

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SEREVENT DISKUS safely and effectively. See full prescribing information for SEREVENT DISKUS.

SEREVENT DISKUS (salmeterol xinafoate inhalation powder)
FOR ORAL INHALATION USE
Initial U.S. Approval: 1994

WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- Long-acting beta₂-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death. A US trial showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 out of 13,179 subjects on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. (5.1)
- Prescribe SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. (1.1, 5.1)
- Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. (5.1)

INDICATIONS AND USAGE

SEREVENT DISKUS is a LABA indicated for:

- Treatment of asthma in patients aged 4 years and older. (1.1)
- Prevention of exercise-induced bronchospasm (EIB) in patients aged 4 years and older. (1.2)
- Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). (1.3)

Important limitation:

- Not indicated for the relief of acute bronchospasm. (1.1, 1.3)

DOSAGE AND ADMINISTRATION

For oral inhalation only.

- Treatment of asthma in patients aged 4 years and older: 1 inhalation twice daily in addition to concomitant treatment with an inhaled corticosteroid. (2.1)
- EIB: 1 inhalation at least 30 minutes before exercise. (2.2)
- Maintenance treatment of bronchospasm associated with COPD: 1 inhalation twice daily. (2.3)

DOSAGE FORMS AND STRENGTHS

Inhalation Powder. Inhaler containing salmeterol (50 mcg) as a powder formulation for oral inhalation. (3)

CONTRAINDICATIONS

- Asthma: Without concomitant use of a long-term asthma control medication such as an inhaled corticosteroid. (4)
- Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins. (4)

WARNINGS and PRECAUTIONS

- LABA increase the risk of asthma-related death and asthma-related hospitalizations. Prescribe for asthma only as concomitant therapy with an inhaled corticosteroid. (5.1)
- Do not initiate in acutely deteriorating asthma or COPD. Do not use to treat acute symptoms. (5.2)
- Not a substitute for corticosteroids. Patients with asthma must take a concomitant inhaled corticosteroid. (5.3)
- Do not use in combination with an additional medicine containing a LABA because of risk of overdose. (5.4)
- If paradoxical bronchospasm occurs, discontinue SEREVENT DISKUS and institute alternative therapy. (5.5)
- Use with caution in patients with cardiovascular or central nervous system disorders because of beta-adrenergic stimulation. (5.6)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.9)
- Be alert to hypokalemia and hyperglycemia. (5.10)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 5\%$) are:

- Asthma: Headache, influenza, nasal/sinus congestion, pharyngitis, rhinitis, tracheitis/bronchitis. (6.1)
- COPD: Cough, headache, musculoskeletal pain, throat irritation, viral respiratory infection. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): Use not recommended. May increase risk of cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of salmeterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

USE IN SPECIFIC POPULATIONS

Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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1 FULL PRESCRIBING INFORMATION

2 **WARNING: ASTHMA-RELATED DEATH**

3 **Long-acting beta₂-adrenergic agonists (LABA), such as salmeterol, the active**
4 **ingredient in SEREVENT[®] DISKUS[®], increase the risk of asthma-related death. Data from**
5 **a large placebo-controlled US trial that compared the safety of salmeterol with placebo**
6 **added to usual asthma therapy showed an increase in asthma-related deaths in subjects**
7 **receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol**
8 **versus 3 deaths out of 13,179 subjects on placebo). Currently available data are inadequate**
9 **to determine whether concurrent use of inhaled corticosteroids or other long-term asthma**
10 **control drugs mitigates the increased risk of asthma-related death from LABA.**

11 **Because of this risk, use of SEREVENT DISKUS for the treatment of asthma**
12 **without a concomitant long-term asthma control medication, such as an inhaled**
13 **corticosteroid, is contraindicated. Use SEREVENT DISKUS only as additional therapy for**
14 **patients with asthma who are currently taking but are inadequately controlled on a long-**
15 **term asthma control medication, such as an inhaled corticosteroid. Once asthma control is**
16 **achieved and maintained, assess the patient at regular intervals and step down therapy**
17 **(e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and**
18 **maintain the patient on a long-term asthma control medication, such as an inhaled**
19 **corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately**
20 **controlled on low- or medium-dose inhaled corticosteroids.**

21 **Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest**
22 **that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent**
23 **patients. For pediatric and adolescent patients with asthma who require addition of a**
24 **LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an**
25 **inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with**

26 **both drugs. In cases where use of a separate long-term asthma control medication (e.g.,**
27 **inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken**
28 **to ensure adherence with both treatment components. If adherence cannot be assured, a**
29 **fixed-dose combination product containing both an inhaled corticosteroid and a LABA is**
30 **recommended.**

31 **1 INDICATIONS AND USAGE**

32 **1.1 Treatment of Asthma**

33 SEREVENT DISKUS is indicated for the treatment of asthma and in the prevention of
34 bronchospasm only as concomitant therapy with a long-term asthma control medication, such as
35 an inhaled corticosteroid, in patients aged 4 years and older with reversible obstructive airway
36 disease, including patients with symptoms of nocturnal asthma. LABA, such as salmeterol, the
37 active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death [*see*
38 *Warnings and Precautions (5.1)*]. Use of SEREVENT DISKUS for the treatment of asthma
39 without concomitant use of a long-term asthma control medication, such as an inhaled
40 corticosteroid, is contraindicated [*see Contraindications (4)*]. Use SEREVENT DISKUS only as
41 additional therapy for patients with asthma who are currently taking but are inadequately
42 controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once
43 asthma control is achieved and maintained, assess the patient at regular intervals and step down
44 therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and
45 maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.
46 Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or
47 medium-dose inhaled corticosteroids.

48 Pediatric and Adolescent Patients: Available data from controlled clinical trials
49 suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent
50 patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an
51 inhaled corticosteroid, a fixed-dose combination product containing both an inhaled
52 corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In
53 cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid)
54 and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with
55 both treatment components. If adherence cannot be assured, a fixed-dose combination product
56 containing both an inhaled corticosteroid and a LABA is recommended.

57 Important Limitation of Use: SEREVENT DISKUS is NOT indicated for the relief of
58 acute bronchospasm.

59 **1.2 Prevention of Exercise-Induced Bronchospasm**

60 SEREVENT DISKUS is also indicated for prevention of exercise-induced bronchospasm
61 (EIB) in patients aged 4 years and older. Use of SEREVENT DISKUS as a single agent for the
62 prevention of EIB may be clinically indicated in patients who do not have persistent asthma. In
63 patients with persistent asthma, use of SEREVENT DISKUS for the prevention of EIB may be

64 clinically indicated, but the treatment of asthma should include a long-term asthma control
65 medication, such as an inhaled corticosteroid.

66 **1.3 Maintenance Treatment of Chronic Obstructive Pulmonary Disease**

67 SEREVENT DISKUS is indicated for the long-term twice-daily administration in the
68 maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease
69 (COPD) (including emphysema and chronic bronchitis).

70 Important Limitation of Use: SEREVENT DISKUS is NOT indicated for the relief of
71 acute bronchospasm.

72 **2 DOSAGE AND ADMINISTRATION**

73 SEREVENT DISKUS should be administered by the orally inhaled route only.

74 More frequent administration or a greater number of inhalations (more than 1 inhalation
75 twice daily) is not recommended as some patients are more likely to experience adverse effects.
76 Patients using SEREVENT DISKUS should not use additional LABA for any reason. [*See*
77 *Warnings and Precautions (5.4, 5.6).*]

78 **2.1 Asthma**

79 LABA, such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the
80 risk of asthma-related death [*see Warnings and Precautions (5.1)*].

81 **Because of this risk, use of SEREVENT DISKUS for the treatment of asthma**
82 **without concomitant use of a long-term asthma control medication, such as an inhaled**
83 **corticosteroid is contraindicated.** Use SEREVENT DISKUS only as additional therapy for
84 patients with asthma who are currently taking but are inadequately controlled on a long-term
85 asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved
86 and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue
87 SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a
88 long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT
89 DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled
90 corticosteroids.

91 Pediatric and Adolescent Patients: Available data from controlled clinical trials
92 suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent
93 patients. For patients with asthma younger than 18 years who require addition of a LABA to an
94 inhaled corticosteroid, a fixed-dose combination product containing both an inhaled
95 corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In
96 cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid)
97 and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with
98 both treatment components. If adherence cannot be assured, a fixed-dose combination product
99 containing both an inhaled corticosteroid and a LABA is recommended.

100 For bronchodilatation and prevention of symptoms of asthma, including the symptoms of
101 nocturnal asthma, the usual dosage for adults and children aged 4 years and older is 1 inhalation
102 (50 mcg) twice daily, approximately 12 hours apart. If a previously effective dosage regimen

103 fails to provide the usual response, medical advice should be sought immediately as this is often
104 a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be
105 reevaluated. If symptoms arise in the period between doses, an inhaled, short-acting beta₂-
106 agonist should be taken for immediate relief.

107 **2.2 Exercise-Induced Bronchospasm**

108 Use of SEREVENT DISKUS as a single agent for the prevention of EIB may be
109 clinically indicated in patients who do not have persistent asthma. In patients with persistent
110 asthma, use of SEREVENT DISKUS for the prevention of EIB may be clinically indicated, but
111 the treatment of asthma should include a long-term asthma control medication, such as an
112 inhaled corticosteroid. One inhalation of SEREVENT DISKUS at least 30 minutes before
113 exercise has been shown to protect patients against EIB. When used intermittently as needed for
114 prevention of EIB, this protection may last up to 9 hours in adults and adolescents and up to 12
115 hours in patients aged 4 to 11 years. Additional doses of SEREVENT should not be used for 12
116 hours after the administration of this drug. Patients who are receiving SEREVENT DISKUS
117 twice daily should not use additional SEREVENT for prevention of EIB.

118 **2.3 Chronic Obstructive Pulmonary Disease**

119 For maintenance treatment of bronchospasm associated with COPD (including chronic
120 bronchitis and emphysema), the dosage for adults is 1 inhalation (50 mcg) twice daily,
121 approximately 12 hours apart.

122 **3 DOSAGE FORMS AND STRENGTHS**

123 Inhalation Powder. Inhaler containing a foil blister strip of powder formulation for oral
124 inhalation. The strip contains salmeterol 50 mcg per blister.

125 **4 CONTRAINDICATIONS**

126 **Because of the risk of asthma-related death and hospitalization, use of SEREVENT**
127 **DISKUS for the treatment of asthma without concomitant use of a long-term asthma**
128 **control medication, such as an inhaled corticosteroid, is contraindicated [see Warnings and**
129 **Precautions (5.1)].**

130 The use of SEREVENT DISKUS is contraindicated in the following conditions:

- 131 • Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where
132 intensive measures are required [see Warnings and Precautions (5.2)]
- 133 • Severe hypersensitivity to milk proteins [see Warnings and Precautions (5.7), Adverse
134 Reactions (6.3), Description (11)]

135 **5 WARNINGS AND PRECAUTIONS**

136 **5.1 Asthma-Related Death**

137 **LABA, such as salmeterol, the active ingredient in SEREVENT DISKUS, increase**
138 **the risk of asthma-related death. Currently available data are inadequate to determine**
139 **whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs**
140 **mitigates the increased risk of asthma-related death from LABA.**

141 **Because of this risk, use of SEREVENT DISKUS for the treatment of asthma**
142 **without concomitant use of a long-term asthma control medication, such as an inhaled**
143 **corticosteroid, is contraindicated. Use SEREVENT DISKUS only as additional therapy for**
144 **patients with asthma who are currently taking but are inadequately controlled on a long-**
145 **term asthma control medication, such as an inhaled corticosteroid. Once asthma control is**
146 **achieved and maintained, assess the patient at regular intervals and step down therapy**
147 **(e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and**
148 **maintain the patient on a long-term asthma control medication, such as an inhaled**
149 **corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately**
150 **controlled on low- or medium-dose inhaled corticosteroids.**

151 **Pediatric and Adolescent Patients: Available data from controlled clinical trials**
152 **suggest that LABA increase the risk of asthma-related hospitalization in pediatric and**
153 **adolescent patients. For pediatric and adolescent patients with asthma who require**
154 **addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product**
155 **containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure**
156 **adherence with both drugs. In cases where use of a separate long-term asthma control**
157 **medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate**
158 **steps must be taken to ensure adherence with both treatment components. If adherence**
159 **cannot be assured, a fixed-dose combination product containing both an inhaled**
160 **corticosteroid and a LABA is recommended.**

161 The Salmeterol Multi-center Asthma Research Trial (SMART) was a large 28-week
162 placebo-controlled US trial comparing the safety of salmeterol (SEREVENT Inhalation Aerosol)
163 with placebo, each added to usual asthma therapy, that showed an increase in asthma-related
164 deaths in subjects receiving salmeterol [*see Clinical Studies (14.1)*]. Given the similar basic
165 mechanisms of action of beta₂-agonists, the findings seen in the SMART trial are considered a
166 class effect.

167 A 16-week clinical trial performed in the United Kingdom, the Salmeterol Nationwide
168 Surveillance (SNS) trial, showed results similar to the SMART trial. In the SNS trial, the rate of
169 asthma-related death was numerically, though not statistically significantly, greater in subjects
170 with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol (180
171 mcg 4 times daily) added to usual asthma therapy.

172 **The SNS and SMART trials enrolled subjects with asthma. No trials have been**
173 **conducted that were primarily designed to determine whether the rate of death in patients**
174 **with COPD is increased by LABA.**

175 **5.2 Deterioration of Disease and Acute Episodes**

176 SEREVENT DISKUS should not be initiated in patients during rapidly deteriorating or
177 potentially life-threatening episodes of asthma or COPD. SEREVENT DISKUS has not been
178 studied in subjects with acutely deteriorating asthma or COPD. The initiation of SEREVENT
179 DISKUS in this setting is not appropriate.

180 Serious acute respiratory events, including fatalities, have been reported when salmeterol
181 has been initiated in patients with significantly worsening or acutely deteriorating asthma. In
182 most cases, these have occurred in patients with severe asthma (e.g., patients with a history of
183 corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent
184 hospitalizations, previous life-threatening acute asthma exacerbations) and in some patients with
185 acutely deteriorating asthma (e.g., patients with significantly increasing symptoms; increasing
186 need for inhaled, short-acting beta₂-agonists; decreasing response to usual medications;
187 increasing need for systemic corticosteroids; recent emergency room visits; deteriorating lung
188 function). However, these events have occurred in a few patients with less severe asthma as well.
189 It was not possible from these reports to determine whether salmeterol contributed to these
190 events.

191 Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma.
192 In this situation, the patient requires immediate reevaluation with reassessment of the treatment
193 regimen, giving special consideration to the possible need for adding additional inhaled
194 corticosteroid or initiating systemic corticosteroids. Patients should not use more than 1
195 inhalation twice daily of SEREVENT DISKUS.

196 SEREVENT DISKUS should not be used for the relief of acute symptoms, i.e., as rescue
197 therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta₂-
198 agonist, not SEREVENT DISKUS, should be used to relieve acute symptoms such as shortness
199 of breath. When prescribing SEREVENT DISKUS, the healthcare provider should also prescribe
200 an inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of acute symptoms.

201 When beginning treatment with SEREVENT DISKUS, patients who have been taking
202 oral or inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be
203 instructed to discontinue the regular use of these drugs.

204 **5.3 SEREVENT DISKUS is Not a Substitute for Corticosteroids**

205 There are no data demonstrating that SEREVENT DISKUS has a clinical anti-
206 inflammatory effect such as that associated with corticosteroids. When initiating and throughout
207 treatment with SEREVENT DISKUS in patients receiving oral or inhaled corticosteroids for
208 treatment of asthma, patients must continue taking a suitable dosage of corticosteroids to
209 maintain clinical stability even if they feel better as a result of initiating SEREVENT DISKUS.
210 Any change in corticosteroid dosage should be made ONLY after clinical evaluation.

211 **5.4 Excessive Use of SEREVENT DISKUS and Use With Other Long-Acting 212 Beta₂-Agonists**

213 SEREVENT DISKUS should not be used more often than recommended, at higher doses
214 than recommended, or in conjunction with other medicines containing LABA, as an overdose
215 may result. Clinically significant cardiovascular effects and fatalities have been reported in
216 association with excessive use of inhaled sympathomimetic drugs. Patients using SEREVENT
217 DISKUS should not use another medicine containing a LABA (e.g., formoterol fumarate,
218 arformoterol tartrate, indacaterol) for any reason.

219 **5.5 Paradoxical Bronchospasm and Upper Airway Symptoms**

220 As with other inhaled medicines, SEREVENT DISKUS can produce paradoxical
221 bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following
222 dosing with SEREVENT DISKUS, it should be treated immediately with an inhaled, short-acting
223 bronchodilator. SEREVENT DISKUS should be discontinued immediately, and alternative
224 therapy should be instituted. Upper airway symptoms of laryngeal spasm, irritation, or swelling,
225 such as stridor and choking, have been reported in patients receiving SEREVENT DISKUS.

226 **5.6 Cardiovascular and Central Nervous System Effects**

227 Excessive beta-adrenergic stimulation has been associated with seizures, angina,
228 hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias,
229 nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia
230 [see *Overdosage (10)*]. Therefore, SEREVENT DISKUS, like all products containing
231 sympathomimetic amines, should be used with caution in patients with cardiovascular disorders,
232 especially coronary insufficiency, cardiac arrhythmias, and hypertension.

233 Salmeterol can produce a clinically significant cardiovascular effect in some patients as
234 measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon
235 after administration of salmeterol at recommended doses, if they occur, the drug may need to be
236 discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG)
237 changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment
238 depression. The clinical significance of these findings is unknown. Large doses of inhaled or oral
239 salmeterol (12 to 20 times the recommended dose) have been associated with clinically
240 significant prolongation of the QTc interval, which has the potential for producing ventricular
241 arrhythmias. Fatalities have been reported in association with excessive use of inhaled
242 sympathomimetic drugs.

243 **5.7 Immediate Hypersensitivity Reactions**

244 Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm,
245 hypotension), including anaphylaxis, may occur after administration of SEREVENT DISKUS.
246 There have been reports of anaphylactic reactions in patients with severe milk protein allergy
247 after inhalation of powder products containing lactose; therefore, patients with severe milk
248 protein allergy should not take SEREVENT DISKUS [see *Contraindications (4)*].

249 **5.8 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors**

250 The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir,
251 clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole,
252 telithromycin) with SEREVENT DISKUS is not recommended because increased cardiovascular
253 adverse effects may occur [see *Drug Interactions (7.1)*, *Clinical Pharmacology (12.3)*].

254 **5.9 Coexisting Conditions**

255 SEREVENT DISKUS, like all medicines containing sympathomimetic amines, should be
256 used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are
257 unusually responsive to sympathomimetic amines. Doses of the related beta₂-adrenoceptor
258 agonist albuterol, when administered intravenously, have been reported to aggravate preexisting
259 diabetes mellitus and ketoacidosis.

260 **5.10 Hypokalemia and Hyperglycemia**

261 Beta-adrenergic agonist medicines may produce significant hypokalemia in some
262 patients, possibly through intracellular shunting, which has the potential to produce adverse
263 cardiovascular effects [see *Clinical Pharmacology (12.2)*]. The decrease in serum potassium is
264 usually transient, not requiring supplementation. Clinically significant and dose-related changes
265 in blood glucose and/or serum potassium were seen infrequently during clinical trials with
266 SEREVENT DISKUS at recommended doses.

267 **6 ADVERSE REACTIONS**

268 **LABA, including salmeterol, the active ingredient in SEREVENT DISKUS, increase**
269 **the risk of asthma-related death. Data from a large 28-week placebo-controlled US trial**
270 **that compared the safety of salmeterol or placebo added to usual asthma therapy showed**
271 **an increase in asthma-related deaths in subjects receiving salmeterol. Available data from**
272 **controlled clinical trials suggest that LABA increase the risk of asthma-related**
273 **hospitalization in pediatric and adolescent patients [see *Warnings and Precautions (5.1)*,**
274 ***Clinical Studies (14.1)*].**

275 Because clinical trials are conducted under widely varying conditions, adverse reaction
276 rates observed in the clinical trials of a drug cannot be directly compared with rates in the
277 clinical trials of another drug and may not reflect the rates observed in practice.

278 **6.1 Clinical Trials Experience in Asthma**

279 Adult and Adolescent Subjects Aged 12 Years and Older: Two multicenter, 12-
280 week, placebo-controlled clinical trials evaluated twice-daily doses of SEREVENT DISKUS in
281 subjects aged 12 years and older with asthma. Table 1 reports the incidence of adverse reactions
282 in these 2 trials.

283

284 **Table 1. Adverse Reactions With SEREVENT DISKUS With ≥ 3 Incidence and More**
 285 **Common Than Placebo in Adult and Adolescent Subjects With Asthma**

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

286
 287 Table 1 includes all events (whether considered drug-related or nondrug-related by the
 288 investigator) that occurred at a rate of $\geq 3\%$ in the group treated with SEREVENT DISKUS and
 289 were more common than in the placebo group.

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

293 Additional Adverse Reactions: Other adverse reactions not previously listed, whether
 294 considered drug-related or not by the investigators, that were reported more frequently by
 295 subjects with asthma treated with SEREVENT DISKUS compared with subjects treated with
 296 placebo include the following: contact dermatitis, eczema, localized aches and pains, nausea, oral
 297 mucosal abnormality, pain in joint, paresthesia, pyrexia of unknown origin, sinus headache, and
 298 sleep disturbance.

299 Pediatric Subjects Aged 4 to 11 Years: Two multicenter, 12-week, controlled trials
 300 have evaluated twice-daily doses of SEREVENT DISKUS in subjects aged 4 to 11 years with
 301 asthma. Table 2 includes all events (whether considered drug-related or nondrug-related by the
 302 investigator) that occurred at a rate of 3% or greater in the group receiving SEREVENT
 303 DISKUS and were more common than in the placebo group.

304

305 **Table 2. Adverse Reaction Incidence in Two 12-Week Pediatric Clinical Trials in**
 306 **Subjects With Asthma**

Adverse Event	Percent of Subjects		
	Placebo (n = 215)	SEREVENT DISKUS 50 mcg Twice Daily (n = 211)	Albuterol Inhalation Aerosol 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

307
 308 The following events were reported at an incidence of greater than 1% in the salmeterol
 309 group and with a higher incidence than in the albuterol and placebo groups: gastrointestinal signs
 310 and symptoms, lower respiratory signs and symptoms, photodermatitis, and arthralgia and
 311 articular rheumatism.

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

315 Laboratory Test Abnormalities: Elevation of hepatic enzymes was reported in $\geq 1\%$ of
 316 subjects in clinical trials. The elevations were transient and did not lead to discontinuation from
 317 the trials. In addition, there were no clinically relevant changes noted in glucose or potassium.

318 **6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease**

319 Two multicenter, 24-week, placebo-controlled US trials evaluated twice-daily doses of
 320 SEREVENT DISKUS in subjects with COPD. For presentation (Table 3), the placebo data from
 321 a third trial, identical in design, subject entrance criteria, and overall conduct but comparing
 322 fluticasone propionate with placebo, were integrated with the placebo data from these 2 trials
 323 (total N = 341 for salmeterol and 576 for placebo).

324

325 **Table 3. Adverse Reactions With SEREVENT DISKUS With $\geq 3\%$ Incidence in US**
 326 **Controlled Clinical Trials in Subjects With Chronic Obstructive Pulmonary Disease^a**

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

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

331
 332 **Additional Adverse Reactions:** Other adverse reactions occurring in the group
 333 receiving SEREVENT DISKUS that occurred at a frequency of $\geq 1\%$ and were more common
 334 than in the placebo group were as follows: anxiety; arthralgia and articular rheumatism; bone and
 335 skeletal pain; candidiasis mouth/throat; dental discomfort and pain; dyspeptic symptoms; edema
 336 and swelling; gastrointestinal infections; hyperglycemia; hyposalivation; keratitis and
 337 conjunctivitis; lower respiratory signs and symptoms; migraines; muscle pain; muscle stiffness,
 338 tightness, and rigidity; musculoskeletal inflammation; pain; and skin rashes.

339 Adverse reactions to salmeterol are similar in nature to those seen with other selective
340 beta₂-adrenoceptor agonists, e.g., tachycardia; palpitations; immediate hypersensitivity reactions,
341 including urticaria, angioedema, rash, bronchospasm; headache; tremor; nervousness; and
342 paradoxical bronchospasm.

343 Laboratory Abnormalities: There were no clinically relevant changes in these trials.
344 Specifically, no changes in potassium were noted.

345 **6.3 Postmarketing Experience**

346 In addition to adverse reactions reported from clinical trials, the following adverse
347 reactions have been identified during postapproval use of salmeterol. Because these reactions are
348 reported voluntarily from a population of uncertain size, it is not always possible to reliably
349 estimate their frequency or establish a causal relationship to drug exposure. These events have
350 been chosen for inclusion due to either their seriousness, frequency of reporting, or causal
351 connection to salmeterol or a combination of these factors.

352 In extensive US and worldwide postmarketing experience with salmeterol, serious
353 exacerbations of asthma, including some that have been fatal, have been reported. In most cases,
354 these have occurred in patients with severe asthma and/or in some patients in whom asthma has
355 been acutely deteriorating [*see Warnings and Precautions (5.2)*], but they have also occurred in
356 a few patients with less severe asthma. It was not possible from these reports to determine
357 whether salmeterol contributed to these events.

358 Cardiovascular: Arrhythmias (including atrial fibrillation, supraventricular tachycardia,
359 extrasystoles) and anaphylaxis.

360 Non-Site Specific: Very rare anaphylactic reaction in patients with severe milk protein
361 allergy.

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

364 **7 DRUG INTERACTIONS**

365 **7.1 Inhibitors of Cytochrome P450 3A4**

366 Salmeterol is a substrate of CYP3A4. The use of strong CYP3A4 inhibitors (e.g.,
367 ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir,
368 ketoconazole, telithromycin) with SEREVENT DISKUS is not recommended because increased
369 cardiovascular adverse effects may occur.

370 In a drug interaction trial in 20 healthy subjects, coadministration of inhaled salmeterol
371 (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in greater
372 systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold). Three (3)
373 subjects were withdrawn due to beta₂-agonist side effects (2 with prolonged QTc and 1 with
374 palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc,
375 coadministration of salmeterol and ketoconazole was associated with more frequent increases in
376 QTc duration compared with salmeterol and placebo administration.

377 **7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants**

378 SEREVENT DISKUS should be administered with extreme caution to patients being
379 treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of
380 discontinuation of such agents, because the action of salmeterol on the vascular system may be
381 potentiated by these agents.

382 **7.3 Beta-Adrenergic Receptor Blocking Agents**

383 Beta-blockers not only block the pulmonary effect of beta-agonists, such as SEREVENT
384 DISKUS, but may also produce severe bronchospasm in patients with asthma or COPD.
385 Therefore, patients with asthma or COPD should not normally be treated with beta-blockers.
386 However, under certain circumstances, there may be no acceptable alternatives to the use of beta-
387 adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered,
388 although they should be administered with caution.

389 **7.4 Non-Potassium-Sparing Diuretics**

390 The ECG changes and/or hypokalemia that may result from the administration of non-
391 potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-
392 agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the
393 clinical significance of these effects is not known, caution is advised in the coadministration of
394 SEREVENT DISKUS with non-potassium-sparing diuretics.

395 **8 USE IN SPECIFIC POPULATIONS**

396 **8.1 Pregnancy**

397 Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled
398 trials with SEREVENT DISKUS in pregnant women. Beta₂-agonists have been shown to be
399 teratogenic in laboratory animals when administered systemically at relatively low dosage levels.
400 Because animal reproductive studies are not always predictive of human response, SEREVENT
401 DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk
402 to the fetus. Women should be advised to contact their physicians if they become pregnant while
403 taking SEREVENT DISKUS.

404 No teratogenic effects occurred in rats at salmeterol doses approximately 160 times the
405 maximum recommended daily inhalation dose (MRHDID) (on a mg/m² basis at maternal oral
406 doses up to 2 mg/kg/day). In pregnant Dutch rabbits administered oral doses approximately 50
407 times the MRHDID (on an AUC basis at maternal oral doses of 1 mg/kg/day and higher), fetal
408 toxic effects were observed characteristically resulting from beta-adrenoceptor stimulation.
409 These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures,
410 and delayed ossification of the frontal cranial bones. No such effects occurred at a salmeterol
411 dose approximately 20 times the MRHDID (on an AUC basis at a maternal oral dose of 0.6
412 mg/kg/day).

413 New Zealand White rabbits were less sensitive since only delayed ossification of the
414 frontal cranial bones was seen at an oral dose approximately 1,600 times the MRHDID (on a
415 mg/m² basis at a maternal oral dose of 10 mg/kg/day).

416 Salmeterol crossed the placenta following oral administration to mice and rats.

417 **8.2 Labor and Delivery**

418 There are no well-controlled human trials that have investigated effects of salmeterol on
419 preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine
420 contractility, use of SEREVENT DISKUS during labor should be restricted to those patients in
421 whom the benefits clearly outweigh the risks.

422 **8.3 Nursing Mothers**

423 Plasma levels of salmeterol after inhaled therapeutic doses are very low. In rats,
424 salmeterol xinafoate is excreted in the milk. Since there are no data from controlled trials on the
425 use of SEREVENT DISKUS by nursing mothers, caution should be exercised when SEREVENT
426 DISKUS is administered to a nursing woman.

427 **8.4 Pediatric Use**

428 Available data from controlled clinical trials suggest that LABA increase the risk of
429 asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent
430 patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose
431 combination product containing both an inhaled corticosteroid and a LABA should ordinarily be
432 used to ensure adherence with both drugs [*see Indications and Usage (1.1), Warnings and*
433 *Precautions (5.1)*].

434 The safety and efficacy of SEREVENT DISKUS in adolescents (aged 12 years and older)
435 have been established based on adequate and well-controlled trials conducted in adults and
436 adolescents [*see Clinical Studies (14.1)*]. A large 28-week placebo-controlled US trial
437 comparing salmeterol (SEREVENT Inhalation Aerosol) and placebo, each added to usual asthma
438 therapy, showed an increase in asthma-related deaths in patients receiving salmeterol [*see*
439 *Clinical Studies (14.1)*]. Post-hoc analyses in pediatric patients aged 12 to 18 years were also
440 performed. Pediatric patients accounted for approximately 12% of patients in each treatment
441 arm. Respiratory-related death or life-threatening experience occurred at a similar rate in the
442 salmeterol group (0.12% [2/1,653]) and the placebo group (0.12% [2/1,622]; relative risk: 1.0
443 [95% CI: 0.1, 7.2]). All-cause hospitalization, however, was increased in the salmeterol group
444 (2% [35/1,653]) versus the placebo group (less than 1% [16/1,622]; relative risk: 2.1 [95% CI:
445 1.1, 3.7]).

446 The safety and efficacy of SEREVENT DISKUS have been evaluated in over
447 2,500 patients aged 4 to 11 years with asthma, 346 of whom were administered SEREVENT
448 DISKUS for 1 year. Based on available data, no adjustment of dosage of SEREVENT DISKUS
449 in pediatric patients is warranted for either asthma or EIB.

450 In 2 randomized, double-blind, controlled clinical trials of 12 weeks' duration,
451 SEREVENT DISKUS 50 mcg was administered to 211 pediatric patients with asthma who did
452 and who did not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT
453 DISKUS was demonstrated over the 12-week treatment period with respect to peak expiratory
454 flow (PEF) and forced expiratory volume in 1 second (FEV₁). SEREVENT DISKUS was
455 effective in demographic subgroups (gender and age) of the population.

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

459 **8.5 Geriatric Use**

460 Of the total number of adult and adolescent subjects with asthma who received
461 SEREVENT DISKUS in chronic dosing clinical trials, 209 were aged 65 years and older. Of the
462 total number of subjects with COPD who received SEREVENT DISKUS in chronic dosing
463 clinical trials, 167 were aged 65 years and older and 45 were aged 75 years and older. No
464 apparent differences in the safety of SEREVENT DISKUS were observed when geriatric
465 subjects were compared with younger subjects in clinical trials. As with other beta₂-agonists,
466 however, special caution should be observed when using SEREVENT DISKUS in geriatric
467 patients who have concomitant cardiovascular disease that could be adversely affected by beta-
468 agonists. Data from the trials in subjects with COPD suggested a greater effect on FEV₁ of
469 SEREVENT DISKUS in subjects younger than 65 years, as compared with subjects aged 65
470 years and older. However, based on available data, no adjustment of dosage of SEREVENT
471 DISKUS in geriatric patients is warranted.

472 **8.6 Hepatic Impairment**

473 Formal pharmacokinetic studies using SEREVENT DISKUS have not been conducted in
474 patients with hepatic impairment. Since salmeterol is predominantly cleared by hepatic
475 metabolism, impairment of liver function may lead to accumulation of salmeterol in plasma.
476 Therefore, patients with hepatic disease should be closely monitored.

477 **10 OVERDOSAGE**

478 The expected signs and symptoms with overdosage of SEREVENT DISKUS are those of
479 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and
480 symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension,
481 tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle
482 cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia,
483 hypokalemia, metabolic acidosis). Overdosage with SEREVENT DISKUS can lead to clinically
484 significant prolongation of the QTc interval, which can produce ventricular arrhythmias.

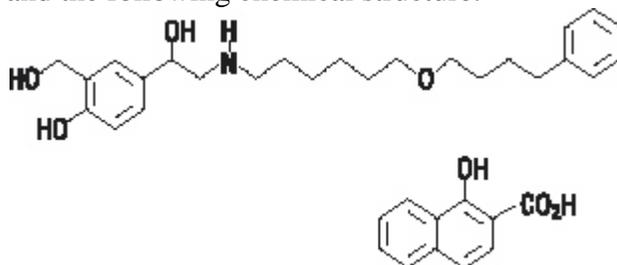
485 As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be
486 associated with an overdose of SEREVENT DISKUS.

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

492 **11 DESCRIPTION**

493 The active component of SEREVENT DISKUS is salmeterol xinafoate, a beta₂-
494 adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-

495 naphthoic acid salt of salmeterol. It has the chemical name 4-hydroxy- α^1 -[[[6-(4-
496 phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-
497 naphthalenecarboxylate and the following chemical structure:



498
499 Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the
500 empirical formula is $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in
501 ethanol, chloroform, and isopropanol; and sparingly soluble in water.

502 SEREVENT DISKUS is a teal green plastic inhaler containing a foil blister strip. Each
503 blister on the strip contains a white powder mix of micronized salmeterol xinafoate salt (72.5
504 mcg, equivalent to 50 mcg of salmeterol base) in 12.5 mg of formulation containing lactose
505 monohydrate (which contains milk proteins). After the inhaler is activated, the powder is
506 dispersed into the airstream created by the patient inhaling through the mouthpiece.

507 Under standardized in vitro test conditions, SEREVENT DISKUS delivers 47 mcg of
508 salmeterol base per blister when tested at a flow rate of 60 L/min for 2 seconds.

509 In adult subjects with obstructive lung disease and severely compromised lung function
510 (mean FEV₁ 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS[®]
511 inhaler was 82.4 L/min (range: 46.1 to 115.3 L/min).

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

514 **12 CLINICAL PHARMACOLOGY**

515 **12.1 Mechanism of Action**

516 Salmeterol is a selective LABA. In vitro studies show salmeterol to be at least 50 times
517 more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the
518 predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the
519 predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart
520 comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors
521 has not been established, but their presence raises the possibility that even selective beta₂-
522 agonists may have cardiac effects.

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

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

535 **12.2 Pharmacodynamics**

536 Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related
537 cardiovascular effects and effects on blood glucose and/or serum potassium [*see Warnings and*
538 *Precautions (5.6, 5.10)*]. The cardiovascular effects (heart rate, blood pressure) associated with
539 salmeterol inhalation aerosol occur with similar frequency, and are of similar type and severity,
540 as those noted following albuterol administration.

541 The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol
542 were studied in volunteers and in subjects with asthma. Salmeterol doses up to 84 mcg
543 administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the
544 same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adult and
545 adolescent subjects receiving 50-mcg doses of salmeterol inhalation powder (n = 60) underwent
546 continuous electrocardiographic monitoring during two 12-hour periods after the first dose and
547 after 1 month of therapy, and no clinically significant dysrhythmias were noted. Also, pediatric
548 patients receiving 50-mcg doses of salmeterol inhalation powder (n = 67) underwent continuous
549 electrocardiographic monitoring during two 12-hour periods after the first dose and after
550 3 months of therapy, and no clinically significant dysrhythmias were noted.

551 In 24-week clinical studies in patients with COPD, the incidence of clinically significant
552 abnormalities on the predose ECGs at Weeks 12 and 24 in patients who received salmeterol
553 50 mcg was not different compared with placebo.

554 No effect of treatment with salmeterol 50 mcg was observed on pulse rate and systolic
555 and diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial
556 vital sign measurements after the first dose (n = 91) and after 12 weeks of therapy (n = 74).
557 Median changes from baseline in pulse rate and systolic and diastolic blood pressure were
558 similar for patients receiving either salmeterol or placebo [*see Adverse Reactions (6.1)*].

559 **Concomitant Use of SEREVENT DISKUS With Other Respiratory Medications:**
560 ***Short-Acting Beta₂-Agonists:*** In two 12-week repetitive-dose clinical trials in adult and
561 adolescent subjects with asthma (N = 149), the mean daily need for additional beta₂-agonist in
562 subjects using SEREVENT DISKUS was approximately 1½ inhalations/day. Twenty-six percent
563 (26%) of the subjects in these trials used between 8 and 24 inhalations of short-acting beta-
564 agonist per day on 1 or more occasions. Nine percent (9%) of the subjects in these trials averaged
565 over 4 inhalations/day over the course of the 12-week trials. No increase in frequency of
566 cardiovascular events was observed among the 3 subjects who averaged 8 to 11 inhalations/day;
567 however, the safety of concomitant use of more than 8 inhalations/day of short-acting beta₂-
568 agonist with SEREVENT DISKUS has not been established. In 29 subjects who experienced

569 worsening of asthma while receiving SEREVENT DISKUS during these trials, albuterol therapy
570 administered via either nebulizer or inhalation aerosol (1 dose in most cases) led to improvement
571 in FEV₁ and no increase in occurrence of cardiovascular adverse events.

572 In 2 clinical trials in subjects with COPD, the mean daily need for additional beta₂-
573 agonist for subjects using SEREVENT DISKUS was approximately 4 inhalations/day. Twenty-
574 four percent (24%) of subjects using SEREVENT DISKUS averaged 6 or more inhalations of
575 albuterol per day over the course of the 24-week trials. No increase in frequency of
576 cardiovascular adverse reactions was observed among subjects who averaged 6 or more
577 inhalations per day.

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

585 In 2 clinical trials in subjects with COPD, 39 subjects receiving SEREVENT DISKUS
586 concurrently with a theophylline product had adverse event rates similar to those in 302 subjects
587 receiving SEREVENT DISKUS without theophylline. Based on the available data, the
588 concomitant administration of methylxanthines with SEREVENT DISKUS did not alter the
589 observed adverse event profile.

590 **Cromoglycate:** In clinical trials, inhaled cromolyn sodium did not alter the safety
591 profile of salmeterol when administered concurrently.

592 **12.3 Pharmacokinetics**

593 Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-
594 hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and
595 eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not
596 predict therapeutic effect.

597 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low
598 or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder
599 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol
600 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7
601 subjects with asthma; plasma concentrations were very low, with mean peak concentrations of
602 167 pg/mL at 20 minutes and no accumulation with repeated doses.

603 **Distribution:** The percentage of salmeterol bound to human plasma proteins averages
604 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much
605 higher concentrations than those achieved following therapeutic doses of salmeterol.

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

609 An in vitro study using human liver microsomes showed that salmeterol is extensively
610 metabolized to α -hydroxysalmeterol (aliphatic oxidation) by CYP3A4. Ketoconazole, a strong
611 inhibitor of CYP3A4, essentially completely inhibited the formation of α -hydroxysalmeterol in
612 vitro.

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

617 The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is
618 highly protein bound (greater than 99%) and has a long elimination half-life of 11 days.

619 Drug Interactions: Inhibitors of Cytochrome P450 3A4: Ketoconazole: In a placebo-
620 controlled crossover drug interaction trial in 20 healthy male and female subjects,
621 coadministration of salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor
622 ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma
623 salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without
624 ketoconazole 15.76 [90% CI: 10.66, 23.31]) mainly due to increased bioavailability of the
625 swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold
626 (90% CI: 1.23, 1.68). Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and
627 ketoconazole coadministration due to beta-agonist-mediated systemic effects (2 with QTc
628 prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and
629 ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood
630 potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc,
631 coadministration of salmeterol and ketoconazole was associated with more frequent increases in
632 QTc duration compared with salmeterol and placebo administration.

633 Erythromycin: In a repeat-dose trial in 13 healthy subjects, concomitant
634 administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol
635 resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with and without erythromycin
636 1.4 [90% CI: 0.96, 2.03], $P = 0.12$), a 3.6-beat/min increase in heart rate ([95% CI: 0.19, 7.03],
637 $P < 0.04$), a 5.8-msec increase in QTc interval ([95% CI: -6.14, 17.77], $P = 0.34$), and no change
638 in plasma potassium.

639 **13 NONCLINICAL TOXICOLOGY**

640 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

641 In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg
642 and above (approximately 20 times the MRHDID for adults and children based on comparison of
643 the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia,
644 cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen
645 at 0.2 mg/kg (approximately 3 times the MRHDID for adults and children based on comparison
646 of the AUCs).

647 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats,
648 salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and
649 ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 and 25 times the MRHDID
650 for adults and children, respectively, on a mg/m² basis). No tumors were seen at 0.21 mg/kg
651 (approximately 15 and 8 times the MRHDID for adults and children, respectively, on a mg/m²
652 basis). These findings in rodents are similar to those reported previously for other beta-
653 adrenergic agonist drugs. The relevance of these findings to human use is unknown.

654 Salmeterol produced no detectable or reproducible increases in microbial and mammalian
655 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo
656 in a rat micronucleus test. No effects on fertility were identified in rats treated with salmeterol at
657 oral doses up to 2 mg/kg (approximately 160 times the MRHDID for adults on a mg/m² basis).

658 **13.2 Animal Toxicology and/or Pharmacology**

659 Preclinical: Studies in laboratory animals (minipigs, rodents, and dogs) have
660 demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence
661 of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently.
662 The clinical relevance of these findings is unknown.

663 **14 CLINICAL STUDIES**

664 **14.1 Asthma**

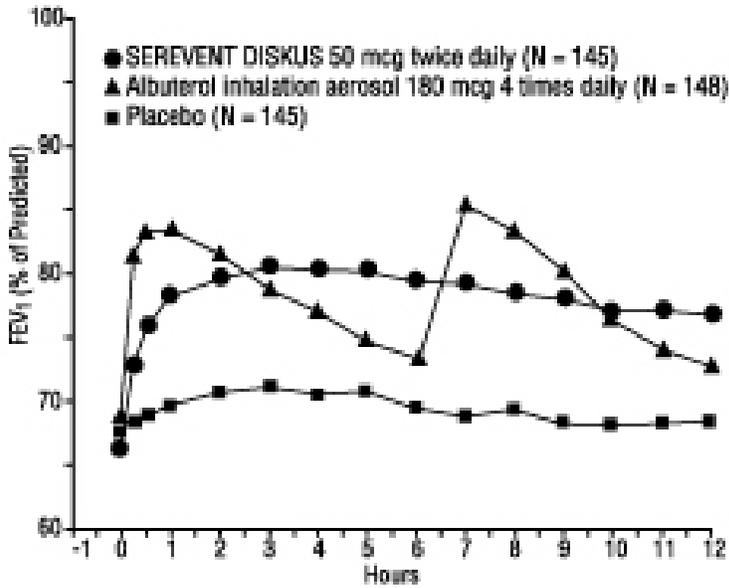
665 The initial trials supporting the approval of SEREVENT DISKUS for the treatment of
666 asthma did not require the regular use of inhaled corticosteroids. However, for the treatment of
667 asthma, SEREVENT DISKUS is currently indicated only as concomitant therapy with an inhaled
668 corticosteroid [*see Indications and Usage (1.1)*].

669 Adult and Adolescent Subjects Aged 12 Years and Older: In 2 randomized double-
670 blind trials, SEREVENT DISKUS was compared with albuterol inhalation aerosol and placebo
671 in adolescent and adult subjects with mild-to-moderate asthma (protocol defined as 50% to 80%
672 predicted FEV₁, actual mean of 67.7% at baseline), including subjects who did and who did not
673 receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was
674 demonstrated over the 12-week period with no change in effectiveness over this time period (see
675 Figure 1). There were no gender- or age-related differences in safety or efficacy. No
676 development of tachyphylaxis to the bronchodilator effect was noted in these trials. FEV₁
677 measurements (mean change from baseline) from these two 12-week trials are shown in Figure 1
678 for both the first and last treatment days.

679

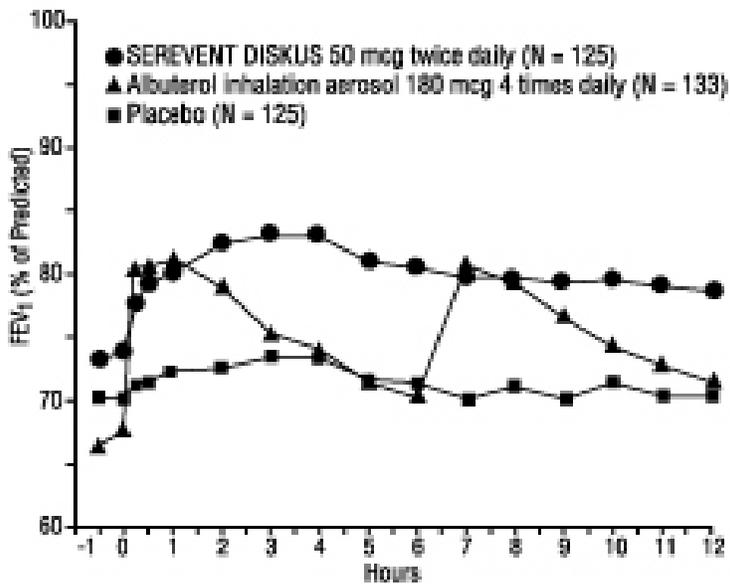
680 **Figure 1. Serial 12-Hour FEV₁ From Two 12-Week**
 681 **Clinical Trials in Subjects With Asthma**

682 **First Treatment Day**



683
 684
 685

Last Treatment Day (Week 12)



686
 687 Table 4 shows the treatment effects seen during daily treatment with SEREVENT
 688 DISKUS for 12 weeks in adolescent and adult subjects with mild-to-moderate asthma.
 689

690 **Table 4. Daily Efficacy Measurements in Two 12-Week Clinical Trials (Combined Data)**

Parameter	Time	Placebo	SEREVENT DISKUS	Albuterol Inhalation Aerosol
No. of randomized subjects		152	149	148
Mean AM peak expiratory flow (L/min)	Baseline	394	395	394
	12 weeks	396	427 ^a	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 ^a	71
Rescue medications (mean no. of inhalations per day)	Baseline	4.2	4.3	4.3
	12 weeks	3.3	1.6 ^b	2.2
Asthma exacerbations (%)		14	15	16

691 ^aStatistically superior to placebo and albuterol ($P < 0.001$).

692 ^bStatistically superior to placebo ($P < 0.001$).

693

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

695 SEREVENT DISKUS and SEREVENT Inhalation Aerosol were compared with placebo
696 in 2 additional randomized double-blind clinical trials in adolescent and adult subjects with mild-
697 to-moderate asthma. SEREVENT DISKUS 50 mcg and SEREVENT Inhalation Aerosol 42 mcg,
698 both administered twice daily, produced significant improvements in pulmonary function
699 compared with placebo over the 12-week period. While no statistically significant differences
700 were observed between the active treatments for any of the efficacy assessments or safety
701 evaluations performed, there were some efficacy measures on which the metered-dose inhaler
702 appeared to provide better results. Similar findings were noted in 2 randomized, single-dose,
703 crossover comparisons of SEREVENT DISKUS and SEREVENT Inhalation Aerosol for the
704 prevention of EIB. Therefore, while SEREVENT DISKUS was comparable to SEREVENT
705 Inhalation Aerosol in clinical trials in mild-to-moderate subjects with asthma, it should not be
706 assumed that they will produce clinically equivalent outcomes in all subjects.

707 *Subjects on Concomitant Inhaled Corticosteroids:* In 4 clinical trials in adult and
708 adolescent subjects with asthma (N = 1,922), the effect of adding SEREVENT Inhalation
709 Aerosol to inhaled corticosteroid therapy was evaluated over a 24-week treatment period. The
710 trials compared the addition of salmeterol therapy to an increase (at least doubling) of the inhaled
711 corticosteroid dose.

712 Two randomized, double-blind, controlled, parallel-group clinical trials (N = 997)
713 enrolled subjects (aged 18 to 82 years) with persistent asthma who were previously maintained
714 but not adequately controlled on inhaled corticosteroid therapy. During the 2-week run-in period,
715 all subjects were switched to beclomethasone dipropionate (BDP) 168 mcg twice daily. Subjects

716 still not adequately controlled were randomized to either the addition of SEREVENT Inhalation
717 Aerosol 42 mcg twice daily or an increase of BDP to 336 mcg twice daily. As compared with the
718 doubled dose of BDP, the addition of SEREVENT Inhalation Aerosol resulted in statistically
719 significantly greater improvements in pulmonary function and asthma symptoms, and
720 statistically significantly greater reduction in supplemental albuterol use. The percent of subjects
721 who experienced asthma exacerbations overall was not different between groups (i.e., 16.2% in
722 the group receiving SEREVENT Inhalation Aerosol versus 17.9% in the higher-dose
723 beclomethasone dipropionate group).

724 Two randomized, double-blind, controlled, parallel-group clinical trials (N = 925)
725 enrolled subjects (aged 12 to 78 years) with persistent asthma who were previously maintained
726 but not adequately controlled on prior asthma therapy. During the 2- to 4-week run-in period, all
727 subjects were switched to fluticasone propionate 88 mcg twice daily. Subjects still not
728 adequately controlled were randomized to either the addition of SEREVENT Inhalation Aerosol
729 42 mcg twice daily or an increase of fluticasone propionate to 220 mcg twice daily. As compared
730 with the increased (2.5 times) dose of fluticasone propionate, the addition of SEREVENT
731 Inhalation Aerosol resulted in statistically significantly greater improvements in pulmonary
732 function and asthma symptoms, and statistically significantly greater reductions in supplemental
733 albuterol use. Fewer subjects receiving SEREVENT Inhalation Aerosol experienced asthma
734 exacerbations than those receiving the higher dose of fluticasone propionate (8.8% versus
735 13.8%).

736 Table 5 shows the treatment effects seen during daily treatment with SEREVENT
737 Inhalation Aerosol for 24 weeks in adolescent and adult subjects with mild-to-moderate asthma.

738 *Onset of Action:* During the initial treatment day in several multiple-dose clinical
739 trials with SEREVENT DISKUS in subjects with asthma, the median time to onset of clinically
740 significant bronchodilatation ($\geq 15\%$ improvement in FEV₁) ranged from 30 to 48 minutes after a
741 50-mcg dose.

742 One hour after a single dose of 50 mcg of SEREVENT DISKUS, the majority of subjects
743 had $\geq 15\%$ improvement in FEV₁. Maximum improvement in FEV₁ generally occurred within
744 180 minutes, and clinically significant improvement continued for 12 hours in most subjects.

745 Pediatric Subjects: In a randomized, double-blind, controlled trial (N = 449), 50 mcg of
746 SEREVENT DISKUS was administered twice daily to pediatric subjects with asthma who did
747 and who did not receive concurrent inhaled corticosteroids. The efficacy of salmeterol inhalation
748 powder was demonstrated over the 12-week treatment period with respect to periodic serial PEF
749 (36% to 39% postdose increase from baseline) and FEV₁ (32% to 33% postdose increase from
750 baseline). Salmeterol was effective in demographic subgroup analyses (gender and age) and was
751 effective when coadministered with other inhaled asthma medications such as short-acting
752 bronchodilators and inhaled corticosteroids. A second randomized, double-blind, placebo-
753 controlled trial (N = 207) with 50 mcg of salmeterol inhalation powder via an alternate device
754 supported the findings of the trial with the DISKUS.

755 Salmeterol Multi-center Asthma Research Trial: The SMART trial was a randomized
756 double-blind trial that enrolled LABA-naive subjects with asthma (average age of 39 years; 71%
757 Caucasian, 18% African American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT
758 Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared with placebo when added to
759 usual asthma therapy.

760 A planned interim analysis was conducted when approximately half of the intended
761 number of subjects had been enrolled (N = 26,355), which led to premature termination of the
762 trial. The results of the interim analysis showed that subjects receiving salmeterol were at
763 increased risk for fatal asthma events (see Table 5 and Figure 2). In the total population, a higher
764 rate of asthma-related death occurred in subjects treated with salmeterol than those treated with
765 placebo (0.10% versus 0.02%, relative risk: 4.37 [95% CI: 1.25, 15.34]).

766 Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death
767 occurred at a higher rate in subjects treated with salmeterol than in subjects treated with placebo
768 (0.07% versus 0.01%, relative risk: 5.82 [95% CI: 0.70, 48.37]). In African Americans also,
769 asthma-related death occurred at a higher rate in subjects treated with salmeterol than those
770 treated with placebo (0.31% versus 0.04%, relative risk: 7.26 [95% CI: 0.89, 58.94]). Although
771 the relative risks of asthma-related death were similar in Caucasians and African Americans, the
772 estimate of excess deaths in subjects treated with salmeterol was greater in African Americans
773 because there was a higher overall rate of asthma-related death in African American subjects (see
774 Table 5).

775 Post-hoc analyses in pediatric subjects aged 12 to 18 years were also performed. Pediatric
776 subjects accounted for approximately 12% of subjects in each treatment arm. Respiratory-related
777 death or life-threatening experience occurred at a similar rate in the salmeterol group (0.12%
778 [2/1,653]) and the placebo group (0.12% [2/1,622]; relative risk: 1.0 [95% CI: 0.1, 7.2]). All-
779 cause hospitalization, however, was increased in the salmeterol group (2% [35/1,653]) versus the
780 placebo group (less than 1% [16/1,622]; relative risk: 2.1 [95% CI: 1.1, 3.7]).

781 The data from the SMART trial are not adequate to determine whether concurrent use of
782 inhaled corticosteroids or other long-term asthma control therapy mitigates the risk of asthma-
783 related death.

784

785 **Table 5: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research**
 786 **Trial (SMART)**

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

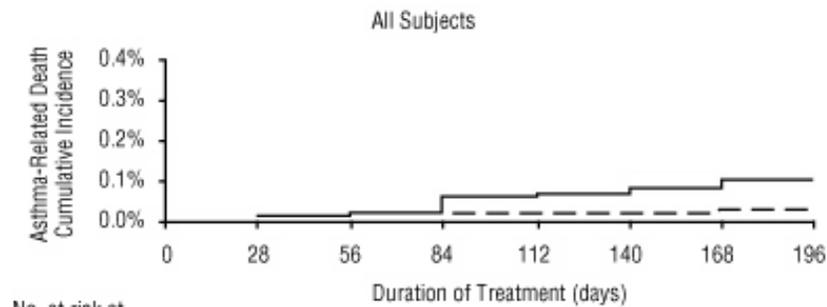
787 ^a Life-table 28-week estimate, adjusted according to the subjects' actual lengths of exposure to
 788 study treatment to account for early withdrawal of subjects from the study.

789 ^b Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the
 790 rate in the placebo group. The relative risk indicates how many more times likely an asthma-
 791 related death occurred in the salmeterol group than in the placebo group in a 28-week
 792 treatment period.

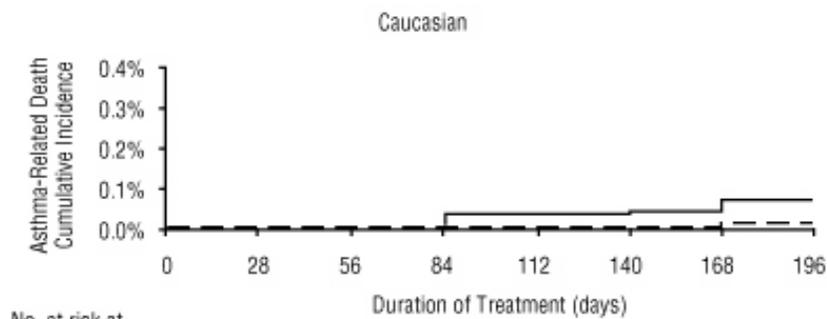
793 ^c Estimate of the number of additional asthma-related deaths in subjects treated with salmeterol
 794 in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period.
 795 Estimate calculated as the difference between the salmeterol and placebo groups in the rates of
 796 asthma-related death multiplied by 10,000.

797 ^d The Total Population includes the following ethnic origins listed on the case report form:
 798 Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population
 799 includes those subjects whose ethnic origin was not reported. The results for Caucasian and
 800 African American subpopulations are shown above. No asthma-related deaths occurred in the
 801 Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149),
 802 or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death
 803 occurred in the placebo group in the subpopulation whose ethnic origin was not reported
 804 (salmeterol n = 130, placebo n = 127).
 805

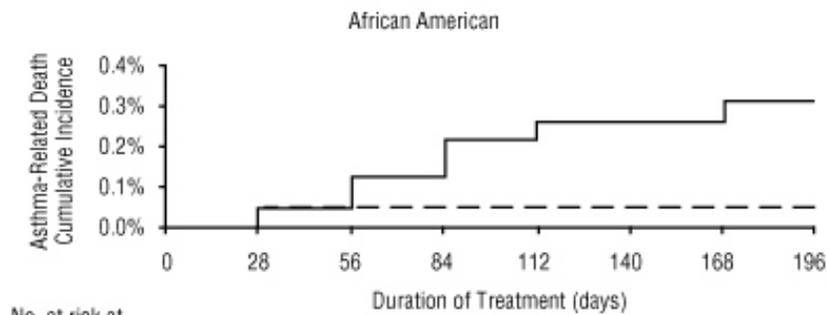
806 **Figure 2. Cumulative Incidence of Asthma-Related Deaths**
 807 **in the 28-Week Salmeterol Multi-center Asthma Research**
 808 **Trial (SMART), by Duration of Treatment**



No. at risk at start of interval		0	28	56	84	112	140	168	196
—	Salmeterol	13,176	13,065	12,764	12,480	12,211	11,913	11,535	
- -	Placebo	13,179	13,050	12,706	12,416	12,136	11,865	11,525	



No. at risk at start of interval		0	28	56	84	112	140	168	196
—	Salmeterol	9,281	9,202	9,020	8,850	8,699	8,503	8,271	
- -	Placebo	9,361	9,266	9,053	8,884	8,722	8,546	8,330	



No. at risk at start of interval		0	28	56	84	112	140	168	196
—	Salmeterol	2,366	2,351	2,271	2,201	2,114	2,048	1,972	
- -	Placebo	2,319	2,303	2,225	2,156	2,078	2,023	1,953	

809

810

811 **14.2 Exercise-Induced Bronchospasm**

812 In 2 randomized, single-dose, crossover trials in adolescents and adults with EIB
 813 (N = 52), 50 mcg of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to
 814 exercise. For some subjects, this protective effect against EIB was still apparent up to 8.5 hours
 815 following a single dose (see Table 6).
 816

817 **Table 6. Results of 2 Exercise-Induced Bronchospasm Studies in Adolescents and Adults**

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

818
 819 In 2 randomized trials in children aged 4 to 11 years with asthma and EIB (N = 50), a
 820 single 50-mcg dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to
 821 exercise, with protection lasting up to 11.5 hours in repeat testing following this single dose in
 822 many subjects.

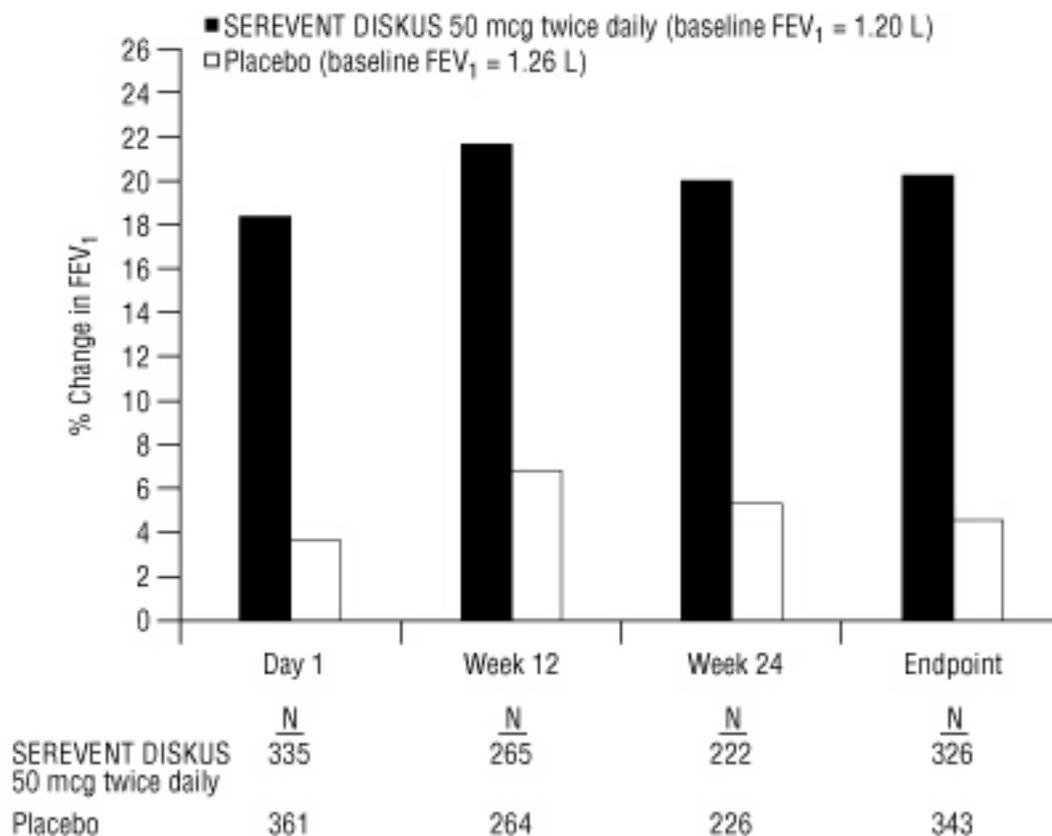
823 **14.3 Chronic Obstructive Pulmonary Disease**

824 In 2 clinical trials evaluating twice-daily treatment with SEREVENT DISKUS 50 mcg
 825 (n = 336) compared with placebo (n = 366) in patients with chronic bronchitis with airflow
 826 limitation, with or without emphysema, improvements in pulmonary function endpoints were
 827 greater with salmeterol 50 mcg than with placebo. Treatment with SEREVENT DISKUS did not
 828 result in significant improvements in secondary endpoints assessing COPD symptoms in either
 829 clinical trial. Both trials were randomized, double-blind, parallel-group trials of 24 weeks'
 830 duration and were identical in design, patient entrance criteria, and overall conduct.

831 Figure 3 displays the integrated 2-hour postdose FEV₁ results from the 2 clinical trials.
 832 The percent change in FEV₁ refers to the change from baseline, defined as the predose value on
 833 Treatment Day 1. To account for subject withdrawals during the trial, Endpoint (last evaluable
 834 FEV₁) data are provided. Subjects receiving SEREVENT DISKUS 50 mcg had significantly
 835 greater improvements in 2-hour postdose FEV₁ at Endpoint (216 mL, 20%) compared with
 836 placebo (43 mL, 5%). Improvement was apparent on the first day of treatment and maintained
 837 throughout the 24 weeks of treatment.

838

839 **Figure 3. Mean Percent Change From Baseline in Postdose FEV₁ Integrated Data**
840 **From 2 Trials of Subjects With Chronic Bronchitis and Airflow Limitation**

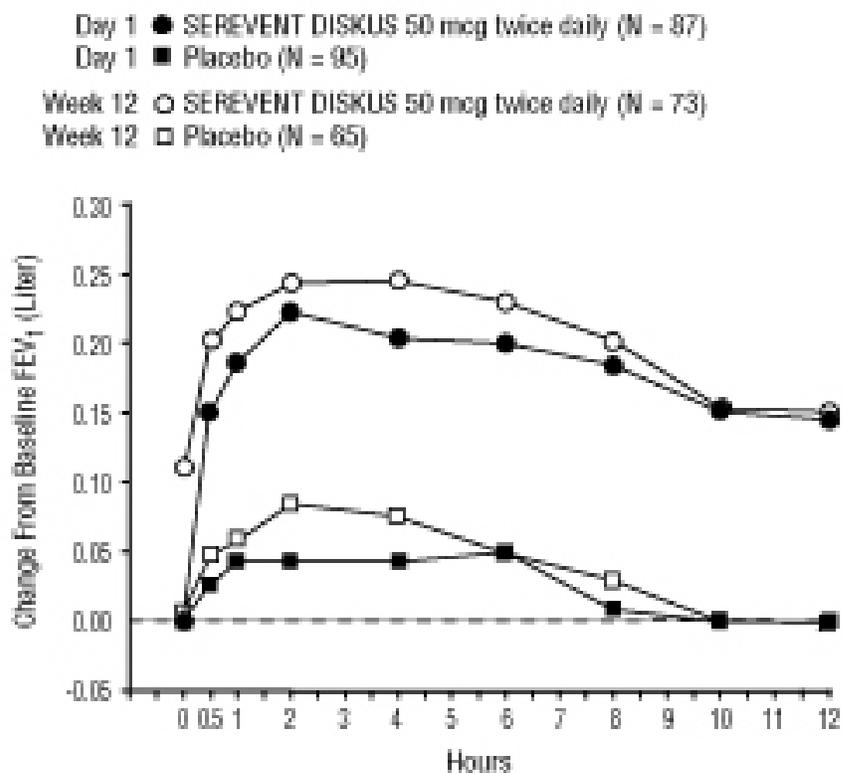


841

842 Onset of Action and Duration of Effect: The onset of action and duration of effect of
843 SEREVENT DISKUS were evaluated in a subset of subjects (n = 87) from 1 of the 2 clinical
844 trials discussed above. Following the first 50-mcg dose, significant improvement in pulmonary
845 function (mean FEV₁ increase of 12% or more and at least 200 mL) occurred at 2 hours. The
846 mean time to peak bronchodilator effect was 4.75 hours. As seen in Figure 4, evidence of
847 bronchodilatation was seen throughout the 12-hour period. Figure 4 also demonstrates that the
848 bronchodilating effect after 12 weeks of treatment was similar to that observed after the first
849 dose. The mean time to peak bronchodilator effect after 12 weeks of treatment was 3.27 hours.

850

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



853

854 **16 HOW SUPPLIED/STORAGE AND HANDLING**

855 SEREVENT DISKUS is supplied as a disposable teal green plastic inhaler containing a
 856 foil blister strip with 60 blisters. The inhaler is packaged in a plastic-coated, moisture-protective
 857 foil pouch (NDC 0173-0521-00).

858 SEREVENT DISKUS is also supplied in an institutional pack containing 28 blisters
 859 (NDC 0173-0520-00).

860 Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions
 861 permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in
 862 a dry place away from direct heat or sunlight. Keep out of reach of children.

863 SEREVENT DISKUS should be stored inside the unopened moisture-protective foil
 864 pouch and only removed from the pouch immediately before initial use. Discard SEREVENT
 865 DISKUS 6 weeks after opening the foil pouch or when the counter reads “0” (after all blisters
 866 have been used), whichever comes first. The inhaler is not reusable. Do not attempt to take the
 867 inhaler apart.

868 **17 PATIENT COUNSELING INFORMATION**

869 Advise the patient to read the FDA-approved patient labeling (Medication Guide and
 870 Instructions for Use).

871 **Asthma-Related Death: Inform patients that salmeterol increases the risk of**
872 **asthma-related death and may increase the risk of asthma-related hospitalization in**
873 **pediatric and adolescent patients. Inform patients that SEREVENT DISKUS should not be**
874 **the only therapy for the treatment of asthma and must only be used as additional therapy**
875 **when long-term asthma control medications (e.g., inhaled corticosteroids) do not**
876 **adequately control asthma symptoms. Also inform them that currently available data are**
877 **inadequate to determine whether concurrent use of inhaled corticosteroids or other long-**
878 **term asthma control drugs mitigates the increased risk of asthma-related death from**
879 **LABA. Inform patients that when SEREVENT DISKUS is added to their treatment**
880 **regimen they must continue to use their long-term asthma control medication.**

881 **Not for Acute Symptoms: Inform patients that SEREVENT DISKUS is not meant to**
882 **relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for**
883 **that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta₂-agonist**
884 **such as albuterol. Provide patients with such medication and instruct them in how it should be**
885 **used.**

886 Instruct patients to seek medical attention immediately if they experience any of the
887 following:

- 888 • Decreasing effectiveness of inhaled, short-acting beta₂-agonists
- 889 • Need for more inhalations than usual of inhaled, short-acting beta₂-agonists
- 890 • Significant decrease in lung function as outlined by the physician

891 Tell patients they should not stop therapy with SEREVENT DISKUS without
892 physician/provider guidance since symptoms may recur after discontinuation.

893 **Not a Substitute for Corticosteroids: Advise all patients with asthma that they must**
894 **also continue regular maintenance treatment with an inhaled corticosteroid if they are taking**
895 **SEREVENT DISKUS.**

896 SEREVENT DISKUS should not be used as a substitute for oral or inhaled
897 corticosteroids. The dosage of these medications should not be changed and they should not be
898 stopped without consulting the physician, even if the patient feels better after initiating treatment
899 with SEREVENT DISKUS.

900 **Do Not Use Additional Long-Acting Beta₂-Agonists: Instruct patients not to use other**
901 **LABA.**

902 **Immediate Hypersensitivity Reactions: Advise patients that immediate**
903 **hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension),**
904 **including anaphylaxis, may occur after administration of SEREVENT DISKUS. Patients should**
905 **discontinue SEREVENT DISKUS if such reactions occur. There have been reports of**
906 **anaphylactic reactions in patients with severe milk protein allergy after inhalation of powder**
907 **products containing lactose; therefore, patients with severe milk protein allergy should not take**
908 **SEREVENT DISKUS.**

909 **Risks Associated With Beta-Agonist Therapy: Inform patients of adverse effects**
910 **associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or**
911 **nervousness.**

912 Treatment of Exercise-Induced Bronchospasm: Patients using SEREVENT DISKUS
913 for the treatment of EIB should not use additional doses for 12 hours. Patients who are receiving
914 SEREVENT DISKUS twice daily should not use additional SEREVENT for prevention of EIB.

915
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919
920 GlaxoSmithKline
921 Research Triangle Park, NC 27709

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925 SRD:xPI

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MEDICATION GUIDE

929 **SEREVENT® DISKUS® [ser' uh-vent disk' us]**
930 **(salmeterol xinafoate inhalation powder)**

931
932 Read the Medication Guide that comes with SEREVENT DISKUS before you start
933 using it and each time you get a refill. There may be new information. This
934 Medication Guide does not take the place of talking to your healthcare provider
935 about your medical condition or treatment.

936
937 **What is the most important information I should know about SEREVENT**
938 **DISKUS?**

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

- 940 • **People with asthma who take long-acting beta₂-adrenergic agonist**
941 **(LABA) medicines, such as salmeterol xinafoate (the medicine in**
942 **SEREVENT DISKUS), have an increased risk of death from asthma**
943 **problems.**
- 944 • **It is not known if LABA medicines such as salmeterol xinafoate increase**
945 **the risk of death in people with COPD.**
- 946 • **Call your healthcare provider if breathing problems worsen over time**
947 **while using SEREVENT DISKUS. You may need different treatment.**

- 948 • **Get emergency medical care if:**
949 • your breathing problems worsen quickly.
950 • you use your rescue inhaler, but it does not relieve your breathing problems.
- 951 • **Do not use SEREVENT DISKUS as your only asthma medicine. SEREVENT**
952 **DISKUS must only be used with a long-term asthma control medicine,**
953 **such as an inhaled corticosteroid.**
- 954 • SEREVENT DISKUS should be used only if your healthcare provider decides that
955 your asthma is not well controlled with a long-term asthma control medicine,
956 such as an inhaled corticosteroid. When your asthma is well controlled, your
957 healthcare provider may tell you to stop taking SEREVENT DISKUS. Your
958 healthcare provider will decide if you can stop SEREVENT DISKUS without loss of
959 asthma control. You will continue taking your long-term asthma control
960 medicine, such as an inhaled corticosteroid.
- 961 • Children and adolescents who take LABA medicines may have an increased risk
962 of being hospitalized for asthma problems.
963

964 **What is SEREVENT DISKUS?**

- 965 • SEREVENT DISKUS is a prescription inhaled LABA medicine. LABA medicines
966 such as salmeterol xinafoate help the muscles around the airways in your lungs
967 stay relaxed to prevent symptoms, such as wheezing, cough, chest tightness,
968 and shortness of breath. These symptoms can happen when the muscles around
969 the airways tighten. This makes it hard to breathe.
- 970 • SEREVENT DISKUS is not used to relieve sudden breathing problems.
- 971 • It is not known if SEREVENT DISKUS is safe and effective in children younger
972 than 4 years.
- 973 • SEREVENT DISKUS is used for asthma, exercise-induced bronchospasm (EIB),
974 and chronic obstructive pulmonary disease (COPD) as follows:

975 **Asthma:**

976 SEREVENT DISKUS is a prescription medicine used to control symptoms of
977 asthma and to prevent symptoms such as wheezing in adults and children aged
978 4 years and older.

979 SEREVENT DISKUS contains salmeterol xinafoate. LABA medicines such as
980 salmeterol xinafoate increase the risk of death from asthma problems.

981 SEREVENT DISKUS is not for adults and children with asthma who are well
982 controlled with an asthma control medicine, such as a low to medium dose of an
983 inhaled corticosteroid medicine.

984 **Exercise-Induced Bronchospasm (EIB):**

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

- 987 • If you only have EIB, your healthcare provider may only prescribe SEREVENT
988 DISKUS for your condition.
- 989 • If you have EIB and asthma, your healthcare provider should also prescribe
990 an asthma control medicine, such as an inhaled corticosteroid.

991 **Chronic Obstructive Pulmonary Disease (COPD):**

992 COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or
993 both.

994 SEREVENT DISKUS is a prescription medicine used long term as 1 inhalation 2
995 times each day to improve symptoms of COPD for better breathing.

996

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

998 Do not use SEREVENT DISKUS:

- 999 • to treat your asthma without a long-term asthma control medicine, such as an
1000 inhaled corticosteroid.
- 1001 • if you have a severe allergy to milk proteins. Ask your healthcare provider if you
1002 are not sure.
- 1003 • if you are allergic to salmeterol xinafoate or any of the ingredients in SEREVENT
1004 DISKUS. See “What are the ingredients in SEREVENT DISKUS?” below for a
1005 complete list of ingredients.

1006

1007 **What should I tell my healthcare provider before using SEREVENT DISKUS?**

1008 **Tell your healthcare provider about all of your health conditions, including**
1009 **if you:**

- 1010 • have heart problems.
- 1011 • have high blood pressure.
- 1012 • have seizures.
- 1013 • have thyroid problems.
- 1014 • have diabetes.
- 1015 • have liver problems.

- 1016 • are allergic to any of the ingredients in SEREVENT DISKUS, any other medicines,
1017 or food products. See “What are the ingredients in SEREVENT DISKUS?” below
1018 for a complete list of ingredients.
- 1019 • have any other medical conditions.
- 1020 • are pregnant or planning to become pregnant. It is not known if SEREVENT
1021 DISKUS may harm your unborn baby.
- 1022 • are breastfeeding. It is not known if the medicine in SEREVENT DISKUS passes
1023 into your milk and if it can harm your baby

1024 **Tell your healthcare provider about all the medicines you take**, including
1025 prescription and over-the-counter medicines, vitamins, and herbal supplements.
1026 SEREVENT DISKUS and certain other medicines may interact with each other. This
1027 may cause serious side effects. Especially, tell your healthcare provider if you take
1028 antifungal or anti-HIV medicines.

1029 Know the medicines you take. Keep a list of them to show your healthcare provider
1030 and pharmacist when you get a new medicine.

1031

1032 **How should I use SEREVENT DISKUS?**

1033 **Read the step-by-step instructions for using SEREVENT DISKUS at the end**
1034 **of this Medication Guide.**

- 1035 • **Do not** use SEREVENT DISKUS unless your healthcare provider has taught you
1036 how to use the inhaler and you understand how to use it correctly.
- 1037 • Children should use SEREVENT DISKUS with an adult’s help, as instructed by the
1038 child’s healthcare provider.
- 1039 • Use SEREVENT DISKUS exactly as prescribed. **Do not** use SEREVENT DISKUS
1040 more often than prescribed.
- 1041 • **For asthma and COPD**, the usual dose is 1 inhalation of SEREVENT DISKUS
1042 2 times each day. Use SEREVENT DISKUS at the same time each day, about 12
1043 hours apart.
- 1044 • **For preventing exercise-induced bronchospasm**, the usual dose is
1045 1 inhalation at least 30 minutes before exercise. Do not use SEREVENT DISKUS
1046 more often than every 12 hours. Do not use extra SEREVENT DISKUS before
1047 exercise if you already use it 2 times each day.
- 1048 • If you miss a dose of SEREVENT DISKUS, just skip that dose. Take your next
1049 dose at your usual time. Do not take 2 doses at 1 time.

- 1050 • If you take too much SEREVENT DISKUS, call your healthcare provider or go to
1051 the nearest hospital emergency room right away if you have any unusual
1052 symptoms, such as worsening shortness of breath, chest pain, increased heart
1053 rate, or shakiness.
- 1054 • **Do not use other medicines that contain a LABA for any reason.** Ask your
1055 healthcare provider or pharmacist if any of your other medicines are LABA
1056 medicines.
- 1057 • Do not stop using SEREVENT DISKUS unless told to do so by your healthcare
1058 provider because your symptoms might get worse. Your healthcare provider will
1059 change your medicines as needed.
- 1060 • **SEREVENT DISKUS does not relieve sudden symptoms.** Always have a
1061 rescue inhaler with you to treat sudden symptoms. If you do not have a rescue
1062 inhaler, call your healthcare provider to have one prescribed for you.
- 1063 • Call your healthcare provider or get medical care right away if:
- 1064 • your breathing problems get worse.
 - 1065 • you need to use your rescue inhaler more often than usual.
 - 1066 • your rescue inhaler does not work as well to relieve your symptoms.
 - 1067 • you need to use 4 or more inhalations of your rescue inhaler in 24 hours for
1068 2 or more days in a row.
 - 1069 • you use 1 whole canister of your rescue inhaler in 8 weeks.
 - 1070 • your peak flow meter results decrease. Your healthcare provider will tell you
1071 the numbers that are right for you.
 - 1072 • you have asthma and your symptoms do not improve after using SEREVENT
1073 DISKUS regularly for 1 week.
- 1074

1075 **What are the possible side effects with SEREVENT DISKUS?**

1076 **SEREVENT DISKUS can cause serious side effects, including:**

- 1077 • **See “What is the most important information I should know about**
1078 **SEREVENT DISKUS?”**
- 1079 • **sudden breathing problems immediately after inhaling your medicine**
- 1080 • **effects on heart**
 - 1081 • increased blood pressure
 - 1082 • a fast or irregular heartbeat
 - 1083 • chest pain
- 1084 • **effects on nervous system**
 - 1085 • tremor
 - 1086 • nervousness

- 1087 • **serious allergic reactions.** Call your healthcare provider or get emergency
1088 medical care if you get any of the following symptoms of a serious allergic
1089 reaction:
1090 • rash
1091 • hives
1092 • swelling of your face, mouth, and tongue
1093 • breathing problems.

- 1094 • **changes in laboratory blood values (sugar, potassium)**

1095 **Common side effects of SEREVENT DISKUS include:**

1096 **Asthma:**

- 1097 • headache
1098 • nasal congestion
1099 • bronchitis
1100 • throat irritation
1101 • runny nose
1102 • flu

1103 **COPD:**

- 1104 • headache
1105 • musculoskeletal pain
1106 • throat irritation
1107 • cough
1108 • respiratory infection

1109 Tell your healthcare provider about any side effect that bothers you or that does
1110 not go away.

1111 These are not all the side effects with SEREVENT DISKUS. Ask your healthcare
1112 provider or pharmacist for more information.

1113 Call your doctor for medical advice about side effects. You may report side effects
1114 to FDA at 1-800-FDA-1088.

1115

1116 **How should I store SEREVENT DISKUS?**

- 1117 • Store SEREVENT DISKUS at room temperature between 68°F and 77°F (20°C
1118 and 25°C). Keep in a dry place away from heat and sunlight.
1119 • Store SEREVENT DISKUS in the unopened foil pouch and only open when ready
1120 for use.
1121 • Safely throw away SEREVENT DISKUS in the trash 6 weeks after you open the
1122 foil pouch or when the counter reads 0, whichever comes first.

- **Keep SEREVENT DISKUS and all medicines out of the reach of children.**

1124

1125 **General information about SEREVENT DISKUS**

1126 Medicines are sometimes prescribed for purposes not mentioned in a Medication
1127 Guide. Do not use SEREVENT DISKUS for a condition for which it was not
1128 prescribed. Do not give your SEREVENT DISKUS to other people, even if they have
1129 the same condition that you have. It may harm them.

1130 This Medication Guide summarizes the most important information about SEREVENT
1131 DISKUS. If you would like more information, talk with your healthcare provider or
1132 pharmacist. You can ask your healthcare provider or pharmacist for information
1133 about SEREVENT DISKUS that was written for healthcare professionals.

1134 For more information about SEREVENT DISKUS, call 1-888-825-5249 or visit our
1135 website at www.serevent.com.

1136

1137 **What are the ingredients in SEREVENT DISKUS?**

1138 Active ingredient: salmeterol xinafoate

1139 Inactive ingredient: lactose monohydrate (contains milk proteins)

1140

Instructions for Use

1142 **For Oral Inhalation Only**

1143

1144 **Your SEREVENT DISKUS inhaler**

1145



1146
1147 **Figure A**
1148

1149 **Read this information before you start using your SEREVENT DISKUS** 1150 **inhaler:**

- Take SEREVENT DISKUS out of the foil pouch just before you use it for the first time. Safely throw away the pouch. The DISKUS will be in the closed position.

1153 • Write the date you opened the foil pouch in the first blank line on the label. **See**
1154 **Figure A.**

1155 • Write the “use by” date in the second blank line on the label. **See Figure A.**
1156 That date is 6 weeks after the date you wrote in the first line.

1157 • The counter should read **60**. If you have an institutional pack (with
1158 “INSTITUTIONAL PACK” on the foil pouch), the counter should read **28**.

1159

1160 **How to use your SEREVENT DISKUS inhaler**

1161 **Follow these steps every time you use SEREVENT DISKUS.**

1162 **Step 1. Open your SEREVENT DISKUS.**

1163 • Hold the DISKUS in your left hand and place the thumb of your right hand in the
1164 thumb grip. Push the thumb grip away from you as far as it will go until the
1165 mouthpiece shows and snaps into place. **See Figure B.**

1166 **Step 2. Slide the lever until you hear it click.**

1167 • **Hold the DISKUS in a level, flat position** with the mouthpiece towards you.
1168 Slide the lever away from the mouthpiece as far as it will go until it **clicks**. **See**
1169 **Figure C.**

1170 • The number on the counter will count down by 1. The DISKUS is now ready to
1171 use.



1172 **Figure B**



1173 **Figure C**

1174

1175 Follow the instructions below so you will not accidentally waste a dose:

- 1176 • **Do not** close the DISKUS.
- 1177 • **Do not** tilt the DISKUS.
- 1178 • **Do not** move the lever on the DISKUS.

1179 **Step 3. Inhale your medicine.**

1180 • Before you breathe in your dose from the DISKUS, breathe out (exhale) as long
1181 as you can while you hold the DISKUS level and away from your mouth. **See**

1182 **Figure D.** Do not breathe into the mouthpiece.

- 1183 • Put the mouthpiece to your lips. **See Figure E.** Breathe in quickly and deeply
1184 through the DISKUS. Do not breathe in through your nose.



1185
1186 **Figure D**



1187
1188 **Figure E**

- 1188 • Remove the DISKUS from your mouth **and hold your breath for about**
1189 **10 seconds**, or for as long as is comfortable for you.
- 1190 • **Breathe out slowly as long as you can. See Figure D.**
- 1191 • The DISKUS delivers your dose of medicine as a very fine powder that you may
1192 or may not taste or feel. **Do not** take an extra dose from the DISKUS even if
1193 you do not taste or feel the medicine.

1194 **Step 4. Close the DISKUS.**

- 1195 • Place your thumb in the thumb grip and slide it back towards you as far as it will
1196 go. **See Figure F.** Make sure the DISKUS clicks shut and you cannot see the
1197 mouthpiece.
- 1198 • The DISKUS is now ready for you to take your next scheduled dose in about 12
1199 hours. **When you are ready to take your next dose, repeat Steps 1**
1200 **through 4.**



1201
1202 **Figure F**

1203
1204 **When should you get a refill?**

1205 The counter on top of the DISKUS shows you how many doses are left. After you
1206 have taken **55** doses (**23** doses from the institutional pack), the numbers **5** to **0**

1207 will show in red. **See Figure G.** These numbers warn you there are only a few
1208 doses left and are a reminder to get a refill.
1209



1210
1211 **Figure G**
1212

1213 **For correct use of the DISKUS, remember:**

- 1214 • Always use the DISKUS in a level, flat position.
- 1215 • Make sure the lever firmly clicks into place.
- 1216 • Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- 1217 • **Do not** take an extra dose, even if you did not taste or feel the powder.
- 1218 • **Do not** take the DISKUS apart.
- 1219 • **Do not** wash the DISKUS.
- 1220 • Always keep the DISKUS in a dry place.
- 1221 • **Do not** use the DISKUS with a spacer device.

1222
1223 If you have questions about SEREVENT DISKUS or how to use your inhaler, call
1224 GlaxoSmithKline (GSK) at 1-888-825-5249 or visit www.serevent.com.

1225
1226 **This Medication Guide and Instructions for Use have been approved by the**
1227 **U.S. Food and Drug Administration.**

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