalation dose in adults on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of
504 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in
505 adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects
506 characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid
507 openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the
508 frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately
509 20 times the maximum recommended daily inhalation dose in adults based on comparison of the
510 AUCs).

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

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

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

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

531 **Pediatric Use:** The safety and efficacy of salmeterol inhalation powder has been evaluated in
532 over 2,500 patients aged 4 to 11 years with asthma, 346 of whom were administered salmeterol
533 inhalation powder for 1 year. Based on available data, no adjustment of salmeterol dosage in
534 pediatric patients is warranted for either asthma or EIB (see DOSAGE AND
535 ADMINISTRATION).

536 In 2 randomized, double-blind, controlled clinical trials of 12 weeks' duration, salmeterol
537 50-mcg powder was administered to 211 pediatric asthma patients who did and who did not
538 receive concurrent inhaled corticosteroids. The efficacy of salmeterol inhalation powder was
539 demonstrated over the 12-week treatment period with respect to PEF and FEV₁. Salmeterol
540 inhalation powder was effective in demographic subgroups (gender and age) of the population.
541 Salmeterol was effective when coadministered with other inhaled asthma medications, such as
542 short-acting bronchodilators and inhaled corticosteroids. Salmeterol inhalation powder was well
543 tolerated in the pediatric population, and there were no safety issues identified specific to the
544 administration of salmeterol inhalation powder to pediatric patients.

545 In 2 randomized studies in children 4 to 11 years old with asthma and EIB, a single 50-mcg
546 dose of salmeterol inhalation powder prevented EIB when dosed 30 minutes prior to exercise,
547 with protection lasting up to 11.5 hours in repeat testing following this single dose in many
548 patients.

549 **Geriatric Use:** Of the total number of adolescent and adult patients with asthma who received
550 salmeterol inhalation powder in chronic dosing clinical trials, 209 were 65 years of age and older.
551 Of the total number of patients with COPD who received salmeterol inhalation powder in chronic
552 dosing clinical trials, 167 were 65 years of age or older and 45 were 75 years of age or older. No
553 apparent differences in the safety of SEREVENT inhalation powder were observed when
554 geriatric patients were compared with younger patients in clinical trials. As with other
555 beta₂-agonists, however, special caution should be observed when using SEREVENT DISKUS in
556 geriatric patients who have concomitant cardiovascular disease that could be adversely affected
557 by this class of drug. Data from the trials in patients with COPD suggested a greater effect on
558 FEV₁ of salmeterol inhalation powder in the <65 years age-group, as compared with the ≥65
559 years age-group. However, based on available data, no adjustment of salmeterol dosage in
560 geriatric patients is warranted.

561

562 **ADVERSE REACTIONS**

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

567 **Asthma:** Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of
568 salmeterol inhalation powder in patients 12 years of age and older with asthma. Table 3 reports
569 the incidence of adverse experiences in these 2 studies.

570

571 **Table 3. Adverse Experience Incidence in Two 12-Week Adolescent and Adult Clinical**
572 **Trials in Patients With Asthma**

Adverse Experience Type	Percent of Patients		
	Placebo (N = 152)	Salmeterol Inhalation Powder 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

573
574 Table 3 includes all experiences (whether considered drug-related or nondrug-related by the
575 investigator) that occurred at a rate of 3% or greater in the group receiving salmeterol inhalation
576 powder and were more common than in the placebo group.

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

580 Other adverse experiences that occurred in the group receiving salmeterol inhalation powder
581 in these studies with an incidence of 1% to 3% and that occurred at a greater incidence than with
582 placebo were:

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

584 **Gastrointestinal:** Nausea.

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

586 **Musculoskeletal:** Pain in joint.

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

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

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

590 Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of salmeterol
591 inhalation powder in patients aged 4 to 11 years with asthma. Table 4 includes all experiences
592 (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of
593 3% or greater in the group receiving salmeterol inhalation powder and were more common than
594 in the placebo group.

595

596 **Table 4. Adverse Experience Incidence in Two 12-Week Pediatric Clinical Trials in**
597 **Patients With Asthma**

Adverse Experience Type	Percent of Patients		
	Placebo (N = 215)	Salmeterol Inhalation Powder 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

598
599 The following experiences were reported at an incidence of 1% to 2% (3 to 4 patients) in the
600 salmeterol group and with a higher incidence than in the albuterol and placebo groups:
601 gastrointestinal signs and symptoms, lower respiratory signs and symptoms, photodermatitis, and
602 arthralgia and articular rheumatism.

603 In clinical trials evaluating concurrent therapy of salmeterol with inhaled corticosteroids,
604 adverse experiences were consistent with those previously reported for salmeterol, or might
605 otherwise be expected with the used of inhaled corticosteroids.

606 **Chronic Obstructive Pulmonary Disease (COPD):** Two multicenter, 24-week, controlled
607 studies have evaluated twice-daily doses of salmeterol inhalation powder administered via the
608 DISKUS in patients with COPD. For presentation (Table 5), the placebo data from a third trial,
609 identical in design, patient entrance criteria, and overall conduct but comparing fluticasone
610 propionate with placebo, were integrated with the placebo data from these 2 studies (total
611 N = 341 for salmeterol and 576 for placebo).

612

613 **Table 5. Adverse Experiences With ≥3% Incidence in US Controlled Clinical Trials With**
614 **Salmeterol Inhalation Powder in Patients With Chronic Obstructive Pulmonary Disease***

Adverse Experience Type	Percent of Patients	
	Placebo (N = 576)	Salmeterol Inhalation Powder 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

615 *Table 5 includes all events (whether considered drug-related or nondrug-related by the
616 investigator) that occurred at a rate of 3% or greater in the group treated with salmeterol
617 inhalation powder and were more common in the group treated with salmeterol inhalation
618 powder than in the placebo group.

619
620 Other experiences occurring in the group treated with salmeterol inhalation powder that
621 occurred at a frequency of 1% to <3% and were more common than in the placebo group were as
622 follows:

623 **Endocrine and Metabolic:** Hyperglycemia.

624 **Eye:** Keratitis and conjunctivitis.

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

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

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

630 **Neurology:** Migraines.

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

632 **Psychiatry:** Anxiety.

633 **Skin:** Skin rashes.

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

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

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

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

650

651 **OVERDOSAGE**

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

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

664 Treatment consists of discontinuation of SEREVENT DISKUS together with appropriate
665 symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be
666 considered, bearing in mind that such medication can produce bronchospasm. There is

667 insufficient evidence to determine if dialysis is beneficial for overdose of SEREVENT
668 DISKUS. Cardiac monitoring is recommended in cases of overdose.

669 No deaths were seen in rats at an inhalation dose of 2.9 mg/kg (approximately 240 times the
670 maximum recommended daily inhalation dose in adults and approximately 110 times the
671 maximum recommended daily inhalation dose in children on a mg/m² basis) and in dogs at an
672 inhalation dose of 0.7 mg/kg (approximately 190 times the maximum recommended daily
673 inhalation dose in adults and approximately 90 times the maximum recommended daily
674 inhalation dose in children on a mg/m² basis). By the oral route, no deaths occurred in mice at
675 150 mg/kg (approximately 6,100 times the maximum recommended daily inhalation dose in
676 adults and approximately 2,900 times the maximum recommended daily inhalation dose in
677 children on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 81,000 times the maximum
678 recommended daily inhalation dose in adults and approximately 38,000 times the maximum
679 recommended daily inhalation dose in children on a mg/m² basis).

680

681 **DOSAGE AND ADMINISTRATION**

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

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

694 **Chronic Obstructive Pulmonary Disease (COPD):** For maintenance treatment of
695 bronchospasm associated with COPD (including chronic bronchitis and emphysema), the usual
696 dosage for adults is 1 inhalation (50 mcg) twice daily (morning and evening, approximately
697 12 hours apart).

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

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

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

705 **Prevention of Exercise-Induced Bronchospasm (EIB):** One inhalation of SEREVENT
706 DISKUS at least 30 minutes before exercise has been shown to protect patients against EIB.

707 When used intermittently as needed for prevention of EIB, this protection may last up to 9 hours
708 in adolescents and adults and up to 12 hours in patients 4 to 11 years of age. Additional doses of
709 SEREVENT should not be used for 12 hours after the administration of this drug. Patients who
710 are receiving SEREVENT DISKUS twice daily should not use additional SEREVENT for
711 prevention of EIB. If regular, twice-daily dosing is not effective in preventing EIB, other
712 appropriate therapy for EIB should be considered.

713

714 **HOW SUPPLIED**

715 SEREVENT DISKUS is supplied as a disposable, teal green-colored unit containing
716 60 blisters. The drug product is packaged within a teal green-colored, plastic-coated,
717 moisture-protective foil pouch (NDC 0173-0521-00).

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

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

726



727

728 GlaxoSmithKline

729 Research Triangle Park, NC 27709

730

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732

733 March 22, 2002

RL-1068

Patient's Instructions for Use

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

FOR ORAL INHALATION ONLY

(illustration of device with parts labeled:

Outer Case
Mouthpiece
Lever
Thumbgrip
Dose Indicator)

Read this leaflet carefully before you start to take your medicine. It provides a summary of information about your medicine. Keep it for future use. Read the leaflet every time you refill your prescription because there may be new information.

For more information ask your doctor or pharmacist.

What Is SEREVENT[®] DISKUS[®]?

SEREVENT DISKUS contains a medicine called salmeterol xinafoate, which is a long-acting bronchodilator that helps prevent and relieve bronchospasm, making it easier to breathe.

When inhaled regularly, SEREVENT DISKUS improves lung function and helps to prevent symptoms of asthma. In patients with chronic obstructive pulmonary disease (COPD), regular use of SEREVENT DISKUS improves lung function.

Important Points to Remember About Using SEREVENT DISKUS

1. TELL YOUR DOCTOR IMMEDIATELY:

- if you are pregnant (or intending to become pregnant).
- if you are breastfeeding a baby.
- if you are allergic to SEREVENT DISKUS or any other orally inhaled bronchodilator. In some circumstances, this medicine may not be suitable and your doctor may wish to give you a different medicine.
- if you are taking any other medicines.

2. It is important that you inhale each dose as your doctor has advised. The label will usually tell you what dose to take and how often. If it doesn't, or if you are not sure, ask your doctor or pharmacist. **Do not use SEREVENT DISKUS more frequently than 2 times daily, morning and evening, approximately 12 hours apart, at the recommended dose of 1 inhalation each time.**
3. **DO NOT USE SEREVENT DISKUS TO RELIEVE SUDDEN ASTHMA OR COPD SYMPTOMS** (e.g., sudden severe onset or worsening of wheezing, cough, chest tightness, and/or shortness of breath that has been diagnosed by your doctor as due to asthma or COPD). **If you experience sudden asthma or COPD symptoms, you should not take SEREVENT DISKUS to relieve these symptoms.** Sudden symptoms should be treated with a fast-acting inhaler. If you do not have a fast-acting inhaler, contact your doctor to have one prescribed for you.
4. Do not stop using SEREVENT DISKUS without speaking to your doctor since symptoms may recur after discontinuation.
5. **Tell your doctor immediately if your asthma or COPD is getting worse, as indicated by any of the following situations.**
 - Your fast-acting inhaler becomes less effective.
 - You need more inhalations than usual of your fast-acting inhaler.
 - You are using 4 or more inhalations per day of your fast-acting inhaler for 2 or more days consecutively.
 - You use more than 1 canister (200 inhalations per canister) of your fast-acting inhaler in an 8-week period.
6. **If you are using SEREVENT DISKUS for exercise-induced bronchospasm, 1 inhalation should be taken 30 minutes before exercise. Additional doses of SEREVENT should not be taken for 12 hours. If you are using SEREVENT DISKUS twice daily, you should not use additional SEREVENT for the prevention of exercise-induced bronchospasm.**
7. Do not use SEREVENT DISKUS as a substitute for oral or inhaled corticosteroids. **If you have been prescribed corticosteroids, you should not change your dosage of these medicines or stop taking these medicines without talking to your doctor, even if you feel better.**
8. Use other inhaled medicines only as prescribed by your doctor.
9. Do not use SEREVENT DISKUS with a spacer device.

How to Use Your SEREVENT DISKUS

Follow the instructions below. If you have any questions, ask your doctor or pharmacist.

When you take the SEREVENT DISKUS out of the box and foil overwrap pouch, write the **“Pouch opened”** and **“Use by”** dates on the label in the spaces provided on the DISKUS[®] inhalation unit. **The “Use by” date is 6 weeks from date of opening.**

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

The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose indicator number will decrease each time you use the DISKUS. After the DISKUS has delivered 55 doses (23 doses for the institutional or sample pack), numbers 5 to 0 will appear in **red** to warn you that there are only a few doses left (*see Figure 1*).

Figure 1

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

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

Figure 2

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

Figure 3

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

- **Do not close the DISKUS.**
 - **Do not tilt the DISKUS.**
 - **Do not play with the lever.**
 - **Do not advance the lever more than once.**
3. **INHALE:** Before inhaling your dose of SEREVENT DISKUS, breathe out as far as is comfortable, holding the DISKUS level and away from your mouth (*see Figure 4*). **Remember, never breathe out into the DISKUS mouthpiece.**

Figure 4

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

Figure 5

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

CLOSE THE DISKUS when you are finished taking a dose so that the DISKUS will be ready for you to take your next dose. Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go (*see Figure 6*). The DISKUS will click shut. The lever will automatically return to its original position. The DISKUS is now ready for you to take your next scheduled dose. (Repeat steps 1 through 3.)

Figure 6

REMEMBER:

- Never exhale into the DISKUS.
- Never attempt to take the DISKUS apart.
- Always activate and use the DISKUS in a level, horizontal position.
- Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
- Always keep the DISKUS in a dry place.

Storing Your SEREVENT DISKUS

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

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

Further Information

This leaflet does not contain the complete information about your medicine. *If you have any questions, or are not sure about something, then you should ask your doctor or pharmacist.*

You may want to read this leaflet again. Please **DO NOT THROW IT AWAY** until you have finished your medicine.

Your doctor has determined that this product is likely to help your personal health. **USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.** If you have any questions about the use of SEREVENT DISKUS, consult with your doctor.



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