

1 **PRESCRIBING INFORMATION**

2 **ADVAIR<sup>®</sup> HFA 45/21**

3 **(fluticasone propionate 45 mcg and salmeterol 21 mcg\*)**

4 **Inhalation Aerosol**

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6 **ADVAIR<sup>®</sup> HFA 115/21**

7 **(fluticasone propionate 115 mcg and salmeterol 21 mcg\*)**

8 **Inhalation Aerosol**

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10 **ADVAIR<sup>®</sup> HFA 230/21**

11 **(fluticasone propionate 230 mcg and salmeterol 21 mcg\*)**

12 **Inhalation Aerosol**

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14 \*As salmeterol xinafoate salt 30.45 mcg, equivalent to salmeterol base 21 mcg

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16 **For Oral Inhalation Only**

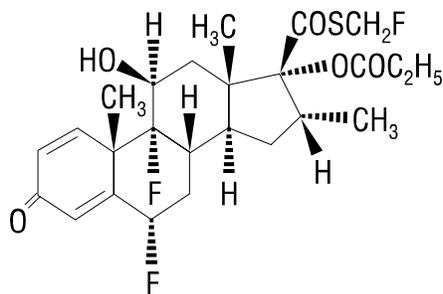
17 **WARNING**

18 Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, one of the active ingredients in  
19 ADVAIR HFA, may increase the risk of asthma-related death. Therefore, when treating patients  
20 with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately  
21 controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled  
22 corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2  
23 maintenance therapies. Data from a large placebo-controlled US study that compared the safety  
24 of salmeterol (SEREVENT<sup>®</sup> Inhalation Aerosol) or placebo added to usual asthma therapy  
25 showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of  
26 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on  
27 placebo) (see WARNINGS).

28 **DESCRIPTION**

29 ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR HFA 115/21 Inhalation Aerosol, and  
30 ADVAIR HFA 230/21 Inhalation Aerosol are combinations of fluticasone propionate and  
31 salmeterol xinafoate.

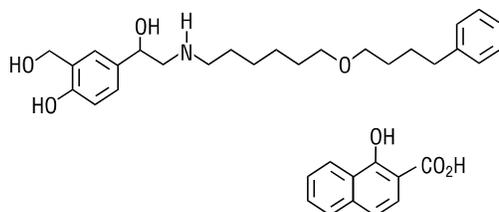
32 One active component of ADVAIR HFA is fluticasone propionate, a corticosteroid having the  
33 chemical name *S*-(fluoromethyl) 6 $\alpha$ ,9-difluoro-11 $\beta$ ,17-dihydroxy-16 $\alpha$ -methyl-3-oxoandrosta-  
34 1,4-diene-17 $\beta$ -carbothioate, 17-propionate and the following chemical structure:  
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Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is  $C_{25}H_{31}F_3O_5S$ . It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of ADVAIR HFA is salmeterol xinafoate, a beta<sub>2</sub>-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy- $\alpha^1$ -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:



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

ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR HFA 115/21 Inhalation Aerosol, and ADVAIR HFA 230/21 Inhalation Aerosol are pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) and salmeterol xinafoate (micronized) in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

After priming, each actuation of the inhaler delivers 50, 125, or 250 mcg of fluticasone propionate and 25 mcg of salmeterol in 75 mg of suspension from the valve. Each actuation delivers 45, 115, or 230 mcg of fluticasone propionate and 21 mcg of salmeterol from the actuator. Twenty-one micrograms (21 mcg) of salmeterol base is equivalent to 30.45 mcg of salmeterol xinafoate. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the device and inspiration through the delivery system.

Each 12-g canister provides 120 inhalations.

65 ADVAIR HFA should be primed before using for the first time by releasing 4 test sprays into  
66 the air away from the face, shaking well for 5 seconds before each spray. In cases where the  
67 inhaler has not been used for more than 4 weeks or when it has been dropped, prime the inhaler  
68 again by shaking well before each spray and releasing 2 test sprays into the air away from the  
69 face.

70 This product does not contain any chlorofluorocarbon (CFC) as the propellant.

## 71 **CLINICAL PHARMACOLOGY**

72 **Mechanism of Action: ADVAIR HFA Inhalation Aerosol:** Since ADVAIR HFA contains  
73 both fluticasone propionate and salmeterol, the mechanisms of action described below for the  
74 individual components apply to ADVAIR HFA. These drugs represent 2 classes of medications  
75 (a synthetic corticosteroid and a selective, long-acting beta<sub>2</sub>-adrenergic receptor agonist) that  
76 have different effects on clinical, physiologic, and inflammatory indices of asthma.

77 **Fluticasone Propionate:** Fluticasone propionate is a synthetic trifluorinated corticosteroid  
78 with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations  
79 have established fluticasone propionate as a human glucocorticoid receptor agonist with an  
80 affinity 18 times greater than dexamethasone, almost twice that of  
81 beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone  
82 dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor  
83 assay in man are consistent with these results.

84 Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have  
85 been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes,  
86 macrophages, and neutrophils) and mediator production or secretion (e.g., histamine,  
87 eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These  
88 anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

89 **Salmeterol Xinafoate:** Salmeterol is a long-acting beta<sub>2</sub>-adrenergic agonist. In vitro studies  
90 and in vivo pharmacologic studies demonstrate that salmeterol is selective for  
91 beta<sub>2</sub>-adrenoceptors compared with isoproterenol, which has approximately equal agonist  
92 activity on beta<sub>1</sub>- and beta<sub>2</sub>-adrenoceptors. In vitro studies show salmeterol to be at least 50 times  
93 more selective for beta<sub>2</sub>-adrenoceptors than albuterol. Although beta<sub>2</sub>-adrenoceptors are the  
94 predominant adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-adrenoceptors are the  
95 predominant receptors in the heart, there are also beta<sub>2</sub>-adrenoceptors in the human heart  
96 comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors  
97 has not been established, but their presence raises the possibility that even selective  
98 beta<sub>2</sub>-agonists may have cardiac effects.

99 The pharmacologic effects of beta<sub>2</sub>-adrenoceptor agonist drugs, including salmeterol, are at  
100 least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes  
101 the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic  
102 AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition  
103 of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

104 In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast  
105 cell mediators, such as histamine, leukotrienes, and prostaglandin D<sub>2</sub>, from human lung.  
106 Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet  
107 activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered  
108 by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol  
109 attenuate allergen-induced bronchial hyper-responsiveness.

110 **Preclinical:** In animals and humans, propellant HFA-134a was found to be rapidly absorbed  
111 and rapidly eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to  
112 7 minutes in humans. Time to maximum plasma concentration (T<sub>max</sub>) and mean residence time  
113 are both extremely short, leading to a transient appearance of HFA-134a in the blood with no  
114 evidence of accumulation.

115 Propellant HFA-134a is devoid of pharmacological activity except at very high doses in  
116 animals (i.e., 380 to 1,300 times the maximum human exposure based on comparisons of area  
117 under the plasma concentration versus time curve [AUC] values), primarily producing ataxia,  
118 tremors, dyspnea, or salivation. These events are similar to effects produced by the structurally  
119 related CFCs, which have been used extensively in metered-dose inhalers. In drug interaction  
120 studies in male and female dogs, there was a slight increase in the salmeterol-related effect on  
121 heart rate (a known effect of beta<sub>2</sub>-agonists) when given in combination with high doses of  
122 fluticasone propionate. This effect was not observed in clinical studies.

123 **Pharmacokinetics: ADVAIR HFA Inhalation Aerosol:** Three single-dose,  
124 placebo-controlled, crossover studies were conducted in healthy subjects: (1) a study using  
125 4 inhalations of ADVAIR HFA 230/21, salmeterol CFC inhalation aerosol 21 mcg, or  
126 fluticasone propionate CFC inhalation aerosol 220 mcg, (2) a study using 8 inhalations of  
127 ADVAIR HFA 45/21, ADVAIR HFA 115/21, or ADVAIR HFA 230/21, and (3) a study using  
128 4 inhalations of ADVAIR HFA 230/21; 2 inhalations of ADVAIR DISKUS<sup>®</sup> 500/50 (fluticasone  
129 propionate 500 mcg and salmeterol 50 mcg inhalation powder); 4 inhalations of fluticasone  
130 propionate CFC inhalation aerosol 220 mcg; or 1,010 mcg of fluticasone propionate given  
131 intravenously. Peak plasma concentrations of fluticasone propionate were achieved in 0.33 to  
132 1.5 hours and those of salmeterol were achieved in 5 to 10 minutes.

133 Peak plasma concentrations of fluticasone propionate (N = 20 subjects) following  
134 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, and ADVAIR HFA 230/21  
135 averaged 41, 108, and 173 pg/mL, respectively. Peak plasma salmeterol concentrations ranged  
136 from 220 to 470 pg/mL.

137 Systemic exposure (N = 20 subjects) from 4 inhalations of ADVAIR HFA 230/21 was 53% of  
138 the value from the individual inhaler for fluticasone propionate CFC inhalation aerosol and 42%  
139 of the value from the individual inhaler for salmeterol CFC inhalation aerosol. Peak plasma  
140 concentrations from ADVAIR HFA for fluticasone propionate (86 vs. 120 pg/mL) and  
141 salmeterol (170 vs. 510 pg/mL) were significantly lower compared to individual inhalers.

142 In 15 healthy subjects, systemic exposure to fluticasone propionate from 4 inhalations of  
143 ADVAIR HFA 230/21 (920/84 mcg) and 2 inhalations of ADVAIR DISKUS 500/50

144 (1,000/100 mcg) were similar between the 2 inhalers (i.e., 799 vs. 832 pg•h/mL, respectively)  
145 but approximately half the systemic exposure from 4 inhalations of fluticasone propionate CFC  
146 inhalation aerosol 220 mcg (880 mcg, AUC = 1,543 pg•h/mL). Similar results were observed for  
147 peak fluticasone propionate plasma concentrations (186 and 182 pg/mL from ADVAIR HFA and  
148 ADVAIR DISKUS, respectively, and 307 pg/mL from the fluticasone propionate CFC inhalation  
149 aerosol). Systemic exposure to salmeterol was higher (317 vs. 169 pg•h/mL) and peak salmeterol  
150 concentrations were lower (196 vs. 223 pg/mL) following ADVAIR HFA compared to ADVAIR  
151 DISKUS, although pharmacodynamic results were comparable.

152 Absolute bioavailability of fluticasone propionate from ADVAIR HFA in 15 healthy subjects  
153 was 5.3%. Terminal half-life estimates of fluticasone propionate for ADVAIR HFA, ADVAIR  
154 DISKUS, and fluticasone propionate CFC inhalation aerosol were similar and averaged  
155 5.6 hours. No terminal half-life estimates were calculated for salmeterol.

156 A double-blind crossover study was conducted in 13 adult patients with asthma to evaluate the  
157 steady-state pharmacokinetics of fluticasone propionate and salmeterol following administration  
158 of 2 inhalations of ADVAIR HFA 115/21 twice daily or 1 inhalation of ADVAIR DISKUS  
159 250/50 twice daily for 4 weeks. Systemic exposure (AUC) to fluticasone propionate was similar  
160 for ADVAIR HFA (274 pg•h/mL [95% CI 150, 502]) and ADVAIR DISKUS (338 pg•h/mL  
161 [95% CI 197, 581]). Systemic exposure to salmeterol was also similar for ADVAIR HFA  
162 (53 pg•h/mL [95% CI 17, 164]) and ADVAIR DISKUS (70 pg•h/mL [95% CI 19, 254]).

163 **Special Populations: Hepatic and Renal Impairment:** Formal pharmacokinetic  
164 studies using ADVAIR HFA have not been conducted to examine gender differences or in  
165 special populations, such as elderly patients or patients with hepatic or renal impairment.  
166 However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic  
167 metabolism, impairment of liver function may lead to accumulation of fluticasone propionate  
168 and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

169 **Drug Interactions:** In repeat- and single-dose studies, there was no evidence of  
170 significant drug interaction on systemic exposure to fluticasone propionate and salmeterol when  
171 given alone or in combination via the DISKUS. Similar definitive studies have not been  
172 performed with ADVAIR HFA.

173 **Fluticasone Propionate: Absorption:** Fluticasone propionate acts locally in the lung;  
174 therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled  
175 and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone  
176 propionate is negligible (<1%), primarily due to incomplete absorption and presystemic  
177 metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered  
178 to the lung is systemically absorbed.

179 **Distribution:** Following intravenous administration, the initial disposition phase for  
180 fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding.  
181 The volume of distribution averaged 4.2 L/kg.

182 The percentage of fluticasone propionate bound to human plasma proteins averages 99%.  
183 Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly  
184 bound to human transcortin.

185 **Metabolism:** The total clearance of fluticasone propionate is high (average,  
186 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only  
187 circulating metabolite detected in man is the 17 $\beta$ -carboxylic acid derivative of fluticasone  
188 propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had  
189 less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of  
190 human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other  
191 metabolites detected in vitro using cultured human hepatoma cells have not been detected in  
192 man.

193 **Elimination:** Following intravenous dosing, fluticasone propionate showed  
194 polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours.  
195 Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the  
196 remainder excreted in the feces as parent drug and metabolites.

197 **Special Populations: Gender:** In 19 male and 33 female patients with asthma,  
198 systemic exposure was similar from 2 inhalations of fluticasone propionate CFC inhalation  
199 aerosol 44, 110, and 220 mcg twice daily.

200 **Drug Interactions:** Fluticasone propionate is a substrate of cytochrome P450 3A4.  
201 Coadministration of fluticasone propionate and the strong cytochrome P450 3A4 inhibitor  
202 ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18  
203 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was  
204 coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate  
205 concentrations following fluticasone propionate aqueous nasal spray alone were undetectable  
206 (<10 pg/mL) in most subjects, and when concentrations were detectable, peak levels ( $C_{max}$ )  
207 averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and  $AUC_{(0-\tau)}$  averaged 8.43 pg•hr/mL (range,  
208 4.2 to 18.8 pg•hr/mL). Fluticasone propionate  $C_{max}$  and  $AUC_{(0-\tau)}$  increased to 318 pg/mL (range,  
209 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively,  
210 after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This  
211 significant increase in systemic fluticasone propionate exposure resulted in a significant decrease  
212 (86%) in serum cortisol AUC.

213 Caution should be exercised when other strong cytochrome P450 3A4 inhibitors are  
214 coadministered with fluticasone propionate. In a drug interaction study, coadministration of  
215 orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted  
216 in increased systemic fluticasone propionate exposure and reduced plasma cortisol AUC, but had  
217 no effect on urinary excretion of cortisol.

218 In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone  
219 propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect  
220 fluticasone propionate pharmacokinetics.

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

225 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low  
226 or undetectable after inhalation of recommended doses (42 mcg of salmeterol inhalation aerosol  
227 twice daily). Following chronic administration of an inhaled dose of 42 mcg twice daily,  
228 salmeterol was detected in plasma within 5 to 10 minutes in 6 patients with asthma; plasma  
229 concentrations were very low, with mean peak concentrations of 150 pg/mL and no  
230 accumulation with repeated doses.

231 **Distribution:** The percentage of salmeterol bound to human plasma proteins averages  
232 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much  
233 higher concentrations than those achieved following therapeutic doses of salmeterol.

234 **Metabolism:** Salmeterol base is extensively metabolized by hydroxylation, with  
235 subsequent elimination predominately in the feces. No significant amount of unchanged  
236 salmeterol base was detected in either urine or feces.

237 An in vitro study using human liver microsomes showed that salmeterol is extensively  
238 metabolized to  $\alpha$ -hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4).  
239 Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of  
240  $\alpha$ -hydroxysalmeterol in vitro.

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

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

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

248 **Inhibitors of Cytochrome P450 3A4: Ketoconazole:** In a placebo-controlled,  
249 crossover drug interaction study in 20 healthy male and female subjects, coadministration of  
250 salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once  
251 daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined  
252 by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76; 90% CI: 10.66, 23.31)  
253 mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma  
254 salmeterol concentrations were increased by 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20  
255 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-  
256 agonist-mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus  
257 tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically  
258 significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although  
259 there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole  
260 was associated with more frequent increases in QTc duration compared with salmeterol and

261 placebo administration. Due to the potential increased risk of cardiovascular adverse events, the  
262 concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir,  
263 atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir,  
264 telithromycin) is not recommended.

265 **Erythromycin:** In a repeat-dose study in 15 healthy subjects, concomitant  
266 administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol  
267 resulted in a 40% increase in salmeterol  $C_{max}$  at steady state (ratio with and without erythromycin  
268 1.4; 90% CI: 0.96, 2.03;  $p = 0.12$ ). Coadministration of salmeterol and erythromycin did not  
269 result in a clinically significant effect on mean heart rate, QTc, or plasma potassium.

270 **Pharmacodynamics: ADVAIR HFA Inhalation Aerosol:** Since systemic  
271 pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher  
272 doses were used to produce measurable effects. Four placebo-controlled, crossover studies were  
273 conducted in healthy subjects: (1) a cumulative-dose study using 42 to 336 mcg of salmeterol  
274 CFC inhalation aerosol given alone or as ADVAIR HFA 115/21, (2) a single-dose study using  
275 4 inhalations of ADVAIR HFA 230/21, salmeterol CFC inhalation aerosol 21 mcg, or  
276 fluticasone propionate CFC inhalation aerosol 220 mcg, (3) a single-dose study using  
277 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, or ADVAIR HFA 230/21, and  
278 (4) a single-dose study using 4 inhalations of ADVAIR HFA 230/21; 2 inhalations of ADVAIR  
279 DISKUS 500/50; 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg; or  
280 1,010 mcg of fluticasone propionate given intravenously. In these studies pulse rate, blood  
281 pressure, QTc interval, glucose, and/or potassium were measured. Comparable or lower effects  
282 were observed for ADVAIR HFA compared to ADVAIR DISKUS or salmeterol alone. The  
283 effect of salmeterol on pulse rate and potassium was not altered by the presence of different  
284 amounts of fluticasone propionate in ADVAIR HFA. The potential effect of salmeterol on the  
285 effects of fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis was also  
286 evaluated in 3 of these studies. Compared with fluticasone propionate CFC inhalation aerosol,  
287 ADVAIR HFA had less effect on 24-hour urinary cortisol excretion and less or comparable  
288 effect on 24-hour serum cortisol. In these crossover studies in healthy subjects, ADVAIR HFA  
289 and ADVAIR DISKUS had similar effects on urinary and serum cortisol.

290 In clinical studies with ADVAIR HFA in patients with asthma, systemic pharmacodynamic  
291 effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) were  
292 similar to or slightly lower in patients treated with ADVAIR HFA compared with patients treated  
293 with salmeterol CFC inhalation aerosol 21 mcg. In 61 adolescent and adult patients with asthma  
294 given ADVAIR HFA (45/21 or 115/21 mcg), continuous 24-hour electrocardiographic  
295 monitoring was performed after the first dose and after 12 weeks of twice-daily therapy, and no  
296 clinically significant dysrhythmias were noted.

297 A 4-way crossover study in 13 patients with asthma compared pharmacodynamics at steady  
298 state following 4 weeks of twice-daily treatment with 2 inhalations of ADVAIR HFA 115/21,  
299 1 inhalation of ADVAIR DISKUS 250/50 mcg, 2 inhalations of fluticasone propionate HFA  
300 inhalation aerosol 110 mcg, and placebo. No significant differences in serum cortisol AUC were

301 observed between active treatments and placebo. Mean 12-hour serum cortisol AUC ratios  
302 comparing active treatment with placebo ranged from 0.9 to 1.2. No statistically or clinically  
303 significant increases in heart rate or QTc interval were observed for any active treatment  
304 compared with placebo.

305 In a 12-week study (see CLINICAL TRIALS: Studies Comparing ADVAIR HFA to  
306 Fluticasone Propionate Alone or Salmeterol Alone: *Study 3*) in patients with asthma,  
307 ADVAIR HFA 115/21 was compared with the individual components, fluticasone propionate  
308 CFC inhalation aerosol 110 mcg and salmeterol CFC inhalation aerosol 21 mcg, and placebo. All  
309 treatments were administered as 2 inhalations twice daily. After 12 weeks of treatment with these  
310 therapeutic doses, the geometric mean ratio of urinary cortisol excretion compared with baseline  
311 was 0.9 for ADVAIR HFA and fluticasone propionate and 1.0 for placebo and salmeterol. In  
312 addition, the ability to increase cortisol production in response to stress, as assessed by  
313 30-minute cosyntropin stimulation in 23 to 32 patients per treatment group, remained intact for  
314 the majority of patients and was similar across treatments. Three patients who received  
315 ADVAIR HFA 115/21 had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing,  
316 compared with 1 patient who received placebo, 2 patients who received fluticasone propionate  
317 110 mcg, and 1 patient who received salmeterol.

318 In another 12-week study (see CLINICAL TRIALS: Studies Comparing ADVAIR HFA to  
319 Fluticasone Propionate Alone or Salmeterol Alone: *Study 4*) in patients with asthma,  
320 ADVAIR HFA 230/21 (2 inhalations twice daily) was compared with ADVAIR DISKUS 500/50  
321 (1 inhalation twice daily) and fluticasone propionate CFC inhalation aerosol 220 mcg  
322 (2 inhalations twice daily). The geometric mean ratio of 24-hour urinary cortisol excretion at  
323 week 12 compared with baseline was 0.9 for all 3 treatment groups.

324 **Fluticasone Propionate:** In clinical trials with fluticasone propionate inhalation powder  
325 using doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin  
326 tests (peak serum cortisol <18 mcg/dL) were noted both in patients receiving fluticasone  
327 propionate and in patients receiving placebo. The incidence of abnormal tests at 500 mcg twice  
328 daily was greater than placebo. In a 2-year study carried out in 64 patients with mild, persistent  
329 asthma (mean FEV<sub>1</sub> 91% of predicted) randomized to fluticasone propionate 500 mcg twice  
330 daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6-hour  
331 cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of  
332 <35 mcg/dL, 1 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year;  
333 repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone  
334 propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal  
335 response at 1 or 2 years.

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

341 The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol were  
342 studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg resulted in  
343 heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by  
344 inhalation aerosol (4 to 10 beats/min). In 2 double-blind asthma studies, patients receiving either  
345 42 mcg of salmeterol inhalation aerosol twice daily (n = 81) or 180 mcg of albuterol inhalation  
346 aerosol 4 times daily (n = 80) underwent continuous electrocardiographic monitoring during four  
347 24-hour periods; no clinically significant dysrhythmias were noted.

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

## 352 **CLINICAL TRIALS**

353 ADVAIR HFA has been studied in patients with asthma 12 years of age and older.  
354 ADVAIR HFA has not been studied in patients under 12 years of age or in patients with COPD.  
355 In clinical trials comparing ADVAIR HFA Inhalation Aerosol with the individual components,  
356 improvements in most efficacy endpoints were greater with ADVAIR HFA than with the use of  
357 either fluticasone propionate or salmeterol alone. In addition, clinical trials showed comparable  
358 results between ADVAIR HFA and ADVAIR DISKUS.

359 **Studies Comparing ADVAIR HFA to Fluticasone Propionate Alone or Salmeterol**  
360 **Alone:** Four (4) double-blind, parallel-group clinical trials were conducted with ADVAIR HFA  
361 in 1,517 adolescent and adult patients ( $\geq 12$  years, mean baseline forced expiratory volume in  
362 1 second [FEV<sub>1</sub>] 65% to 75% of predicted normal) with asthma that was not optimally controlled  
363 on their current therapy. All metered-dose inhaler treatments were inhalation aerosols given as  
364 2 inhalations twice daily, and other maintenance therapies were discontinued.

365 **Study 1: Clinical Trial With ADVAIR HFA 45/21 Inhalation Aerosol:** This  
366 placebo-controlled, 12-week, US study compared ADVAIR HFA 45/21 with fluticasone  
367 propionate CFC inhalation aerosol 44 mcg or salmeterol CFC inhalation aerosol 21 mcg, each  
368 given as 2 inhalations twice daily. The primary efficacy endpoints were predose FEV<sub>1</sub> and  
369 withdrawals due to worsening asthma. This study was stratified according to baseline asthma  
370 therapy: patients using beta-agonists (albuterol alone [n = 142], salmeterol [n = 84], or inhaled  
371 corticosteroids [n = 134] [daily doses of beclomethasone dipropionate 252 to 336 mcg;  
372 budesonide 400 to 600 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol  
373 176 mcg; fluticasone propionate inhalation powder 200 mcg; or triamcinolone acetonide 600 to  
374 800 mcg]). Baseline FEV<sub>1</sub> measurements were similar across treatments: ADVAIR HFA 45/21,  
375 2.29 L; fluticasone propionate 44 mcg, 2.20 L; salmeterol, 2.33 L; and placebo, 2.27 L.

376 Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were  
377 utilized for this placebo-controlled study. Worsening asthma was defined as a clinically  
378 important decrease in FEV<sub>1</sub> or peak expiratory flow (PEF), increase in use of VENTOLIN<sup>®</sup>  
379 (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency

380 intervention or hospitalization due to asthma, or requirement for asthma medication not allowed  
 381 by the protocol. As shown in Table 1, statistically significantly fewer patients receiving  
 382 ADVAIR HFA 45/21 were withdrawn due to worsening asthma compared with salmeterol and  
 383 placebo. Fewer patients receiving ADVAIR HFA 45/21 were withdrawn due to worsening  
 384 asthma compared to fluticasone propionate 44 mcg; however, the difference was not statistically  
 385 significant.

386

387 **Table 1. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously**  
 388 **Treated With Beta<sub>2</sub>-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids**  
 389 **(Study 1)**

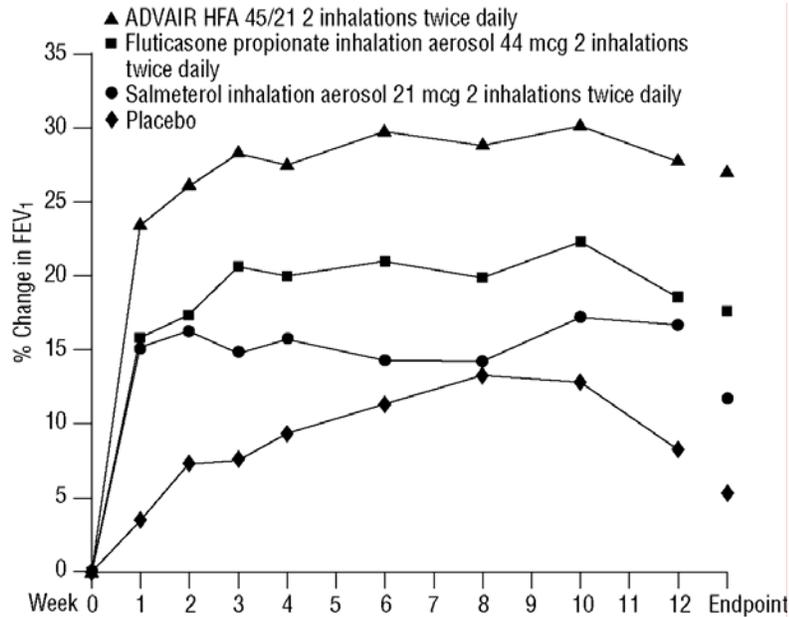
ADVAIR HFA 45/21 (n = 92)	Fluticasone Propionate CFC Inhalation Aerosol 44 mcg (n = 89)	Salmeterol CFC Inhalation Aerosol 21 mcg (n = 92)	Placebo HFA Inhalation Aerosol (n = 87)
2%	8%	25%	28%

390

391 The FEV<sub>1</sub> results are displayed in Figure 1. Because this trial used predetermined criteria for  
 392 worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV<sub>1</sub>  
 393 results at Endpoint (last available FEV<sub>1</sub> result) are also provided. Patients receiving ADVAIR  
 394 HFA 45/21 had significantly greater improvements in FEV<sub>1</sub> (0.58 L, 27%) compared with  
 395 fluticasone propionate 44 mcg (0.36 L, 18%), salmeterol (0.25 L, 12%), and placebo (0.14 L,  
 396 5%). These improvements in FEV<sub>1</sub> with ADVAIR HFA 45/21 were achieved regardless of  
 397 baseline asthma therapy (albuterol alone, salmeterol, or inhaled corticosteroids).

398

399 **Figure 1. Mean Percent Change From Baseline in FEV<sub>1</sub> in Patients**  
 400 **Previously Treated With Either Beta<sub>2</sub>-Agonists (Albuterol or**  
 401 **Salmeterol) or Inhaled Corticosteroids (Study 1)**  
 402



	Week 0	Week 6	Week 12
	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR HFA 45/21	92	88	85
Fluticasone propionate inhalation aerosol 44 mcg	89	84	76
Salmeterol inhalation aerosol 21 mcg	92	72	65
Placebo	87	63	58

403  
 404  
 405 The effect of ADVAIR HFA 45/21 on the secondary efficacy parameters, including morning  
 406 and evening PEF, usage of VENTOLIN Inhalation Aerosol, and asthma symptoms over 24 hours  
 407 on a scale of 0 to 5 is shown in Table 2.  
 408

409 **Table 2. Secondary Efficacy Variable Results for Patients Previously Treated With**  
 410 **Beta<sub>2</sub>-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)**

Efficacy Variable *	ADVAIR HFA 45/21 (n = 92)	Fluticasone Propionate CFC Inhalation Aerosol 44 mcg (n = 89)	Salmeterol CFC Inhalation Aerosol 21 mcg (n = 92)	Placebo HFA Inhalation Aerosol (n = 87)
AM PEF (L/min)				
Baseline	377	369	381	382
Change from baseline	58	27	25	1
PM PEF (L/min)				
Baseline	397	387	402	407
Change from baseline	48	20	16	3
Use of VENTOLIN Inhalation Aerosol (inhalations/day)				
Baseline	3.1	2.4	2.7	2.7
Change from baseline	-2.1	-0.4	-0.8	0.2
Asthma symptom score/day				
Baseline	1.8	1.6	1.7	1.7
Change from baseline	-1.0	-0.3	-0.4	0

411 \*Change from baseline = change from baseline at Endpoint (last available data).  
 412

413 The subjective impact of asthma on patients' perceptions of health was evaluated through use  
 414 of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point  
 415 scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR HFA 45/21  
 416 had clinically meaningful improvements in overall asthma-specific quality of life as defined by a  
 417 difference between groups of  $\geq 0.5$  points in change from baseline AQLQ scores (difference in  
 418 AQLQ score of 1.14 [95% CI 0.85, 1.44] compared to placebo).

419 **Study 2: Clinical Trial With ADVAIR HFA 45/21 Inhalation Aerosol:** This  
 420 active-controlled, 12-week, US study compared ADVAIR HFA 45/21 with fluticasone  
 421 propionate CFC inhalation aerosol 44 mcg and salmeterol CFC inhalation aerosol 21 mcg, each  
 422 given as 2 inhalations twice daily, in 283 patients using as-needed albuterol alone. The primary  
 423 efficacy endpoint was predose FEV<sub>1</sub>. Baseline FEV<sub>1</sub> measurements were similar across  
 424 treatments: ADVAIR HFA 45/21, 2.37 L; fluticasone propionate 44 mcg, 2.31 L; and salmeterol,  
 425 2.34 L.

426 Efficacy results in this study were similar to those observed in Study 1. Patients receiving  
427 ADVAIR HFA 45/21 had significantly greater improvements in FEV<sub>1</sub> (0.69 L, 33%) compared  
428 with fluticasone propionate 44 mcg (0.51 L, 25%) and salmeterol (0.47 L, 22%).

429 **Study 3: Clinical Trial With ADVAIR HFA 115/21 Inhalation Aerosol:** This  
430 placebo-controlled, 12-week, US study compared ADVAIR HFA 115/21 with fluticasone  
431 propionate CFC inhalation aerosol 110 mcg or salmeterol CFC inhalation aerosol 21 mcg, each  
432 given as 2 inhalations twice daily, in 365 patients using inhaled corticosteroids (daily doses of  
433 beclomethasone dipropionate 378 to 840 mcg; budesonide 800 to 1,200 mcg; flunisolide 1,250 to  
434 2,000 mcg; fluticasone propionate inhalation aerosol 440 to 660 mcg; fluticasone propionate  
435 inhalation powder 400 to 600 mcg; or triamcinolone acetonide 900 to 1,600 mcg). The primary  
436 efficacy endpoints were predose FEV<sub>1</sub> and withdrawals due to worsening asthma. Baseline FEV<sub>1</sub>  
437 measurements were similar across treatments: ADVAIR HFA 115/21, 2.23 L; fluticasone  
438 propionate 110 mcg, 2.18 L; salmeterol, 2.22 L; and placebo, 2.17 L.

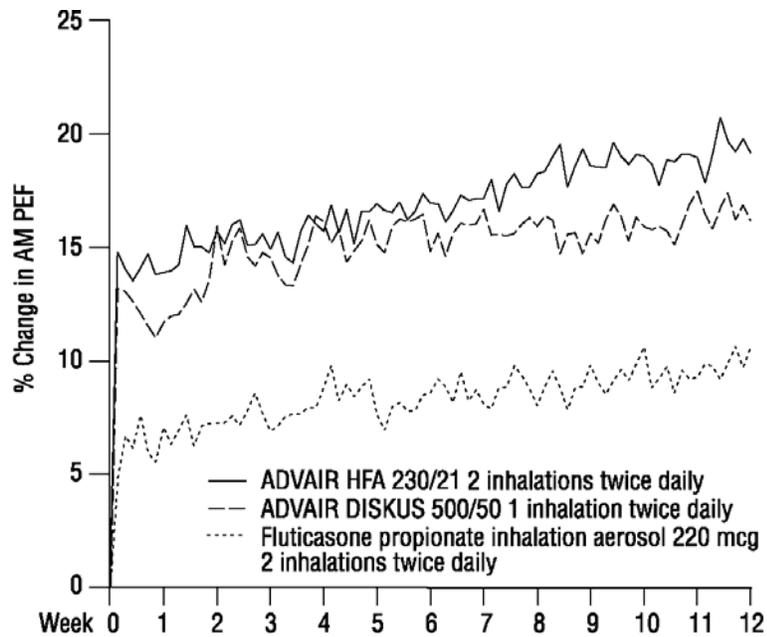
439 Efficacy results in this study were similar to those observed in Studies 1 and 2. Patients  
440 receiving ADVAIR HFA 115/21 had significantly greater improvements in FEV<sub>1</sub> (0.41 L, 20%)  
441 compared with fluticasone propionate 110 mcg (0.19 L, 9%), salmeterol (0.15 L, 8%), and  
442 placebo (-0.12 L, -6%). Significantly fewer patients receiving ADVAIR HFA 115/21 were  
443 withdrawn from this study for worsening asthma (7%) compared to salmeterol (24%) and  
444 placebo (54%). Fewer patients receiving ADVAIR HFA 115/21 were withdrawn due to  
445 worsening asthma (7%) compared to fluticasone propionate 110 mcg (11%); however, the  
446 difference was not statistically significant.

447 **Study 4: Clinical Trial With ADVAIR HFA 230/21 Inhalation Aerosol:** This  
448 active-controlled, 12-week, non-US study compared ADVAIR HFA 230/21 with fluticasone  
449 propionate CFC inhalation aerosol 220 mcg, each given as 2 inhalations twice daily, and with  
450 ADVAIR DISKUS 500/50 given as 1 inhalation twice daily in 509 patients using inhaled  
451 corticosteroids (daily doses of beclomethasone dipropionate CFC inhalation aerosol 1,500 to  
452 2,000 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; fluticasone  
453 propionate inhalation aerosol 660 to 880 mcg; or fluticasone propionate inhalation powder 750 to  
454 1,000 mcg). The primary efficacy endpoint was morning PEF.

455 Baseline morning PEF measurements were similar across treatments: ADVAIR HFA 230/21,  
456 327 L/min; ADVAIR DISKUS 500/50, 341 L/min; and fluticasone propionate 220 mcg,  
457 345 L/min. As shown in Figure 2, morning PEF improved significantly with ADVAIR HFA  
458 230/21 compared with fluticasone propionate 220 mcg over the 12-week treatment period.  
459 Improvements in morning PEF observed with ADVAIR HFA 230/21 were similar to  
460 improvements observed with ADVAIR DISKUS 500/50.

461

462 **Figure 2. Mean Percent Change From Baseline in Morning Peak**  
 463 **Expiratory Flow in Patients Previously Treated With Inhaled**  
 464 **Corticosteroids (Study 4)**  
 465



	Week 0 N	Week 6 N	Week 12 N
ADVAIR HFA 230/21	176	159	130
ADVAIR DISKUS 500/50	161	147	119
Fluticasone propionate inhalation aerosol 220 mcg	172	155	133

466  
467

468 **One-Year Safety Study: Clinical Trial With ADVAIR HFA 45/21, 115/21, and 230/21**  
 469 **Inhalation Aerosol:** This 1-year, open-label, non-US study evaluated the safety of ADVAIR  
 470 HFA 45/21, 115/21, and 230/21 given as 2 inhalations twice daily in 325 patients. This study  
 471 was stratified into 3 groups according to baseline asthma therapy: patients using short-acting  
 472 beta<sub>2</sub>-agonists alone (n = 42), salmeterol (n = 91), or inhaled corticosteroids (n = 277). Patients  
 473 treated with short-acting beta<sub>2</sub>-agonists alone, salmeterol, or low doses of inhaled corticosteroids  
 474 with or without concurrent salmeterol received ADVAIR HFA 45/21. Patients treated with  
 475 moderate doses of inhaled corticosteroids with or without concurrent salmeterol received  
 476 ADVAIR HFA 115/21. Patients treated with high doses of inhaled corticosteroids with or  
 477 without concurrent salmeterol received ADVAIR HFA 230/21. Baseline FEV<sub>1</sub> measurements  
 478 ranged from 2.3 to 2.6 L.

479 Improvements in FEV<sub>1</sub> (0.17 to 0.35 L at 4 weeks) were seen across all 3 treatments and were  
 480 sustained throughout the 52-week treatment period. Few patients (3%) were withdrawn due to  
 481 worsening asthma over 1 year.

482 **Onset of Action and Progression of Improvement in Asthma Control:** The onset of  
 483 action and progression of improvement in asthma control were evaluated in 2 placebo-controlled

484 US trials and 1 active-controlled US trial. Following the first dose, the median time to onset of  
 485 clinically significant bronchodilatation ( $\geq 15\%$  improvement in FEV<sub>1</sub>) in most patients was seen  
 486 within 30 to 60 minutes. Maximum improvement in FEV<sub>1</sub> occurred within 4 hours, and clinically  
 487 significant improvement was maintained for 12 hours (see Figure 3).

488 Following the initial dose, predose FEV<sub>1</sub> relative to day 1 baseline improved markedly over  
 489 the first week of treatment and continued to improve over the 12 weeks of treatment in all  
 490 3 studies.

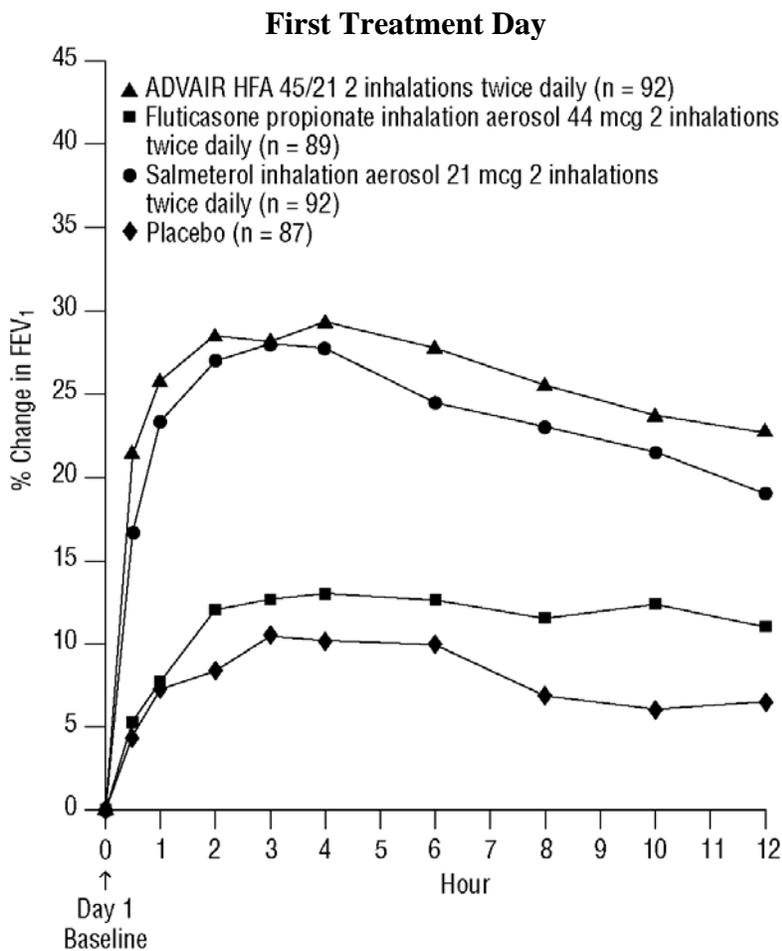
491 No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR HFA  
 492 45/21 (Figures 3 and 4) or ADVAIR HFA 230/21 as assessed by FEV<sub>1</sub> following 12 weeks of  
 493 therapy.

494

495 **Figure 3. Percent Change in Serial 12-Hour FEV<sub>1</sub> in**  
 496 **Patients Previously Using Either Beta<sub>2</sub>-Agonists (Albuterol**  
 497 **or Salmeterol) or Inhaled Corticosteroids (Study 1)**

498

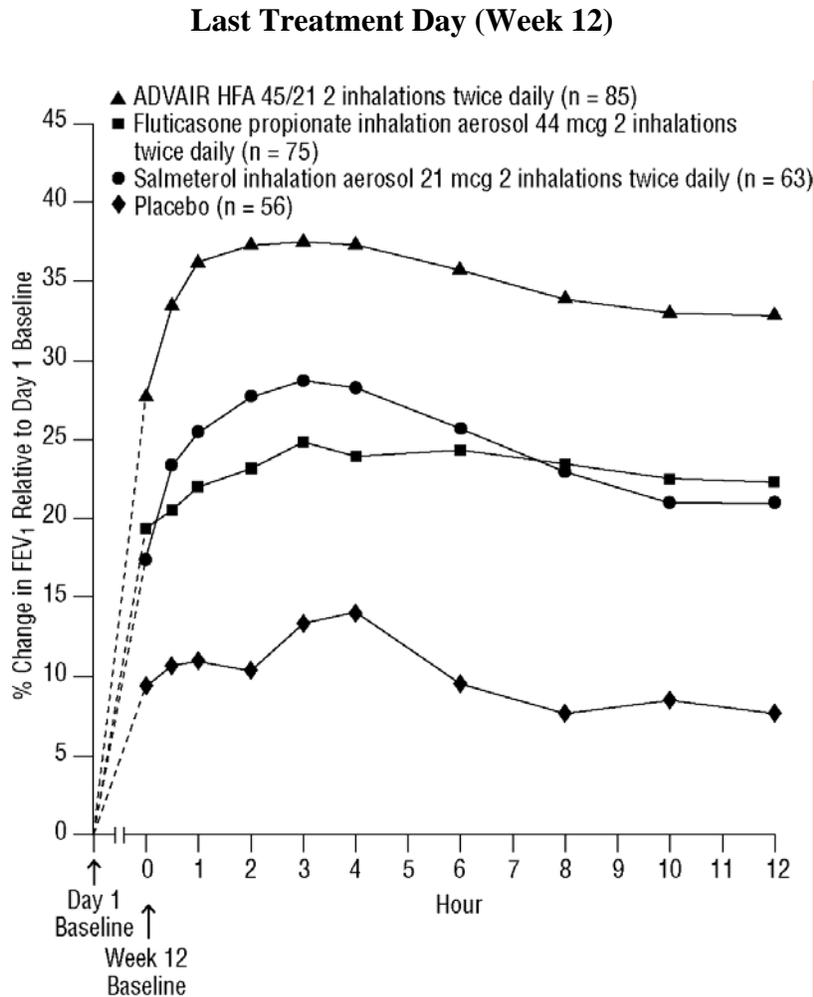
499



500  
501

502 **Figure 4. Percent Change in Serial 12-Hour FEV<sub>1</sub> in**  
 503 **Patients Previously Using Either Beta<sub>2</sub>-Agonists (Albuterol**  
 504 **or Salmeterol) or Inhaled Corticosteroids (Study 1)**

505  
 506  
 507



508  
 509

510 Reduction in asthma symptoms and use of rescue VENTOLIN Inhalation Aerosol and  
 511 improvement in morning and evening PEF also occurred within the first day of treatment with  
 512 ADVAIR HFA, and continued to improve over the 12 weeks of therapy in all 3 studies.

513 **INDICATIONS AND USAGE**

514 ADVAIR HFA is indicated for the long-term, twice-daily maintenance treatment of asthma in  
 515 patients 12 years of age and older.

516 Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, one of the active ingredients in  
 517 ADVAIR HFA, may increase the risk of asthma-related death (see WARNINGS). Therefore,  
 518 when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients  
 519 not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose  
 520 inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2

521 maintenance therapies. ADVAIR HFA is not indicated in patients whose asthma can be  
522 successfully managed by inhaled corticosteroids along with occasional use of inhaled,  
523 short-acting beta<sub>2</sub>-agonists.

524 ADVAIR HFA is NOT indicated for the relief of acute bronchospasm.

## 525 **CONTRAINDICATIONS**

526 ADVAIR HFA is contraindicated in the primary treatment of status asthmaticus or other acute  
527 episodes of asthma where intensive measures are required.

528 Hypersensitivity to any of the ingredients of these preparations contraindicates their use.

## 529 **WARNINGS**

530 **Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, one of the active ingredients**  
531 **in ADVAIR HFA, may increase the risk of asthma-related death. Therefore, when treating**  
532 **patients with asthma, physicians should only prescribe ADVAIR HFA for patients not**  
533 **adequately controlled on other asthma-controller medications (e.g., low- to medium-dose**  
534 **inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment**  
535 **with 2 maintenance therapies.**

536 A large placebo-controlled US study that compared the safety of salmeterol with placebo,  
537 each added to usual asthma therapy, showed an increase in asthma-related deaths in patients  
538 receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a  
539 randomized, double-blind study that enrolled long-acting beta<sub>2</sub>-agonist-naïve patients with  
540 asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily  
541 over 28 weeks compared to placebo when added to usual asthma therapy. A planned interim  
542 analysis was conducted when approximately half of the intended number of patients had been  
543 enrolled (N = 26,355), which led to premature termination of the study. The results of the interim  
544 analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events  
545 (see Table 3 and Figure 5). In the total population, a higher rate of asthma-related death occurred  
546 in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%; relative risk  
547 4.37 [95% CI 1.25, 15.34]).

548 Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death  
549 occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo  
550 (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also,  
551 asthma-related death occurred at a higher rate in patients treated with salmeterol than those  
552 treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the  
553 relative risks of asthma-related death were similar in Caucasians and African Americans, the  
554 estimate of excess deaths in patients treated with salmeterol was greater in African Americans  
555 because there was a higher overall rate of asthma-related death in African American patients (see  
556 Table 3). Given the similar basic mechanisms of action of beta<sub>2</sub>-agonists, it is possible that the  
557 findings seen in the SMART study represent a class effect.

558 The data from the SMART study are not adequate to determine whether concurrent use of  
 559 inhaled corticosteroids, such as fluticasone propionate, the other active ingredient in ADVAIR  
 560 HFA, or other asthma-controller therapy modifies the risk of asthma-related death.

561  
 562 **Table 3: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research**  
 563 **Trial (SMART)**

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

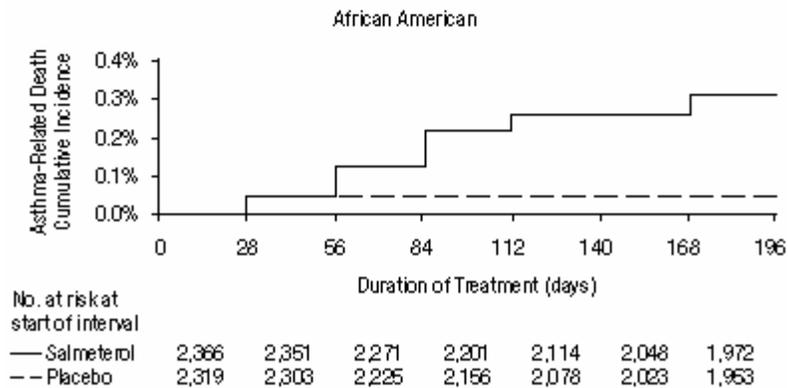
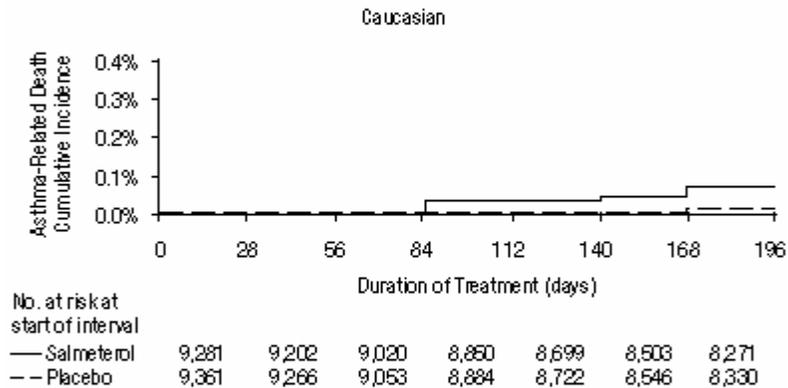
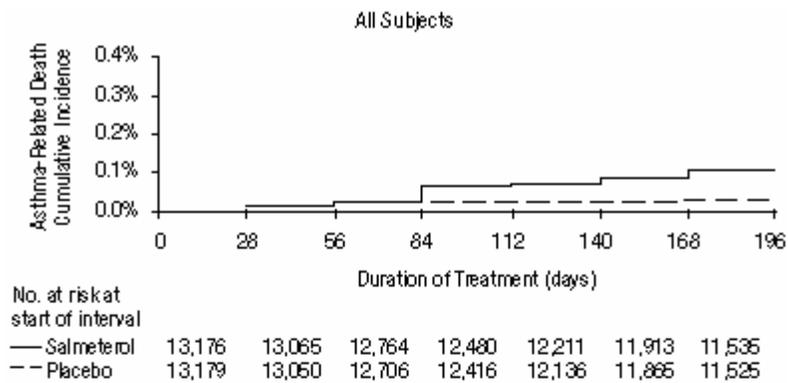
564 \* Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to  
 565 study treatment to account for early withdrawal of patients from the study.

566 † Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the  
 567 rate in the placebo group. The relative risk indicates how many more times likely an  
 568 asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week  
 569 treatment period.

570 ‡ Estimate of the number of additional asthma-related deaths in patients treated with salmeterol  
 571 in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period.  
 572 Estimate calculated as the difference between the salmeterol and placebo groups in the rates of  
 573 asthma-related death multiplied by 10,000.

574 § The Total Population includes the following ethnic origins listed on the case report form:  
 575 Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population  
 576 includes those patients whose ethnic origin was not reported. The results for Caucasian and  
 577 African American subpopulations are shown above. No asthma-related deaths occurred in the  
 578 Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149),  
 579 or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death  
 580 occurred in the placebo group in the subpopulation whose ethnic origin was not reported  
 581 (salmeterol n = 130, placebo n = 127).  
 582

583 **Figure 5. Cumulative Incidence of Asthma-Related**  
 584 **Deaths in the 28-Week Salmeterol Multi-center Asthma**  
 585 **Research Trial (SMART), by Duration of Treatment**  
 586



587  
 588  
 589 A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide  
 590 Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate  
 591 of asthma-related death was numerically, though not statistically significantly, greater in patients

592 with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol  
593 (180 mcg 4 times daily) added to usual asthma therapy.

594 **The following additional WARNINGS about ADVAIR HFA should be noted.**

595 1. ADVAIR HFA should not be initiated in patients during rapidly deteriorating or potentially  
596 life-threatening episodes of asthma. Serious acute respiratory events, including fatalities, have  
597 been reported both in the United States and worldwide when salmeterol, a component of  
598 ADVAIR HFA, has been initiated in patients with significantly worsening or acutely  
599 deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g.,  
600 patients with a history of corticosteroid dependence, low pulmonary function, intubation,  
601 mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma  
602 exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g.,  
603 unresponsive to usual medications; increasing need for inhaled, short-acting beta<sub>2</sub>-agonists;  
604 increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency  
605 room visits; sudden or progressive deterioration in pulmonary function). However, they have  
606 occurred in a few patients with less severe asthma as well. It was not possible from these reports  
607 to determine whether salmeterol contributed to these events.

608 2. ADVAIR HFA should not be used to treat acute symptoms. An inhaled, short-acting  
609 beta<sub>2</sub>-agonist, not ADVAIR HFA, should be used to relieve acute symptoms of shortness of  
610 breath. When prescribing ADVAIR HFA, the physician must also provide the patient with an  
611 inhaled, short-acting beta<sub>2</sub>-agonist (e.g., albuterol) for treatment of shortness of breath that  
612 occurs acutely, despite regular twice-daily (morning and evening) use of ADVAIR HFA.

613 When beginning treatment with ADVAIR HFA, patients who have been taking oral or  
614 inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., 4 times a day) should be instructed to  
615 discontinue the regular use of these drugs. For patients taking ADVAIR HFA, inhaled,  
616 short-acting beta<sub>2</sub>-agonists should only be used for symptomatic relief of acute symptoms of  
617 shortness of breath (see PRECAUTIONS: Information for Patients).

618 3. Increasing use of inhaled, short-acting beta<sub>2</sub>-agonists is a marker of deteriorating asthma. The  
619 physician and patient should be alert to such changes. The patient's condition may deteriorate  
620 acutely over a period of hours or chronically over several days or longer. If the patient's inhaled,  
621 short-acting beta<sub>2</sub>-agonist becomes less effective, the patient needs more inhalations than usual,  
622 or the patient develops a significant decrease in lung function, this may be a marker of  
623 destabilization of the disease. In this setting, the patient requires immediate reevaluation with  
624 reassessment of the treatment regimen, giving special consideration to the possible need for  
625 replacing the current strength of ADVAIR HFA with a higher strength, adding additional inhaled  
626 corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2  
627 inhalations twice daily (morning and evening) of ADVAIR HFA.

628 4. ADVAIR HFA should not be used for transferring patients from systemic corticosteroid  
629 therapy. Particular care is needed for patients who have been transferred from systemically active  
630 corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have  
631 occurred in patients with asthma during and after transfer from systemic corticosteroids to less

632 systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a  
633 number of months are required for recovery of HPA function.

634 Patients who have been previously maintained on 20 mg or more per day of prednisone (or its  
635 equivalent) may be most susceptible, particularly when their systemic corticosteroids have been  
636 almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs  
637 and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection  
638 (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although  
639 inhaled corticosteroids may provide control of asthma symptoms during these episodes, in  
640 recommended doses they supply less than normal physiologic amounts of glucocorticoid  
641 (cortisol) systemically and do NOT provide the mineralocorticoid activity that is necessary for  
642 coping with these emergencies.

643 During periods of stress or a severe asthma attack, patients who have been withdrawn from  
644 systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses)  
645 immediately and to contact their physicians for further instruction. These patients should also be  
646 instructed to carry a warning card indicating that they may need supplementary systemic  
647 corticosteroids during periods of stress or a severe asthma attack.

648 5. ADVAIR HFA should not be used in conjunction with an inhaled, long-acting beta<sub>2</sub>-agonist.

649 Patients who are receiving ADVAIR HFA twice daily should not use additional salmeterol or  
650 other long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for prevention of exercise-induced  
651 bronchospasm (EIB) or the maintenance treatment of asthma. Additional benefit would not be  
652 gained from using supplemental salmeterol or formoterol for prevention of EIB since ADVAIR  
653 HFA already contains an inhaled, long-acting beta<sub>2</sub>-agonist.

654 6. The recommended dosage should not be exceeded. ADVAIR HFA should not be used more  
655 often or at higher doses than recommended. Fatalities have been reported in association with  
656 excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12  
657 to 20 times the recommended dose) have been associated with clinically significant prolongation  
658 of the QTc interval, which has the potential for producing ventricular arrhythmias.

659 7. Paradoxical bronchospasm. As with other inhaled asthma medications, ADVAIR HFA can  
660 produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm  
661 occurs following dosing with ADVAIR HFA, it should be treated immediately with an inhaled,  
662 short-acting bronchodilator; ADVAIR HFA should be discontinued immediately; and alternative  
663 therapy should be instituted.

664 8. Immediate hypersensitivity reactions. Immediate hypersensitivity reactions may occur after  
665 administration of ADVAIR HFA, as demonstrated by cases of urticaria, angioedema, rash, and  
666 bronchospasm.

667 9. Upper airway symptoms. Symptoms of laryngeal spasm, irritation, or swelling, such as stridor  
668 and choking, have been reported in patients receiving fluticasone propionate and salmeterol,  
669 components of ADVAIR HFA.

670 10. Cardiovascular disorders. ADVAIR HFA, like all products containing sympathomimetic  
671 amines, should be used with caution in patients with cardiovascular disorders, especially

672 coronary insufficiency, cardiac arrhythmias, and hypertension. Salmeterol, a component of  
673 ADVAIR HFA, can produce a clinically significant cardiovascular effect in some patients as  
674 measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon  
675 after administration of salmeterol at recommended doses, if they occur, the drug may need to be  
676 discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG)  
677 changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment  
678 depression. The clinical significance of these findings is unknown.

679 11. Discontinuation of systemic corticosteroids. Transfer of patients from systemic corticosteroid  
680 therapy to ADVAIR HFA may unmask conditions previously suppressed by the systemic  
681 corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

682 12. Immunosuppression. Persons who are using drugs that suppress the immune system are more  
683 susceptible to infections than healthy individuals. Chickenpox and measles, for example, can  
684 have a more serious or even fatal course in susceptible children or adults using corticosteroids. In  
685 such children or adults who have not had these diseases or been properly immunized, particular  
686 care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid  
687 administration affect the risk of developing a disseminated infection is not known. The  
688 contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not  
689 known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG)  
690 may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin  
691 (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing  
692 information.) If chickenpox develops, treatment with antiviral agents may be considered.

693 13. Potential drug interaction with CYP 3A4 inhibitors. Both fluticasone propionate and  
694 salmeterol are substrates of CYP 3A4.

695 Fluticasone Propionate: A drug interaction study in healthy subjects has shown that ritonavir  
696 (a strong cytochrome P450 3A4 inhibitor) can significantly increase systemic fluticasone  
697 propionate exposure (AUC), resulting in significantly reduced serum cortisol concentrations (see  
698 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug Interactions*  
699 and PRECAUTIONS: Drug Interactions: *Inhibitors of Cytochrome P450*). During postmarketing  
700 use, there have been reports of clinically significant drug interactions in patients receiving  
701 fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including  
702 Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone  
703 propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs  
704 the risk of systemic corticosteroid side effects.

705 Salmeterol: Because of the potential for drug interactions and the potential for increased risk  
706 of cardiovascular adverse events, the concomitant use of ADVAIR HFA with strong CYP 3A4  
707 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole,  
708 nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended (see CLINICAL  
709 PHARMACOLOGY: Pharmacokinetics: *Salmeterol Xinafoate: Drug Interactions*).

710 **PRECAUTIONS**

711 **General: Cardiovascular Effects:** Cardiovascular and central nervous system effects seen  
712 with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur  
713 after use of salmeterol, a component of ADVAIR HFA, and may require discontinuation of  
714 ADVAIR HFA. ADVAIR HFA, like all medications containing sympathomimetic amines,  
715 should be used with caution in patients with cardiovascular disorders, especially coronary  
716 insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or  
717 thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

718 As has been described with other beta-adrenergic agonist bronchodilators, clinically  
719 significant changes in ECGs have been seen infrequently in individual patients in controlled  
720 clinical studies with ADVAIR HFA and salmeterol. Clinically significant changes in systolic  
721 and/or diastolic blood pressure and pulse rate have been seen infrequently in individual patients  
722 in controlled clinical studies with salmeterol, a component of ADVAIR HFA.

723 **Metabolic and Other Effects:** Long-term use of orally inhaled corticosteroids may  
724 affect normal bone metabolism, resulting in a loss of bone mineral density. In patients with  
725 major risk factors for decreased bone mineral content, such as tobacco use, advanced age,  
726 sedentary lifestyle, poor nutrition, family history of osteoporosis, or chronic use of drugs that can  
727 reduce bone mass (e.g., anticonvulsants and corticosteroids), ADVAIR HFA may pose an  
728 additional risk.

729 Doses of the related beta<sub>2</sub>-adrenoceptor agonist albuterol, when administered intravenously,  
730 have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic  
731 agonist medications may produce significant hypokalemia in some patients, possibly through  
732 intracellular shunting, which has the potential to produce adverse cardiovascular effects. The  
733 decrease in serum potassium is usually transient, not requiring supplementation.

734 Clinically significant changes in blood glucose and/or serum potassium were seen  
735 infrequently during clinical studies with ADVAIR HFA at recommended doses.

736 During withdrawal from oral corticosteroids, some patients may experience symptoms of  
737 systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and  
738 depression, despite maintenance or even improvement of respiratory function.

739 Fluticasone propionate, a component of ADVAIR HFA, will often help control asthma  
740 symptoms with less suppression of HPA function than therapeutically equivalent oral doses of  
741 prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically  
742 active at higher doses, the beneficial effects of ADVAIR HFA in minimizing HPA dysfunction  
743 may be expected only when recommended dosages are not exceeded and individual patients are  
744 titrated to the lowest effective dose. A relationship between plasma levels of fluticasone  
745 propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks  
746 of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects  
747 on cortisol production exists, physicians should consider this information when prescribing  
748 ADVAIR HFA.

749 Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated  
750 with ADVAIR HFA should be observed carefully for any evidence of systemic corticosteroid  
751 effects. Particular care should be taken in observing patients postoperatively or during periods of  
752 stress for evidence of inadequate adrenal response.

753 It is possible that systemic corticosteroid effects such as hypercorticism and adrenal  
754 suppression (including adrenal crisis) may appear in a small number of patients, particularly  
755 when fluticasone propionate is administered at higher than recommended doses over prolonged  
756 periods of time. If such effects occur, the dosage of ADVAIR HFA should be reduced slowly,  
757 consistent with accepted procedures for reducing systemic corticosteroids and for management  
758 of asthma.

759 A reduction of growth velocity in children and adolescents may occur as a result of poorly  
760 controlled asthma or from the therapeutic use of corticosteroids, including inhaled corticosteroids  
761 (see PRECAUTIONS: Pediatric Use). The effects of long-term treatment of children and  
762 adolescents with inhaled corticosteroids, including fluticasone propionate, on final adult height  
763 are not known. Patients should be maintained on the lowest strength of ADVAIR HFA that  
764 effectively controls their asthma.

765 The long-term effects of ADVAIR HFA in human subjects are not fully known. In particular,  
766 the effects resulting from chronic use of fluticasone propionate on developmental or  
767 immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients  
768 received inhaled fluticasone propionate on a continuous basis in a clinical study for up to 4 years.  
769 In clinical studies with patients treated for 2 years with inhaled fluticasone propionate, no  
770 apparent differences in the type or severity of adverse reactions were observed after long- versus  
771 short-term treatment.

772 Glaucoma, increased intraocular pressure, and cataracts have been reported in patients  
773 following the long-term administration of inhaled corticosteroids, including fluticasone  
774 propionate, a component of ADVAIR HFA.

775 Lower respiratory tract infections, including pneumonia, have been reported following the  
776 inhaled administration of corticosteroids, including fluticasone propionate, a component of  
777 ADVAIR HFA.

778 In clinical studies with ADVAIR HFA, the development of localized infections of the pharynx  
779 with *Candida albicans* has occurred. When such an infection develops, it should be treated with  
780 appropriate local or systemic (i.e., oral antifungal) therapy while remaining on treatment with  
781 ADVAIR HFA, but at times therapy with ADVAIR HFA may need to be interrupted.

782 Inhaled corticosteroids should be used with caution, if at all, in patients with active or  
783 quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial,  
784 viral, or parasitic infections; or ocular herpes simplex.

785 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a  
786 component of ADVAIR HFA, may present with systemic eosinophilic conditions, with some  
787 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a  
788 condition that is often treated with systemic corticosteroid therapy. These events usually, but not

789 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy  
790 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions  
791 have also been reported with other inhaled corticosteroids in this clinical setting. Physicians  
792 should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac  
793 complications, and/or neuropathy presenting in their patients. A causal relationship between  
794 fluticasone propionate and these underlying conditions has not been established (see ADVERSE  
795 REACTIONS: Observed During Clinical Practice: *Eosinophilic Conditions*).

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

799 Patients being treated with ADVAIR HFA should receive the following information and  
800 instructions. This information is intended to aid them in the safe and effective use of this  
801 medication. It is not a disclosure of all possible adverse or intended effects. It is important that  
802 patients understand how to use ADVAIR HFA in relation to other asthma medications they are  
803 taking.

- 804 1. **Patients should be informed that salmeterol, one of the active ingredients in ADVAIR**  
805 **HFA, may increase the risk of asthma-related death.** They should also be informed that  
806 data are not adequate to determine whether the concurrent use of inhaled corticosteroids,  
807 such as fluticasone propionate, the other component of ADVAIR HFA, or other  
808 asthma-controller therapy modifies this risk.
- 809 2. ADVAIR HFA is not meant to relieve acute asthma symptoms and extra doses should not be  
810 used for that purpose. Acute symptoms should be treated with an inhaled, short-acting  
811 beta<sub>2</sub>-agonist such as albuterol (the physician should provide the patient with such  
812 medication and instruct the patient in how it should be used).
- 813 3. The physician should be notified immediately if any of the following signs of seriously  
814 worsening asthma occur:
  - 815 • decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonists;
  - 816 • need for more inhalations than usual of inhaled, short-acting beta<sub>2</sub>-agonists;
  - 817 • significant decrease in lung function as outlined by the physician.
- 818 4. Patients should not stop therapy with ADVAIR HFA without physician/provider guidance  
819 since symptoms may recur after discontinuation.
- 820 5. Patients should be cautioned regarding common adverse effects associated with  
821 beta<sub>2</sub>-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 822 6. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of  
823 ADVAIR HFA, may increase the risk of some eye problems (cataracts or glaucoma). Regular  
824 eye examinations should be considered.
- 825 7. When patients are prescribed ADVAIR HFA, other medications for asthma should be used  
826 only as directed by the physician.
- 827 8. Patients who are pregnant or nursing should contact the physician about the use of ADVAIR  
828 HFA.

- 829 9. Patients should use ADVAIR HFA at regular intervals as directed. Results of clinical trials  
830 indicated significant improvement may occur within the first 30 minutes of taking the first  
831 dose; however, the full benefit may not be achieved until treatment has been administered for  
832 1 week or longer. The patient should not use more than the prescribed dosage but should  
833 contact the physician if symptoms do not improve or if the condition worsens.
- 834 10. The bronchodilation from a single dose of ADVAIR HFA may last up to 12 hours or longer.  
835 The recommended dosage (2 inhalations twice daily, morning and evening) should not be  
836 exceeded. Patients who are receiving ADVAIR HFA twice daily should not use salmeterol or  
837 other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for prevention of EIB or  
838 maintenance treatment of asthma.
- 839 11. Patients should be warned to avoid exposure to chickenpox or measles and, if they are  
840 exposed, to consult the physician without delay.
- 841 12. Prime the inhaler before using for the first time by releasing 4 test sprays into the air away  
842 from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has  
843 not been used for more than 4 weeks or when it has been dropped, prime the inhaler again by  
844 shaking well before each spray and releasing 2 test sprays into the air away from the face.
- 845 13. After inhalation, rinse the mouth with water and spit out. Do not swallow.
- 846 14. Clean the inhaler at least once a week after the evening dose. Keeping the canister and plastic  
847 actuator clean is important to prevent medicine buildup. (See Instructions for Using  
848 ADVAIR HFA in the Medication Guide accompanying the product.)
- 849 15. Use ADVAIR HFA only with the actuator supplied with the product. Discard the inhaler  
850 after 120 sprays have been used.
- 851 16. Patients should never immerse the canister into water to determine the amount remaining in  
852 the canister (“float test”).
- 853 17. For the proper use of ADVAIR HFA and to attain maximum improvement, the patient should  
854 read and carefully follow the Instructions for Using ADVAIR HFA in the Medication Guide  
855 accompanying the product.

856 **Drug Interactions:** ADVAIR HFA has been used concomitantly with other drugs, including  
857 short-acting beta<sub>2</sub>-agonists, methylxanthines, and intranasal corticosteroids, commonly used in  
858 patients with asthma, without adverse drug reactions. No formal drug interaction studies have  
859 been performed with ADVAIR HFA.

860 **Short-Acting Beta<sub>2</sub>-Agonists:** In three 12-week US clinical trials, the mean daily need for  
861 additional beta<sub>2</sub>-agonist use in 277 patients receiving ADVAIR HFA was approximately  
862 1.2 inhalations/day and ranged from 0 to 9 inhalations/day. Two percent (2%) of patients  
863 receiving ADVAIR HFA in these trials averaged 6 or more inhalations per day over the course of  
864 the 12-week trials. No increase in frequency of cardiovascular events was observed among  
865 patients who averaged 6 or more inhalations per day.

866 **Methylxanthines:** The concurrent use of intravenously or orally administered  
867 methylxanthines (e.g., aminophylline, theophylline) by patients receiving ADVAIR HFA has not  
868 been completely evaluated. In five 12-week clinical trials (3 US and 2 non-US), 45 patients

869 receiving ADVAIR HFA 45/21, 115/21, or 230/21 twice daily concurrently with a theophylline  
870 product had adverse event rates similar to those in 577 patients receiving ADVAIR HFA without  
871 theophylline.

872 **Fluticasone Propionate Nasal Spray:** In patients receiving ADVAIR HFA in three  
873 12-week US clinical trials, no difference in the profile of adverse events or HPA axis effects was  
874 noted between patients receiving FLONASE<sup>®</sup> (fluticasone propionate) Nasal Spray, 50 mcg  
875 concurrently (n = 89) and those who were not (n = 192).

876 **Monoamine Oxidase Inhibitors and Tricyclic Antidepressants:** ADVAIR HFA  
877 should be administered with extreme caution to patients being treated with monoamine oxidase  
878 inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents,  
879 because the action of salmeterol, a component of ADVAIR HFA, on the vascular system may be  
880 potentiated by these agents.

881 **Beta-Adrenergic Receptor Blocking Agents:** Beta-blockers not only block the  
882 pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR HFA, but may  
883 produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should  
884 not normally be treated with beta-blockers. However, under certain circumstances, there may be  
885 no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma.  
886 In this setting, cardioselective beta-blockers could be considered, although they should be  
887 administered with caution.

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

893 **Inhibitors of Cytochrome P450:** Fluticasone propionate and salmeterol are substrates of  
894 cytochrome P450 3A4.

895 **Fluticasone propionate:** A drug interaction study with fluticasone propionate aqueous  
896 nasal spray in healthy subjects has shown that ritonavir (a strong potent cytochrome P450 3A4  
897 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in  
898 significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY:  
899 Pharmacokinetics: *Fluticasone Propionate: Drug Interactions*). During postmarketing use, there  
900 have been reports of clinically significant drug interactions in patients receiving fluticasone  
901 propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's  
902 syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and  
903 ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of  
904 systemic corticosteroid side effects.

905 In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a  
906 single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of  
907 ketoconazole (200 mg) to steady state resulted in increased systemic fluticasone propionate  
908 exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

909 **Salmeterol:** In a drug interaction study in 20 healthy subjects, coadministration of inhaled  
910 salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in  
911 greater systemic exposure to salmeterol (AUC increased 16-fold and  $C_{max}$  increased 1.4-fold).  
912 Three (3) subjects were withdrawn due to beta<sub>2</sub>-agonist side effects (2 with prolonged QTc and 1  
913 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean  
914 QTc, coadministration of salmeterol and ketoconazole was associated with more frequent  
915 increases in QTc duration compared with salmeterol and placebo administration. Due to the  
916 potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with  
917 strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir,  
918 itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended (see  
919 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Salmeterol Xinafoate: Drug Interactions*).

920 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate:**  
921 Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to  
922 1,000 mcg/kg (approximately 4 times the maximum recommended human daily inhalation dose  
923 on a mcg/m<sup>2</sup> basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than the  
924 maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis) for 104 weeks.

925 Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in  
926 vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in  
927 vitro or in the mouse micronucleus test.

928 No evidence of impairment of fertility was observed in reproductive studies conducted in  
929 male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum  
930 recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis). Prostate weight was significantly  
931 reduced at a subcutaneous dose of 50 mcg/kg.

932 **Salmeterol:** In an 18-month oral carcinogenicity study in CD-mice, salmeterol at oral doses  
933 of 1.4 mg/kg and above (approximately 10 times the maximum recommended human daily  
934 inhalation dose based on comparison of the AUCs) caused a dose-related increase in the  
935 incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus,  
936 and ovarian cysts. The incidence of leiomyosarcomas was not statistically significant. No tumors  
937 were seen at 0.2 mg/kg (approximately 2 times the maximum recommended human daily  
938 inhalation dose in adults based on comparison of the AUCs).

939 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol  
940 caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at  
941 doses of 0.68 mg/kg and above (approximately 65 times the maximum recommended human  
942 daily inhalation dose on a mg/m<sup>2</sup> basis). No tumors were seen at 0.21 mg/kg (approximately  
943 20 times the maximum recommended human daily inhalation dose on a mg/m<sup>2</sup> basis). These  
944 findings in rodents are similar to those reported previously for other beta-adrenergic agonist  
945 drugs. The relevance of these findings to human use is unknown.

946 Salmeterol produced no detectable or reproducible increases in microbial and mammalian  
947 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo  
948 in a rat micronucleus test. No effects on fertility were identified in male and female rats treated

949 with salmeterol at oral doses up to 2 mg/kg (approximately 190 times the maximum  
950 recommended human daily inhalation dose on a mg/m<sup>2</sup> basis).  
951 **Pregnancy: Teratogenic Effects: ADVAIR HFA Inhalation Aerosol:** Pregnancy  
952 Category C. From the reproduction toxicity studies in mice and rats, no evidence of enhanced  
953 toxicity was seen using combinations of fluticasone propionate and salmeterol compared to  
954 toxicity data from the components administered separately. In mice combining 150 mcg/kg  
955 subcutaneously of fluticasone propionate (less than the maximum recommended human daily  
956 inhalation dose on a mcg/m<sup>2</sup> basis) with 10 mg/kg orally of salmeterol (approximately 480 times  
957 the maximum recommended human daily inhalation dose on a mg/m<sup>2</sup> basis) were teratogenic.  
958 Cleft palate, fetal death, increased implantation loss and delayed ossification was seen. These  
959 observations are characteristic of glucocorticoids. No developmental toxicity was observed at  
960 combination doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the  
961 maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis) and up to 1.4 mg/kg  
962 orally of salmeterol (approximately 70 times the maximum recommended human daily  
963 inhalation dose on a mg/m<sup>2</sup> basis). In rats, no teratogenicity was observed at combination doses  
964 up to 30 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended  
965 human daily inhalation dose on a mcg/m<sup>2</sup> basis) and up to 1 mg/kg of salmeterol (approximately  
966 95 times the maximum recommended human daily inhalation dose on a mg/m<sup>2</sup> basis).  
967 Combining 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum  
968 recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis) with 10 mg/kg orally of  
969 salmeterol (approximately 970 times the maximum recommended human daily inhalation dose  
970 on a mg/m<sup>2</sup> basis) produced maternal toxicity, decreased placental weight, decreased fetal  
971 weight, umbilical hernia, delayed ossification, and changes in the occipital bone.

972 There are no adequate and well-controlled studies with ADVAIR HFA in pregnant women.  
973 ADVAIR HFA should be used during pregnancy only if the potential benefit justifies the  
974 potential risk to the fetus.

975 **Fluticasone Propionate:** Pregnancy Category C. Subcutaneous studies in the mouse  
976 and rat at 45 and 100 mcg/kg, respectively (less than and equivalent to, respectively, the  
977 maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis), revealed fetal toxicity  
978 characteristic of potent corticosteroid compounds, including embryonic growth retardation,  
979 omphalocele, cleft palate, and retarded cranial ossification. No teratogenicity was seen in the rat  
980 at inhalation doses up to 68.7 mcg/kg (less than the maximum recommended human daily  
981 inhalation dose on a mcg/m<sup>2</sup> basis).

982 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of  
983 4 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup>  
984 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg  
985 (approximately 5 times the maximum recommended human daily inhalation dose on mcg/m<sup>2</sup>  
986 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this  
987 study, consistent with the established low bioavailability following oral administration (see  
988 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Absorption*).

989 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose  
990 of 100 mcg/kg to mice (less than the maximum recommended human daily inhalation dose on a  
991 mcg/m<sup>2</sup> basis), a subcutaneous or an oral dose of 100 mcg/kg to rats (equivalent to the maximum  
992 recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis), and an oral dose of 300 mcg/kg  
993 to rabbits (approximately 5 times the maximum recommended human daily inhalation dose on a  
994 mcg/m<sup>2</sup> basis).

995 There are no adequate and well-controlled studies in pregnant women. ADVAIR HFA should  
996 be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

997 Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to  
998 physiologic, doses suggests that rodents are more prone to teratogenic effects from  
999 corticosteroids than humans. In addition, because there is a natural increase in corticosteroid  
1000 production during pregnancy, most women will require a lower exogenous corticosteroid dose  
1001 and many will not need corticosteroid treatment during pregnancy.

1002 **Salmeterol:** Pregnancy Category C. No teratogenic effects occurred in the rat at oral  
1003 doses up to 2 mg/kg (approximately 190 times the maximum recommended human daily  
1004 inhalation dose on a mg/m<sup>2</sup> basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg  
1005 and above (approximately 25 times the maximum recommended human daily inhalation dose  
1006 based on the comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically  
1007 resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft  
1008 palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial  
1009 bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 10 times the  
1010 maximum recommended human daily inhalation dose based on comparison of the AUCs).

1011 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal  
1012 cranial bones was seen at an oral dose of 10 mg/kg (approximately 1,900 times the maximum  
1013 recommended human daily inhalation dose on a mg/m<sup>2</sup> basis). Extensive use of other  
1014 beta-agonists has provided no evidence that these class effects in animals are relevant to their use  
1015 in humans.

1016 Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice  
1017 and rats (approximately 480 and 970 times, respectively, the maximum recommended human  
1018 daily inhalation dose on a mg/m<sup>2</sup> basis).

1019 There are no adequate and well-controlled studies with salmeterol in pregnant women.  
1020 Salmeterol should be used during pregnancy only if the potential benefit justifies the potential  
1021 risk to the fetus.

1022 **Use in Labor and Delivery:** There are no well-controlled human studies that have  
1023 investigated effects of ADVAIR HFA on preterm labor or labor at term. Because of the potential  
1024 for beta-agonist interference with uterine contractility, use of ADVAIR HFA for management of  
1025 asthma during labor should be restricted to those patients in whom the benefits clearly outweigh  
1026 the risks.

1027 **Nursing Mothers:** Plasma levels of salmeterol, a component of ADVAIR HFA, after inhaled  
1028 therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There are no

1029 data from controlled trials on the use of salmeterol by nursing mothers. It is not known whether  
1030 fluticasone propionate, a component of ADVAIR HFA, is excreted in human breast milk.  
1031 However, other corticosteroids have been detected in human milk. Subcutaneous administration  
1032 to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the maximum  
1033 recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis) resulted in measurable  
1034 radioactivity in milk.

1035 Since there are no data from controlled trials on the use of ADVAIR HFA by nursing mothers,  
1036 a decision should be made whether to discontinue nursing or to discontinue ADVAIR HFA,  
1037 taking into account the importance of ADVAIR HFA to the mother.

1038 Caution should be exercised when ADVAIR HFA is administered to a nursing woman.

1039 **Pediatric Use:** Thirty-eight (38) patients 12 to 17 years of age were treated with ADVAIR  
1040 HFA in US pivotal clinical trials. Patients in this age-group demonstrated efficacy results similar  
1041 to those observed in patients 18 years of age and older. There were no obvious differences in the  
1042 type or frequency of adverse events reported in this age-group compared with patients 18 years  
1043 of age and older.

1044 The safety and effectiveness of ADVAIR HFA in children under 12 years have not been  
1045 established.

1046 Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in  
1047 growth in pediatric patients. In these studies, the mean reduction in growth velocity was  
1048 approximately 1 cm/year (range, 0.3 to 1.8 cm/year) and appears to depend upon dose and  
1049 duration of exposure. This effect was observed in the absence of laboratory evidence of HPA  
1050 axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic  
1051 corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis  
1052 function. The long-term effects of this reduction in growth velocity associated with orally  
1053 inhaled corticosteroids, including the impact on final adult height, are unknown. The potential  
1054 for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids  
1055 has not been adequately studied. The effects on growth velocity of treatment with orally inhaled  
1056 corticosteroids for over 1 year, including the impact on final adult height, are unknown. The  
1057 growth of children and adolescents receiving orally inhaled corticosteroids, including ADVAIR  
1058 HFA, should be monitored. If a child or adolescent on any corticosteroid appears to have growth  
1059 suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids  
1060 should be considered. The potential growth effects of prolonged treatment should be weighed  
1061 against the clinical benefits obtained and the risks associated with alternative therapies. To  
1062 minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR HFA, each  
1063 patient should be titrated to the lowest strength that effectively controls his/her asthma (see  
1064 DOSAGE AND ADMINISTRATION).

1065 **Geriatric Use:** Of the total number of patients in clinical studies treated with ADVAIR HFA,  
1066 41 were 65 years of age or older and 21 were 75 years of age or older. No overall differences in  
1067 safety were observed between these patients and younger patients, and other reported clinical  
1068 experience, including studies of the individual components, has not identified differences in

1069 responses between the elderly and younger patients, but greater sensitivity of some older  
 1070 individuals cannot be ruled out. As with other products containing beta<sub>2</sub>-agonists, special caution  
 1071 should be observed when using ADVAIR HFA in geriatric patients who have concomitant  
 1072 cardiovascular disease that could be adversely affected by beta<sub>2</sub>-agonists. Based on available  
 1073 data for ADVAIR HFA or its active components, no adjustment of dosage of ADVAIR HFA in  
 1074 geriatric patients is warranted.

1075 **ADVERSE REACTIONS**

1076 **Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, may increase the risk of**  
 1077 **asthma-related death. Data from a large, placebo-controlled US study that compared the**  
 1078 **safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma**  
 1079 **therapy showed an increase in asthma-related deaths in patients receiving salmeterol (see**  
 1080 **WARNINGS). Salmeterol is a component of ADVAIR HFA. However, the data from this**  
 1081 **study are not adequate to determine whether concurrent use of inhaled corticosteroids,**  
 1082 **such as fluticasone propionate, the other component of ADVAIR HFA, or other asthma**  
 1083 **controller therapy modifies the risk of asthma-related death.**

1084 The incidence of common adverse events in Table 4 is based upon 2 placebo-controlled,  
 1085 12-week, US clinical studies (Studies 1 and 3) and 1 active-controlled, 12-week, US clinical  
 1086 study (Study 2). A total of 1,008 adolescent and adult patients with asthma (556 females and 452  
 1087 males) previously treated with albuterol alone, salmeterol, or inhaled corticosteroids were treated  
 1088 twice daily with 2 inhalations of ADVAIR HFA 45/21 or ADVAIR HFA 115/21, fluticasone  
 1089 propionate CFC inhalation aerosol (44- or 110-mcg doses), salmeterol CFC inhalation aerosol  
 1090 21 mcg, or placebo HFA inhalation aerosol.

1091  
 1092 **Table 4. Overall Adverse Events With ≥3% Incidence in US Controlled Clinical Trials**  
 1093 **With ADVAIR HFA Inhalation Aerosol in Patients With Asthma**

Adverse Events	ADVAIR HFA		Fluticasone Propionate CFC Inhalation Aerosol		Salmeterol CFC Inhalation Aerosol	Placebo HFA Inhalation Aerosol
	45/21 (n = 187)	115/21 (n = 94)	44 mcg (n = 186)	110 mcg (n = 91)	21 mcg (n = 274)	(n = 176)
	%	%	%	%	%	%
Ear, nose, & throat						
Upper respiratory tract infection	16	24	13	15	17	13
Throat irritation	9	7	12	13	9	7
Upper respiratory inflammation	4	4	3	7	5	3
Hoarseness/dysphonia	3	1	2	0	1	0

Lower respiratory Viral respiratory infections	3	5	4	5	3	4
Neurology Headaches Dizziness	21 4	15 1	24 1	16 0	20 <1	11 0
Gastrointestinal Nausea & vomiting Viral gastrointestinal infections Gastrointestinal signs & symptoms	5 4 3	3 2 2	4 2 2	2 0 1	2 1 1	3 2 1
Non-site specific Pain	3	1	2	1	2	2
Musculoskeletal Musculoskeletal pain Muscle pain	5 4	7 1	8 1	2 1	4 3	4 <1
Drug interaction, overdose, & trauma Muscle injuries	3	0	2	1	3	2
Reproduction Menstruation symptoms	5	3	1	0	<1	<1
Psychiatry Intoxication & hangover	3	0	0	0	0	0
Average duration of exposure (days)	81.3	78.6	79.9	74.6	71.4	56.3

1094

1095 Table 4 includes all events (whether considered drug-related or nondrug-related by the  
1096 investigator) that occurred at a rate of 3% or greater in any of the groups receiving ADVAIR  
1097 HFA and were more common than in the placebo group. In considering these data, differences in  
1098 average duration of exposure should be taken into account. These adverse reactions were mostly  
1099 mild to moderate in severity.

1100 Other adverse events that occurred in the groups receiving ADVAIR HFA in these studies  
1101 with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1102 **Cardiovascular:** Tachycardia, arrhythmias, myocardial infarction.

1103 **Drug Interaction, Overdose, and Trauma:** Postoperative complications, wounds and  
1104 lacerations, soft tissue injuries, poisoning and toxicity, pressure-induced disorder.

1105 **Ear, Nose, and Throat:** Ear, nose, and throat infection; ear signs and symptoms;  
1106 rhinorrhea/postnasal drip; epistaxis; nasal congestion/blockage; laryngitis; unspecified  
1107 oropharyngeal plaques; dryness of nose.  
1108 **Endocrine and Metabolic:** Weight gain.  
1109 **Eye:** Allergic eye disorders, eye edema and swelling.  
1110 **Gastrointestinal:** Gastrointestinal discomfort and pain, dental discomfort and pain,  
1111 candidiasis mouth/throat, hyposalivation, gastrointestinal infections, disorders of hard tissue of  
1112 teeth, hemorrhoids, gastrointestinal gaseous symptoms, abdominal discomfort and pain,  
1113 constipation, oral abnormalities.  
1114 **Musculoskeletal:** Arthralgia and articular rheumatism, muscle cramps and spasms,  
1115 musculoskeletal inflammation, bone and skeletal pain.  
1116 **Neurology:** Sleep disorders, migraines.  
1117 **Non-Site Specific:** Allergies and allergic reactions, viral infections, bacterial infections,  
1118 candidiasis unspecified site, congestion, inflammation.  
1119 **Reproduction:** Bacterial reproductive infections.  
1120 **Respiratory:** Lower respiratory signs and symptoms, lower respiratory infections, lower  
1121 respiratory hemorrhage.  
1122 **Skin:** Eczema, dermatitis and dermatosis.  
1123 **Urology:** Urinary infections.

1124 Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare  
1125 events of angioedema and bronchospasm, have been reported.

1126 The incidence of common adverse events reported in Study 4, a 12-week, non-US clinical  
1127 study of 509 patients previously treated with inhaled corticosteroids who were treated twice daily  
1128 with 2 inhalations of ADVAIR HFA 230/21, fluticasone propionate CFC inhalation aerosol  
1129 220 mcg, or 1 inhalation of ADVAIR DISKUS 500/50 was similar to the incidences reported in  
1130 Table 4.

1131 **Observed During Clinical Practice:** In addition to adverse events reported from clinical  
1132 trials, the following events have been identified during worldwide use of any formulation of  
1133 ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are  
1134 reported voluntarily from a population of unknown size, estimates of frequency cannot be made.  
1135 These events have been chosen for inclusion due to either their seriousness, frequency of  
1136 reporting, or causal connection to ADVAIR, fluticasone propionate, and/or salmeterol or a  
1137 combination of these factors.

1138 In extensive US and worldwide postmarketing experience with salmeterol, a component of  
1139 ADVAIR HFA, serious exacerbations of asthma, including some that have been fatal, have been  
1140 reported. In most cases, these have occurred in patients with severe asthma and/or in some  
1141 patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also  
1142 occurred in a few patients with less severe asthma. It was not possible from these reports to  
1143 determine whether salmeterol contributed to these events.

1144 **Cardiovascular:** Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular  
1145 tachycardia), hypertension, ventricular tachycardia.  
1146 **Ear, Nose, and Throat:** Aphonia, earache, facial and oropharyngeal edema, paranasal sinus  
1147 pain, rhinitis, throat soreness and irritation, tonsillitis.  
1148 **Endocrine and Metabolic:** Cushing syndrome, Cushingoid features, growth velocity  
1149 reduction in children/adolescents, hypercorticism, hyperglycemia, osteoporosis.  
1150 **Eye:** Cataracts, glaucoma.  
1151 **Gastrointestinal:** Dyspepsia, xerostomia.  
1152 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.  
1153 **Musculoskeletal:** Back pain, myositis.  
1154 **Neurology:** Paresthesia, restlessness.  
1155 **Non-Site Specific:** Fever, immediate and delayed hypersensitivity reaction, pallor.  
1156 **Psychiatry:** Agitation, aggression, anxiety, depression. Behavioral changes, including  
1157 hyperactivity and irritability, have been reported very rarely and primarily in children.  
1158 **Respiratory:** Asthma; asthma exacerbation; chest congestion; chest tightness; cough;  
1159 dyspnea; immediate bronchospasm; influenza; paradoxical bronchospasm; tracheitis; wheezing;  
1160 pneumonia; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling;  
1161 stridor; choking.  
1162 **Skin:** Contact dermatitis, contusions, ecchymoses, photodermatitis, pruritus.  
1163 **Urogenital:** Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal  
1164 candidiasis, vaginitis, vulvovaginitis.  
1165 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a  
1166 component of ADVAIR HFA, may present with systemic eosinophilic conditions, with some  
1167 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a  
1168 condition that is often treated with systemic corticosteroid therapy. These events usually, but not  
1169 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy  
1170 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions  
1171 have also been reported with other inhaled corticosteroids in this clinical setting. While  
1172 ADVAIR HFA should not be used for transferring patients from systemic corticosteroid therapy,  
1173 physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms,  
1174 cardiac complications, and/or neuropathy presenting in their patients. A causal relationship  
1175 between fluticasone propionate and these underlying conditions has not been established (see  
1176 PRECAUTIONS: General: *Eosinophilic Conditions*).

## 1177 **OVERDOSAGE**

1178 **ADVAIR HFA Inhalation Aerosol:** No deaths occurred in rats given a single-dose  
1179 combination of salmeterol 3.6 mg/kg and fluticasone propionate 1.9 mg/kg given as the  
1180 inhalation powder (approximately 290 and 15 times, respectively, the maximum recommended  
1181 human daily inhalation dose on a mg/m<sup>2</sup> basis).

1182 **Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in  
1183 signs/symptoms of hypercorticism (see PRECAUTIONS: General: *Metabolic and Other Effects*).  
1184 Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate  
1185 inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate CFC  
1186 inhalation aerosol were well tolerated. Fluticasone propionate given by inhalation aerosol at  
1187 doses of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well  
1188 tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral  
1189 doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of  
1190 mild or moderate severity, and incidences were similar in active and placebo treatment groups. In  
1191 mice the oral median lethal dose was >1,000 mg/kg (>4,400 times the maximum recommended  
1192 human daily inhalation dose on a mg/m<sup>2</sup> basis). In rats the subcutaneous median lethal dose was  
1193 >1,000 mg/kg (>8,800 times the maximum recommended human daily inhalation dose on a  
1194 mg/m<sup>2</sup> basis).

1195 **Salmeterol:** The expected signs and symptoms with overdosage of salmeterol are those of  
1196 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and  
1197 symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or  
1198 hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache,  
1199 tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.  
1200 Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic  
1201 adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or  
1202 arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to  
1203 clinically significant prolongation of the QTc interval, which can produce ventricular  
1204 arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

1205 As with all sympathomimetic medications, cardiac arrest and even death may be associated  
1206 with abuse of salmeterol.

1207 Treatment consists of discontinuation of salmeterol together with appropriate symptomatic  
1208 therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing  
1209 in mind that such medication can produce bronchospasm. There is insufficient evidence to  
1210 determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is  
1211 recommended in cases of overdosage.

1212 No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg  
1213 (approximately 280 times the maximum recommended human daily inhalation dose on a mg/m<sup>2</sup>  
1214 basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 230 times the maximum  
1215 recommended human daily inhalation dose on a mg/m<sup>2</sup> basis). By the oral route, no deaths  
1216 occurred in mice at 150 mg/kg (approximately 7,200 times the maximum recommended human  
1217 daily inhalation dose on a mg/m<sup>2</sup> basis) and in rats at 1,000 mg/kg (approximately 97,000 times  
1218 the maximum recommended human daily inhalation dose on a mg/m<sup>2</sup> basis).

1219 **DOSAGE AND ADMINISTRATION**

1220 ADVAIR HFA should be administered by the orally inhaled route only in patients 12 years of  
1221 age and older. ADVAIR HFA should not be used for transferring patients from systemic  
1222 corticosteroid therapy. ADVAIR HFA has not been studied in patients under 12 years of age or  
1223 in patients with COPD.

1224 Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, one of the active ingredients in  
1225 ADVAIR HFA, may increase the risk of asthma-related death (see WARNINGS). Therefore,  
1226 when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients  
1227 not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose  
1228 inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2  
1229 maintenance therapies. ADVAIR HFA is not indicated in patients whose asthma can be  
1230 successfully managed by inhaled corticosteroids along with occasional use of inhaled,  
1231 short-acting beta<sub>2</sub>-agonists.

1232 ADVAIR HFA is available in 3 strengths, ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR  
1233 HFA 115/21 Inhalation Aerosol, and ADVAIR HFA 230/21 Inhalation Aerosol, containing 45,  
1234 115, and 230 mcg of fluticasone propionate, respectively, and 21 mcg of salmeterol per  
1235 inhalation.

1236 ADVAIR HFA should be administered as 2 inhalations twice daily every day. More frequent  
1237 administration (more than twice daily) or a higher number of inhalations (more than 2 inhalations  
1238 twice daily) of the prescribed strength of ADVAIR HFA is not recommended as some patients  
1239 are more likely to experience adverse effects with higher doses of salmeterol. The safety and  
1240 efficacy of ADVAIR HFA when administered in excess of recommended doses have not been  
1241 established.

1242 If symptoms arise in the period between doses, an inhaled, short-acting beta<sub>2</sub>-agonist should  
1243 be taken for immediate relief.

1244 Patients who are receiving ADVAIR HFA twice daily should not use additional salmeterol or  
1245 other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for prevention of EIB or for any other  
1246 reason.

1247 For patients 12 years of age and older, the dosage is 2 inhalations twice daily (morning and  
1248 evening, approximately 12 hours apart).

1249 The recommended starting dosages for ADVAIR HFA are based upon patients' current  
1250 asthma therapy.

- 1251 • For patients not adequately controlled on an inhaled corticosteroid, Table 5 provides the  
1252 recommended starting dosage.
- 1253 • For patients not currently on inhaled corticosteroids, whose disease severity clearly warrants  
1254 initiation of treatment with 2 maintenance therapies, the recommended starting dosage is 2  
1255 inhalations of ADVAIR HFA 45/21 or ADVAIR HFA 115/21 twice daily (see  
1256 INDICATIONS AND USAGE).

1257 The maximum recommended dosage is 2 inhalations of ADVAIR HFA 230/21 twice daily.

1258 **For all patients it is desirable to titrate to the lowest effective strength after adequate**  
 1259 **asthma stability is achieved.**

1260

1261 **Table 5. Recommended Dosages of ADVAIR HFA Inhalation Aerosol for Patients Not**  
 1262 **Adequately Controlled on Inhaled Corticosteroids**

Current <b>Daily Dose</b> of Inhaled Corticosteroid		Recommended Strength of ADVAIR HFA (2 inhalations twice daily)
Beclomethasone dipropionate HFA inhalation aerosol	≤160 mcg	45/21
	320 mcg	115/21
	640 mcg	230/21
Budesonide inhalation powder	≤400 mcg	45/21
	800-1,200 mcg	115/21
	1,600 mcg *	230/21
Flunisolide CFC inhalation aerosol	≤1,000 mcg	45/21
	1,250-2,000 mcg	115/21
Flunisolide HFA inhalation aerosol	≤320 mcg	45/21
	640 mcg	115/21
Fluticasone propionate HFA inhalation aerosol	≤176 mcg	45/21
	440 mcg	115/21
	660-880 mcg *	230/21
Fluticasone propionate inhalation powder	≤200 mcg	45/21
	500 mcg	115/21
	1,000 mcg *	230/21
Mometasone furoate inhalation powder	220 mcg	45/21
	440 mcg	115/21
	880 mcg	230/21
Triamcinolone acetonide inhalation aerosol	≤1,000 mcg	45/21
	1,100-1,600 mcg	115/21

1263 \* ADVAIR HFA should not be used for transferring patients from systemic corticosteroid  
 1264 therapy.

1265

1266 Improvement in asthma control following inhaled administration of ADVAIR HFA can occur  
 1267 within 30 minutes of beginning treatment, although maximum benefit may not be achieved for  
 1268 1 week or longer after starting treatment. Individual patients will experience a variable time to  
 1269 onset and degree of symptom relief.

1270 For patients who do not respond adequately to the starting dosage after 2 weeks of therapy,  
 1271 replacing the current strength of ADVAIR HFA with a higher strength may provide additional  
 1272 improvement in asthma control.

1273 If a previously effective dosage regimen of ADVAIR HFA fails to provide adequate  
1274 improvement in asthma control, the therapeutic regimen should be reevaluated and additional  
1275 therapeutic options, e.g., replacing the current strength of ADVAIR HFA with a higher strength,  
1276 adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be considered.

1277 ADVAIR HFA should be primed before using for the first time by releasing 4 test sprays into  
1278 the air away from the face, shaking well for 5 seconds before each spray. In cases where the  
1279 inhaler has not been used for more than 4 weeks or when it has been dropped, prime the inhaler  
1280 again by shaking well before each spray and releasing 2 test sprays into the air, away from the  
1281 face.

1282 **Geriatric Use:** In studies where geriatric patients (65 years of age or older, see  
1283 PRECAUTIONS: Geriatric Use) have been treated with ADVAIR HFA, efficacy and safety did  
1284 not differ from that in younger patients. Based on available data for ADVAIR HFA and its active  
1285 components, no dosage adjustment is recommended.

## 1286 HOW SUPPLIED

1287 Each strength of ADVAIR HFA Inhalation Aerosol is supplied in a 12-g pressurized  
1288 aluminum canister containing 120 metered inhalations in a box of 1. \* Each canister is supplied  
1289 with a purple actuator with a light purple strapcap and is sealed in a plastic-coated,  
1290 moisture-protective foil pouch with a desiccant that should be discarded when the pouch is  
1291 opened. Each canister is packaged with a Medication Guide leaflet.

1292 \*NDC 0173-0715-00 ADVAIR HFA 45/21 Inhalation Aerosol

1293 \*NDC 0173-0716-00 ADVAIR HFA 115/21 Inhalation Aerosol

1294 \*NDC 0173-0717-00 ADVAIR HFA 230/21 Inhalation Aerosol

1295 **The purple actuator supplied with ADVAIR HFA Inhalation Aerosol should not be used**  
1296 **with any other product canisters, and actuators from other products should not be used**  
1297 **with an ADVAIR HFA Inhalation Aerosol canister.**

1298 **The correct amount of medication in each inhalation cannot be assured after**  
1299 **120 inhalations, even though the canister is not completely empty and will continue to**  
1300 **operate. The inhaler should be discarded when 120 actuations have been used. Never**  
1301 **immerse the canister into water to determine the amount remaining in the canister (“float**  
1302 **test”).**

1303 **Keep out of reach of children. Avoid spraying in eyes.**

1304 **Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame.**  
1305 **Exposure to temperatures above 120°F may cause bursting. Never throw container into fire**  
1306 **or incinerator.**

1307 **Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Store the inhaler with**  
1308 **the mouthpiece down. For best results, the inhaler should be at room temperature before**  
1309 **use. SHAKE WELL FOR 5 SECONDS BEFORE USING.**

1310 ADVAIR HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the  
1311 propellant.

1312  
1313



1314  
1315 GlaxoSmithKline  
1316 Research Triangle Park, NC 27709

1317  
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1319  
1320 Month Year

1321

1322 **MEDICATION GUIDE**

1323

1324 **ADVAIR<sup>®</sup> HFA [ad' vair] 45/21 Inhalation Aerosol**  
1325 **(fluticasone propionate 45 mcg and salmeterol 21 mcg)**

1326

1327 **ADVAIR<sup>®</sup> HFA 115/21 Inhalation Aerosol**  
1328 **(fluticasone propionate 115 mcg and salmeterol 21 mcg)**

1329

1330 **ADVAIR<sup>®</sup> HFA 230/21 Inhalation Aerosol**  
1331 **(fluticasone propionate 230 mcg and salmeterol 21 mcg)**

1332

1333 Read the Medication Guide that comes with ADVAIR HFA before you start using it and each  
1334 time you get a refill. There may be new information. This Medication Guide does not take the  
1335 place of talking to your healthcare provider about your medical condition or treatment.

1336

1337 **What is the most important information I should know about ADVAIR HFA?**

1338

- 1339 • **ADVAIR HFA contains 2 medicines:**
  - 1340 • **fluticasone propionate (the same medicine found in FLOVENT<sup>®</sup>),** an inhaled  
1341 corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the  
1342 lungs. Inflammation in the lungs can lead to asthma symptoms.
  - 1343 • **salmeterol (the same medicine found in SEREVENT<sup>®</sup>),** a long-acting beta<sub>2</sub>-agonist  
1344 medicine or LABA. LABA medicines are used in patients with asthma. LABA medicines  
1345 help the muscles around the airways in your lungs stay relaxed to prevent symptoms,  
1346 such as wheezing and shortness of breath. These symptoms can happen when the muscles  
1347 around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can  
1348 stop your breathing and cause death if not treated right away.

- 1349 • **In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in**  
1350 **ADVAIR HFA), may increase the chance of death from asthma problems.** In a large  
1351 asthma study, more patients who used salmeterol died from asthma problems compared with  
1352 patients who did not use salmeterol. It is not known whether fluticasone propionate, the other  
1353 medicine in ADVAIR HFA, changes your chance of death from asthma problems seen with  
1354 salmeterol. Talk with your healthcare provider about this risk and the benefits of treating  
1355 your asthma with ADVAIR HFA.  
1356
- 1357 • **ADVAIR HFA does not relieve sudden symptoms. Always have a short-acting**  
1358 **beta<sub>2</sub>-agonist medicine with you to treat sudden symptoms. If you do not have an**  
1359 **inhaled, short-acting bronchodilator, contact your healthcare provider to have one**  
1360 **prescribed for you.**  
1361
- 1362 • **Do not stop using ADVAIR HFA unless told to do so by your healthcare provider**  
1363 **because your symptoms might get worse.**  
1364
- 1365 • **ADVAIR HFA should be used only if your healthcare provider decides that another**  
1366 **asthma-controller medicine alone does not control your asthma or that you need 2**  
1367 **asthma-controller medicines.**  
1368
- 1369 • **Call your healthcare provider if breathing problems worsen over time while using**  
1370 **ADVAIR HFA. You may need different treatment.**  
1371
- 1372 • **Get emergency medical care if:**
- 1373 • **breathing problems worsen quickly, and**
  - 1374 • **you use your short-acting beta<sub>2</sub>-agonist medicine, but it does not relieve your**  
1375 **breathing problems.**
- 1376

### 1377 **What is ADVAIR HFA?**

1378 ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate (the same  
1379 medicine found in FLOVENT) and a long-acting beta<sub>2</sub>-agonist medicine, salmeterol (the same  
1380 medicine found in SEREVENT). ADVAIR HFA is used for asthma as follows:

1381

1382 ADVAIR HFA is used long term, twice a day to control symptoms of asthma, and prevent  
1383 symptoms such as wheezing in adolescents and adults 12 years of age and older.  
1384

1385 **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). Because**  
1386 **LABA medicines, such as salmeterol, may increase the chance of death from asthma**  
1387 **problems, ADVAIR HFA is not for adults and children with asthma who:**

- 1388 • are well controlled with another asthma-controller medicine, such as a low to medium  
1389 dose of an inhaled corticosteroid medicine
- 1390 • only need short-acting beta<sub>2</sub>-agonist medicines once in awhile

1391

### 1392 **What should I tell my healthcare provider before using ADVAIR HFA?**

#### 1393 **Tell your healthcare provider about all of your health conditions, including if you:**

- 1394 • **have heart problems**
- 1395 • **have high blood pressure**
- 1396 • **have seizures**
- 1397 • **have thyroid problems**
- 1398 • **have diabetes**
- 1399 • **have liver problems**
- 1400 • **have osteoporosis**
- 1401 • **have an immune system problem**
- 1402 • **are pregnant or planning to become pregnant.** It is not known if ADVAIR HFA may harm  
1403 your unborn baby.
- 1404 • **are breastfeeding.** It is not known if ADVAIR HFA passes into your milk and if it can harm  
1405 your baby.
- 1406 • **are allergic to ADVAIR HFA or any other medicines**
- 1407 • **are exposed to chickenpox or measles**

1408

1409 Tell your healthcare provider about all the medicines you take including prescription and  
1410 non-prescription medicines, vitamins, and herbal supplements. ADVAIR HFA and certain other  
1411 medicines may interact with each other. This may cause serious side effects. Especially, tell your  
1412 healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR<sup>®</sup> (ritonavir capsules)  
1413 Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA<sup>®</sup> (lopinavir/ritonavir) Tablets  
1414 contain ritonavir.

1415

1416 Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist  
1417 each time you get a new medicine.

1418

### 1419 **How do I use ADVAIR HFA?**

#### 1420 **See the step-by-step instructions for using ADVAIR HFA at the end of this Medication**

1421 **Guide.** Do not use the ADVAIR HFA unless your healthcare provider has taught you and you  
1422 understand everything. Ask your healthcare provider or pharmacist if you have any questions.

1423

- 1424 • Use ADVAIR HFA exactly as prescribed. **Do not use ADVAIR HFA more often than**  
1425 **prescribed.** ADVAIR HFA comes in 3 strengths. Your healthcare provider will prescribe the  
1426 one that is best for your condition.

1427

- 1428 • The usual dosage of ADVAIR HFA is 2 inhalations twice a day (morning and evening). The  
1429 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR  
1430 HFA.  
1431
- 1432 • If you miss a dose of ADVAIR HFA, just skip that dose. Take your next dose at your usual  
1433 time. Do not take 2 doses at one time.  
1434
- 1435 • **While you are using ADVAIR HFA twice a day, do not use other medicines that contain**  
1436 **a long-acting beta<sub>2</sub>-agonist or LABA for any reason. Other LABA-containing medicines**  
1437 **include ADVAIR DISKUS<sup>®</sup> (fluticasone propionate and salmeterol inhalation powder),**  
1438 **SEREVENT<sup>®</sup> DISKUS<sup>®</sup> (salmeterol xinafoate inhalation powder), FORADIL<sup>®</sup>**  
1439 **AEROLIZER<sup>®</sup> (formoterol fumarate inhalation powder), SYMBICORT<sup>®</sup> (budesonide**  
1440 **and formoterol fumarate dihydrate) Inhalation Aerosol, PERFOROMIST<sup>™</sup>**  
1441 **(formoterol fumarate) Inhalation Solution, and BROVANA<sup>™</sup> (arformoterol tartrate)**  
1442 **Inhalation Solution.**  
1443
- 1444 • Do not change or stop any of your medicines used to control or treat your breathing  
1445 problems. Your healthcare provider will adjust your medicines as needed.  
1446
- 1447 • Make sure you always have a short-acting beta<sub>2</sub>-agonist medicine with you. Use your  
1448 short-acting beta<sub>2</sub>-agonist medicine if you have breathing problems between doses of  
1449 ADVAIR HFA.  
1450
- 1451 • **Call your healthcare provider or get medical care right away if:**
- 1452 • your breathing problems worsen with ADVAIR HFA
  - 1453 • you need to use your short-acting beta<sub>2</sub>-agonist medicine more often than usual
  - 1454 • your short-acting beta<sub>2</sub>-agonist medicine does not work as well for you at relieving  
1455 symptoms
  - 1456 • you need to use 4 or more inhalations of your short-acting beta<sub>2</sub>-agonist medicine for 2 or  
1457 more days in a row
  - 1458 • you use 1 whole canister of your short-acting beta<sub>2</sub>-agonist medicine in 8 weeks' time
  - 1459 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers  
1460 that are right for you.
  - 1461 • you have asthma and your symptoms do not improve after using ADVAIR HFA regularly  
1462 for 1 week
- 1463
- 1464 **What are the possible side effects with ADVAIR HFA?**
- 1465 • **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). In**  
1466 **patients with asthma, LABA medicines, such as salmeterol, may increase the chance of**

1467 **death from asthma problems.** See “What is the most important information I should know  
1468 about ADVAIR HFA?”

1469

1470 **Other possible side effects with ADVAIR HFA include:**

1471 • **serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue;**  
1472 **and breathing problems.** Call your healthcare provider or get emergency medical care if  
1473 you get any symptoms of a serious allergic reaction.

1474 • **increased blood pressure**

1475 • **a fast and irregular heartbeat**

1476 • **chest pain**

1477 • **headache**

1478 • **tremor**

1479 • **nervousness**

1480 • **immune system effects and a higher chance for infections**

1481 • **lower bone mineral density.** This may be a problem for people who already have a higher  
1482 chance for low bone density (osteoporosis).

1483 • **eye problems including glaucoma and cataracts.** You should have regular eye exams  
1484 while using ADVAIR HFA.

1485 • **slowed growth in children.** A child’s growth should be checked often.

1486 • **throat irritation**

1487

1488 Tell your healthcare provider about any side effect that bothers you or that does not go away.

1489

1490 These are not all the side effects with ADVAIR HFA. Ask your healthcare provider or  
1491 pharmacist for more information.

1492

1493 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-  
1494 800-FDA-1088.

1495

1496 **How do I store ADVAIR HFA?**

1497 • **Store ADVAIR HFA at room temperature with the mouthpiece down.**

1498 • **Do not puncture the canister. Do not use or store ADVAIR HFA near heat or an open**  
1499 **flame. Never throw it into a fire or incinerator.**

1500 • **Keep ADVAIR HFA and all medicines out of the reach of children.**

1501

1502 **General Information about ADVAIR HFA**

1503 Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not  
1504 use ADVAIR HFA for a condition for which it was not prescribed. Do not give your ADVAIR  
1505 HFA to other people, even if they have the same condition. It may harm them.

1506 This Medication Guide summarizes the most important information about ADVAIR HFA. If you  
1507 would like more information, talk with your healthcare provider or pharmacist. You can ask your  
1508 healthcare provider or pharmacist for information about ADVAIR HFA that was written for  
1509 healthcare professionals. You can also contact the company that makes ADVAIR HFA (toll free)  
1510 at 1-888-825-5249 or at www.advair.com.

1511

1512

### Instructions for Using Your ADVAIR HFA

1513 Follow the instructions below for using your ADVAIR HFA.

1514 Take your ADVAIR HFA inhaler out of the moisture-protective foil pouch just before you use it  
1515 for the first time. Safely throw away the foil pouch and the drying packet that comes inside the  
1516 pouch.

1517 The inhaler should be at room temperature before you use it.

1518 **The purple actuator that comes with ADVAIR HFA should not be used with any other**  
1519 **product canisters. Actuators that come with other products should not be used with an**  
1520 **ADVAIR HFA canister.**

1521 **Prime the inhaler** before using it for the first time. To prime the inhaler, shake it well for  
1522 5 seconds. Then spray it 1 time into the air away from your face. Shake and spray the inhaler like  
1523 this 3 more times to finish priming it. **Avoid spraying in eyes.**

1524 If you have not used your inhaler in more than 4 weeks or if you have dropped it, shake it well  
1525 for 5 seconds and spray it 2 times into the air away from your face.

1526 **Shake the inhaler well** for 5 seconds just before each use.

1527 **1.** Take the cap off the mouthpiece (see Figure 1). The strap on the cap will stay attached to the  
1528 actuator.

1529 Look for foreign objects inside the inhaler before each use, especially if the strap is no longer  
1530 attached to the actuator or if the cap is not being used to cover the mouthpiece.

1531 Make sure the canister is fully and firmly inserted into the actuator.

1532 **Shake the inhaler well** for 5 seconds right before each use.

1533

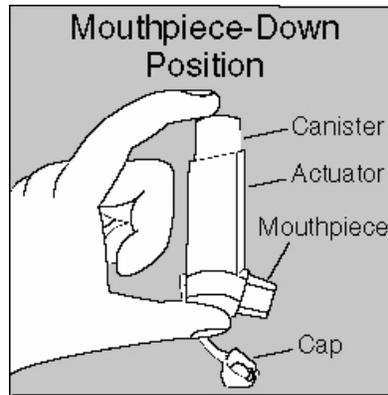


Figure 1

1534

1535

1536

1537 **2. Breathe out fully through your mouth, pushing as much air out of your lungs as you can.**

1538 Put the mouthpiece all the way into your mouth. Hold the inhaler with the mouthpiece down  
1539 (see Figure 1). Close your lips around it.

1540 **3. It is important to get the medicine in the spray into your lungs where it works. To do this, you**  
1541 **need to inhale the spray at the same time you take in a slow, deep breath.**

1542 So, just after starting to take in a slow, deep breath through your mouth, press down firmly on  
1543 the top of the metal canister (see Figure 2) and keep breathing in through your mouth.

1544 Take your finger off the canister after the spray comes out of the canister. Take the  
1545 mouthpiece out of your mouth after you have finished breathing in.

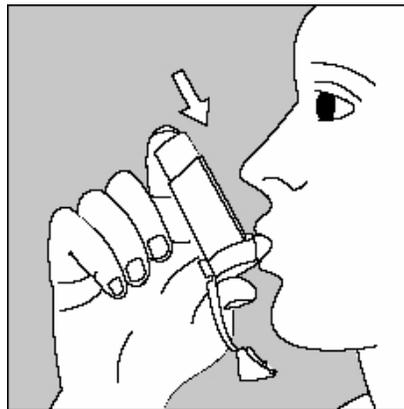


Figure 2

1546

1547

1548 **4. Hold your breath as long as you can, up to 10 seconds. Then breathe normally.**

1549 **5. Wait about 30 seconds and shake the inhaler again. Repeat steps 2 through 4.**

1550 **6. Put the cap back on the mouthpiece after each time you use the inhaler.**

1551 **7. After you finish taking this medicine, rinse your mouth with water. Spit out the water. Do not**  
1552 **swallow it.**

1553 8. Never put the canister in water to find out how much medicine is left in the canister (“float  
1554 test”).

1555 9. You should keep track of the number of inhalations used from your inhaler. **Then throw away**  
1556 **the inhaler after you have used 120 inhalations.** Even though the canister might not be empty  
1557 and will keep spraying, you might not get the right amount of medicine in each inhalation.  
1558 Before you get to 120 inhalations, ask your doctor if you need to refill your prescription.

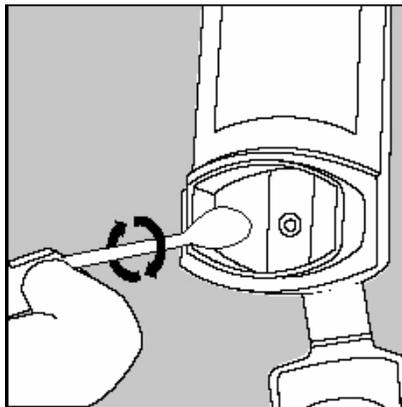
1559 **Do not** use after the expiration date, which is shown as “EXP” on the product label and box.

1560 **Cleaning your ADVAIR HFA Inhalation Aerosol:**

1561 Clean the inhaler at least once a week after your evening dose. Keeping the canister and plastic  
1562 actuator clean is important to prevent medicine buildup.

1563 Step 1. Take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator.  
1564 Do not take the canister out of the plastic actuator.

1565 Step 2. Use a dry cotton swab to clean the small circular opening where the medicine sprays out  
1566 of the canister. Carefully twist the swab in a circular motion to take off any medicine (see Figure  
1567 3). Then wipe the inside of the mouthpiece with a clean tissue dampened with water. Let the  
1568 actuator air-dry overnight.



1569  
1570 Figure 3

1571 Step 3. Put the mouthpiece cover back on after the actuator has dried.

1572  
1573 **Rx only**

1574  
1575

1576  **GlaxoSmithKline**

1577 GlaxoSmithKline  
1578 Research Triangle Park, NC 27709  
1579

1580 ADVAIR, ADVAIR DISKUS, FLOVENT, SEREVENT, and DISKUS are registered trademarks  
1581 of GlaxoSmithKline.

1582 The following are registered trademarks of their respective manufacturers: NORVIR and  
1583 KALETRA/Abbott Laboratories, FORADIL AEROLIZER/Novartis Pharmaceuticals  
1584 Corporation, SYMBICORT/AstraZeneca group of companies. The following are trademarks of  
1585 their respective manufacturers: PERFOROMIST/Dey, L.P.; BROVANA/Sepracor Inc.

1586  
1587 ©Year, GlaxoSmithKline. All rights reserved.

1588  
1589 Month Year

1590  
1591 This Medication Guide has been approved by the U.S. Food and Drug Administration.  
1592

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**PHARMACIST—DETACH HERE AND GIVE MEDICATION GUIDE TO PATIENT**

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1593

**MEDICATION GUIDE**

1594

1595

**ADVAIR<sup>®</sup> HFA [*ad' vair*] 45/21 Inhalation Aerosol  
(fluticasone propionate 45 mcg and salmeterol 21 mcg)**

1596

1597

1598

**ADVAIR<sup>®</sup> HFA 115/21 Inhalation Aerosol  
(fluticasone propionate 115 mcg and salmeterol 21 mcg)**

1599

1600

1601

**ADVAIR<sup>®</sup> HFA 230/21 Inhalation Aerosol  
(fluticasone propionate 230 mcg and salmeterol 21 mcg)**

1602

1603

1604

1605 Read the Medication Guide that comes with ADVAIR HFA before you start using it and each  
1606 time you get a refill. There may be new information. This Medication Guide does not take the  
1607 place of talking to your healthcare provider about your medical condition or treatment.

1608

1609 **What is the most important information I should know about ADVAIR HFA?**

1610

- **ADVAIR HFA contains 2 medicines:**
  - **fluticasone propionate (the same medicine found in FLOVENT<sup>®</sup>),** an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
  - **salmeterol (the same medicine found in SEREVENT<sup>®</sup>),** a long-acting beta<sub>2</sub>-agonist medicine or LABA. LABA medicines are used in patients with asthma. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles

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1618 around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can  
1619 stop your breathing and cause death if not treated right away.

1620

1621 • **In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in**  
1622 **ADVAIR HFA), may increase the chance of death from asthma problems.** In a large  
1623 asthma study, more patients who used salmeterol died from asthma problems compared with  
1624 patients who did not use salmeterol. It is not known whether fluticasone propionate, the other  
1625 medicine in ADVAIR HFA, changes your chance of death from asthma problems seen with  
1626 salmeterol. Talk with your healthcare provider about this risk and the benefits of treating  
1627 your asthma with ADVAIR HFA.

1628

1629 • **ADVAIR HFA does not relieve sudden symptoms. Always have a short-acting**  
1630 **beta<sub>2</sub>-agonist medicine with you to treat sudden symptoms. If you do not have an**  
1631 **inhaled, short-acting bronchodilator, contact your healthcare provider to have one**  
1632 **prescribed for you.**

1633

1634 • **Do not stop using ADVAIR HFA unless told to do so by your healthcare provider**  
1635 **because your symptoms might get worse.**

1636

1637 • **ADVAIR HFA should be used only if your healthcare provider decides that another**  
1638 **asthma-controller medicine alone does not control your asthma or that you need 2**  
1639 **asthma-controller medicines.**

1640

1641 • **Call your healthcare provider if breathing problems worsen over time while using**  
1642 **ADVAIR HFA. You may need different treatment.**

1643

1644 • **Get emergency medical care if:**

1645 • **breathing problems worsen quickly, and**

1646 • **you use your short-acting beta<sub>2</sub>-agonist medicine, but it does not relieve your**  
1647 **breathing problems.**

1648

#### 1649 **What is ADVAIR HFA?**

1650 ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate (the same  
1651 medicine found in FLOVENT) and a long-acting beta<sub>2</sub>-agonist medicine, salmeterol (the same  
1652 medicine found in SEREVENT). ADVAIR HFA is used for asthma as follows:

1653

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1655 symptoms such as wheezing in adolescents and adults 12 years of age and older.

1656

1657 **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). Because**  
1658 **LABA medicines, such as salmeterol, may increase the chance of death from asthma**  
1659 **problems, ADVAIR HFA is not for adults and children with asthma who:**  
1660     • are well controlled with another asthma-controller medicine, such as a low to medium  
1661     dose of an inhaled corticosteroid medicine  
1662     • only need short-acting beta<sub>2</sub>-agonist medicines once in awhile  
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- 1667 • **have high blood pressure**
- 1668 • **have seizures**
- 1669 • **have thyroid problems**
- 1670 • **have diabetes**
- 1671 • **have liver problems**
- 1672 • **have osteoporosis**
- 1673 • **have an immune system problem**
- 1674 • **are pregnant or planning to become pregnant.** It is not known if ADVAIR HFA may harm  
1675 your unborn baby.
- 1676 • **are breastfeeding.** It is not known if ADVAIR HFA passes into your milk and if it can harm  
1677 your baby.
- 1678 • **are allergic to ADVAIR HFA or any other medicines**
- 1679 • **are exposed to chickenpox or measles**

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1682 non-prescription medicines, vitamins, and herbal supplements. ADVAIR HFA and certain other  
1683 medicines may interact with each other. This may cause serious side effects. Especially, tell your  
1684 healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR<sup>®</sup> (ritonavir capsules)  
1685 Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA<sup>®</sup> (lopinavir/ritonavir) Tablets  
1686 contain ritonavir.

1687  
1688 Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist  
1689 each time you get a new medicine.

1690  
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1692 **See the step-by-step instructions for using ADVAIR HFA at the end of this Medication**  
1693 **Guide.** Do not use the ADVAIR HFA unless your healthcare provider has taught you and you  
1694 understand everything. Ask your healthcare provider or pharmacist if you have any questions.  
1695

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1697 **prescribed.** ADVAIR HFA comes in 3 strengths. Your healthcare provider will prescribe the  
1698 one that is best for your condition.  
1699
- 1700 • The usual dosage of ADVAIR HFA is 2 inhalations twice a day (morning and evening). The  
1701 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR  
1702 HFA.  
1703
- 1704 • If you miss a dose of ADVAIR HFA, just skip that dose. Take your next dose at your usual  
1705 time. Do not take 2 doses at one time.  
1706
- 1707 • **While you are using ADVAIR HFA twice a day, do not use other medicines that contain**  
1708 **a long-acting beta<sub>2</sub>-agonist or LABA for any reason. Other LABA-containing medicines**  
1709 **include ADVAIR DISKUS<sup>®</sup> (fluticasone propionate and salmeterol inhalation powder),**  
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1712 **and formoterol fumarate dihydrate) Inhalation Aerosol, PERFOROMIST<sup>™</sup>**  
1713 **(formoterol fumarate) Inhalation Solution, and BROVANA<sup>™</sup> (arformoterol tartrate)**  
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1715
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1717 problems. Your healthcare provider will adjust your medicines as needed.  
1718
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1720 short-acting beta<sub>2</sub>-agonist medicine if you have breathing problems between doses of  
1721 ADVAIR HFA.  
1722
- 1723 • **Call your healthcare provider or get medical care right away if:**  
1724 • your breathing problems worsen with ADVAIR HFA  
1725 • you need to use your short-acting beta<sub>2</sub>-agonist medicine more often than usual  
1726 • your short-acting beta<sub>2</sub>-agonist medicine does not work as well for you at relieving  
1727 symptoms  
1728 • you need to use 4 or more inhalations of your short-acting beta<sub>2</sub>-agonist medicine for 2 or  
1729 more days in a row  
1730 • you use 1 whole canister of your short-acting beta<sub>2</sub>-agonist medicine in 8 weeks' time  
1731 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers  
1732 that are right for you.  
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1735

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1737 • **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). In**  
1738 **patients with asthma, LABA medicines, such as salmeterol, may increase the chance of**  
1739 **death from asthma problems.** See “What is the most important information I should know  
1740 about ADVAIR HFA?”

1741  
1742 **Other possible side effects with ADVAIR HFA include:**  
1743 • **serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue;**  
1744 **and breathing problems.** Call your healthcare provider or get emergency medical care if  
1745 you get any symptoms of a serious allergic reaction.  
1746 • **increased blood pressure**  
1747 • **a fast and irregular heartbeat**  
1748 • **chest pain**  
1749 • **headache**  
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1753 • **lower bone mineral density.** This may be a problem for people who already have a higher  
1754 chance for low bone density (osteoporosis).  
1755 • **eye problems including glaucoma and cataracts.** You should have regular eye exams  
1756 while using ADVAIR HFA.  
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1758 • **throat irritation**

1759  
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1761  
1762 These are not all the side effects with ADVAIR HFA. Ask your healthcare provider or  
1763 pharmacist for more information.

1764  
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1767  
1768 **How do I store ADVAIR HFA?**

1769 • **Store ADVAIR HFA at room temperature with the mouthpiece down.**  
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1771 **flame. Never throw it into a fire or incinerator.**  
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1783

1784

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1802 attached to the actuator or if the cap is not being used to cover the mouthpiece.

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1804 **Shake the inhaler well** for 5 seconds right before each use.

1805

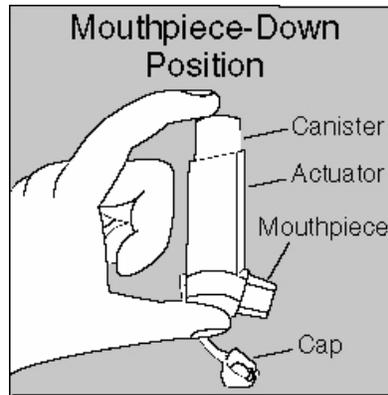


Figure 1

1806

1807

1808

1809 **2. Breathe out fully through your mouth, pushing as much air out of your lungs as you can.**

1810 Put the mouthpiece all the way into your mouth. Hold the inhaler with the mouthpiece down  
1811 (see Figure 1). Close your lips around it.

1812 **3. It is important to get the medicine in the spray into your lungs where it works. To do this, you**  
1813 **need to inhale the spray at the same time you take in a slow, deep breath.**

1814 So, just after starting to take in a slow, deep breath through your mouth, press down firmly on  
1815 the top of the metal canister (see Figure 2) and keep breathing in through your mouth.

1816 Take your finger off the canister after the spray comes out of the canister. Take the  
1817 mouthpiece out of your mouth after you have finished breathing in.

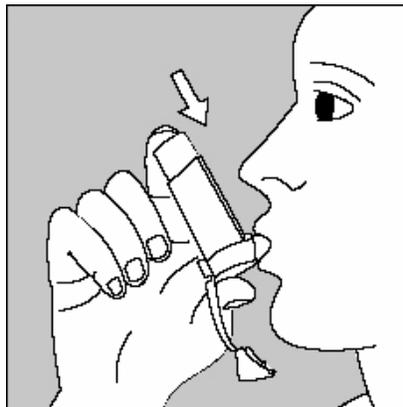


Figure 2

1818

1819

1820 **4. Hold your breath as long as you can, up to 10 seconds. Then breathe normally.**

1821 **5. Wait about 30 seconds and shake the inhaler again. Repeat steps 2 through 4.**

1822 **6. Put the cap back on the mouthpiece after each time you use the inhaler.**

1823 **7. After you finish taking this medicine, rinse your mouth with water. Spit out the water. Do not**  
1824 **swallow it.**

1825 8. Never put the canister in water to find out how much medicine is left in the canister (“float  
1826 test”).

1827 9. You should keep track of the number of inhalations used from your inhaler. **Then throw away**  
1828 **the inhaler after you have used 120 inhalations.** Even though the canister might not be empty  
1829 and will keep spraying, you might not get the right amount of medicine in each inhalation.  
1830 Before you get to 120 inhalations, ask your doctor if you need to refill your prescription.

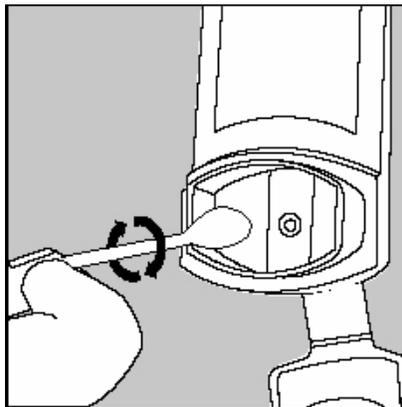
1831 **Do not** use after the expiration date, which is shown as “EXP” on the product label and box.

1832 **Cleaning your ADVAIR HFA Inhalation Aerosol:**

1833 Clean the inhaler at least once a week after your evening dose. Keeping the canister and plastic  
1834 actuator clean is important to prevent medicine buildup.

1835 Step 1. Take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator.  
1836 Do not take the canister out of the plastic actuator.

1837 Step 2. Use a dry cotton swab to clean the small circular opening where the medicine sprays out  
1838 of the canister. Carefully twist the swab in a circular motion to take off any medicine (see Figure  
1839 3). Then wipe the inside of the mouthpiece with a clean tissue dampened with water. Let the  
1840 actuator air-dry overnight.



1841  
1842

Figure 3

1843 Step 3. Put the mouthpiece cover back on after the actuator has dried.

1844

1845 **Rx only**

1846

1847



1848

1849 GlaxoSmithKline

1850 Research Triangle Park, NC 27709

1851

1852 ADVAIR, ADVAIR DISKUS, FLOVENT, SEREVENT, and DISKUS are registered trademarks  
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1858

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1860

1861 Month Year

1862

1863 This Medication Guide has been approved by the U.S. Food and Drug Administration.

1 PRESCRIBING INFORMATION

2 **SEREVENT<sup>®</sup> DISKUS<sup>®</sup>**  
3 **(salmeterol xinafoate inhalation powder)**

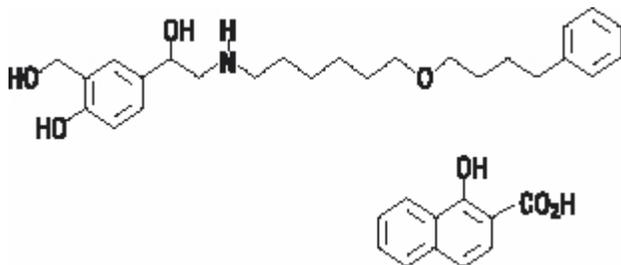
4  
5 **For Oral Inhalation Only**  
6

7 **WARNING**

8 Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, the active ingredient in  
9 SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when treating  
10 patients with asthma, SEREVENT DISKUS should only be used as additional therapy for  
11 patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-  
12 dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment  
13 with 2 maintenance therapies, including SEREVENT DISKUS. Data from a large placebo-  
14 controlled US study that compared the safety of salmeterol (SEREVENT<sup>®</sup> Inhalation Aerosol) or  
15 placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients  
16 receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus  
17 3 deaths out of 13,179 patients on placebo) (see WARNINGS and CLINICAL TRIALS: Asthma:  
18 *Salmeterol Multi-center Asthma Research Trial*).

19 **DESCRIPTION**

20 SEREVENT DISKUS (salmeterol xinafoate inhalation powder) contains salmeterol xinafoate  
21 as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The active component  
22 of the formulation is salmeterol base, a highly selective beta<sub>2</sub>-adrenergic bronchodilator. The  
23 chemical name of salmeterol xinafoate is 4-hydroxy- $\alpha^1$ -[[[6-(4-phenylbutoxy)hexyl]amino]  
24 methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate. Salmeterol xinafoate has  
25 the following chemical structure:  
26



29 Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical  
30 formula is C<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>•C<sub>11</sub>H<sub>8</sub>O<sub>3</sub>. It is freely soluble in methanol; slightly soluble in ethanol,  
31 chloroform, and isopropanol; and sparingly soluble in water.

32 SEREVENT DISKUS is a specially designed plastic inhalation delivery system containing a  
33 double-foil blister strip of a powder formulation of salmeterol xinafoate intended for oral  
34 inhalation only. The DISKUS<sup>®</sup>, which is the delivery component, is an integral part of the drug

35 product. Each blister on the double-foil strip within the unit contains 50 mcg of salmeterol  
36 administered as the salmeterol xinafoate salt in 12.5 mg of formulation containing lactose (which  
37 contains milk proteins). After a blister containing medication is opened by activating the  
38 DISKUS, the medication is dispersed into the airstream created by the patient inhaling through  
39 the mouthpiece.

40 Under standardized in vitro test conditions, SEREVENT DISKUS delivers 47 mcg when  
41 tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and  
42 severely compromised lung function (mean forced expiratory volume in 1 second [FEV<sub>1</sub>] 20% to  
43 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS was 82.4 L/min (range,  
44 46.1 to 115.3 L/min).

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

## 47 **CLINICAL PHARMACOLOGY**

48 **Mechanism of Action:** Salmeterol is a long-acting beta<sub>2</sub>-adrenergic agonist. In vitro studies  
49 and in vivo pharmacologic studies demonstrate that salmeterol is selective for beta<sub>2</sub>-  
50 adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on  
51 beta<sub>1</sub>- and beta<sub>2</sub>-adrenoceptors. In vitro studies show salmeterol to be at least 50 times more  
52 selective for beta<sub>2</sub>-adrenoceptors than albuterol. Although beta<sub>2</sub>-adrenoceptors are the  
53 predominant adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-adrenoceptors are the  
54 predominant receptors in the heart, there are also beta<sub>2</sub>-adrenoceptors in the human heart  
55 comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors  
56 has not been established, but they raise the possibility that even highly selective beta<sub>2</sub>-agonists  
57 may have cardiac effects.

58 The pharmacologic effects of beta<sub>2</sub>-adrenoceptor agonist drugs, including salmeterol, are at  
59 least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes  
60 the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic  
61 AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition  
62 of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

63 In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast  
64 cell mediators, such as histamine, leukotrienes, and prostaglandin D<sub>2</sub>, from human lung.  
65 Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-  
66 activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered  
67 by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol  
68 attenuate allergen-induced bronchial hyper-responsiveness.

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

73 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low or

74 undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder  
75 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol  
76 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in  
77 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of  
78 167 pg/mL at 20 minutes and no accumulation with repeated doses.

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

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

85 An in vitro study using human liver microsomes showed that salmeterol is extensively  
86 metabolized to  $\alpha$ -hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4).  
87 Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of  
88  $\alpha$ -hydroxysalmeterol in vitro.

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

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

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

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

101 **Inhibitors of Cytochrome P450 3A4: Ketoconazole:** In a placebo-controlled,  
102 crossover drug interaction study in 20 healthy male and female subjects, coadministration of  
103 salmeterol (50 mcg twice daily) and the strong CYP3A4 inhibitor ketoconazole (400 mg once  
104 daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined  
105 by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76; 90% CI: 10.66, 23.31)  
106 mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma  
107 salmeterol concentrations were increased by 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20  
108 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-  
109 agonist-mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus  
110 tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically  
111 significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although  
112 there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole  
113 was associated with more frequent increases in QTc duration compared with salmeterol and

114 placebo administration. Due to the potential increased risk of cardiovascular adverse events, the  
115 concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir,  
116 atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir,  
117 telithromycin) is not recommended.

118 **Erythromycin:** In a repeat-dose study in 13 healthy subjects, concomitant  
119 administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol  
120 resulted in a 40% increase in salmeterol  $C_{max}$  at steady state (ratio with and without erythromycin  
121 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;  
122  $p < 0.04$ ), a 5.8-msec increase in QTc interval (95% CI: -6.14, 17.77;  $p = 0.34$ ), and no change in  
123 plasma potassium.

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

129 The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied  
130 in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as  
131 inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as  
132 albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and adult  
133 patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent continuous  
134 electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month  
135 of therapy, and no clinically significant dysrhythmias were noted. Also, pediatric patients  
136 receiving 50-mcg doses of salmeterol inhalation powder (N = 67) underwent continuous  
137 electrocardiographic monitoring during two 12-hour periods after the first dose and after  
138 3 months of therapy, and no clinically significant dysrhythmias were noted.

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

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

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

152 **CLINICAL TRIALS**

153 **Asthma:** During the initial treatment day in several multiple-dose clinical trials with  
154 SEREVENT DISKUS in patients with asthma, the median time to onset of clinically significant  
155 bronchodilatation ( $\geq 15\%$  improvement in FEV<sub>1</sub>) ranged from 30 to 48 minutes after a 50-mcg  
156 dose.

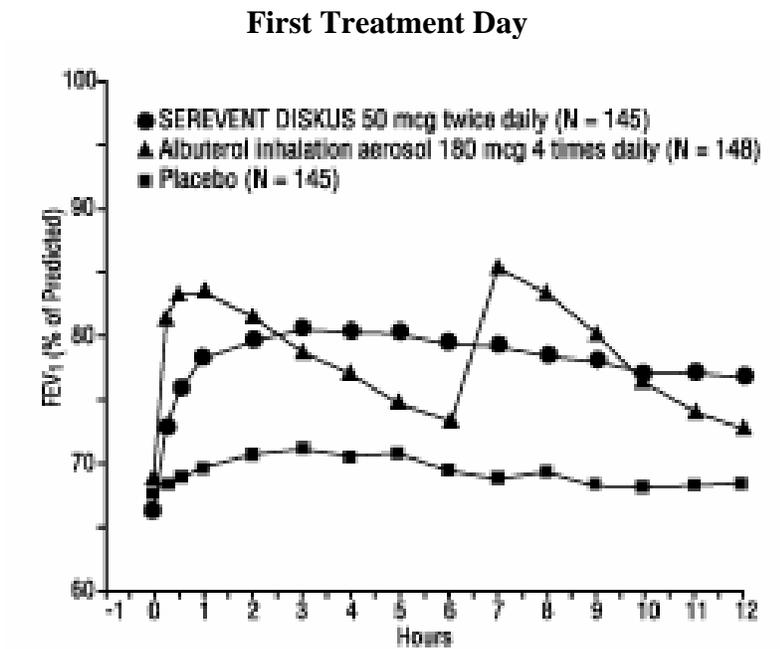
157 One hour after a single dose of 50 mcg of SEREVENT DISKUS, the majority of patients had  
158  $\geq 15\%$  improvement in FEV<sub>1</sub>. Maximum improvement in FEV<sub>1</sub> generally occurred within  
159 180 minutes, and clinically significant improvement continued for 12 hours in most patients.

160 In 2 randomized, double-blind studies, SEREVENT DISKUS was compared with albuterol  
161 inhalation aerosol and placebo in adolescent and adult patients with mild-to-moderate asthma  
162 (protocol defined as 50% to 80% predicted FEV<sub>1</sub>, actual mean of 67.7% at baseline), including  
163 patients who did and who did not receive concurrent inhaled corticosteroids. The efficacy of  
164 SEREVENT DISKUS was demonstrated over the 12-week period with no change in  
165 effectiveness over this time period (see Figure 1). There were no gender- or age-related  
166 differences in safety or efficacy. No development of tachyphylaxis to the bronchodilator effect  
167 was noted in these studies. FEV<sub>1</sub> measurements (mean change from baseline) from these two 12-  
168 week studies are shown in Figure 1 for both the first and last treatment days.

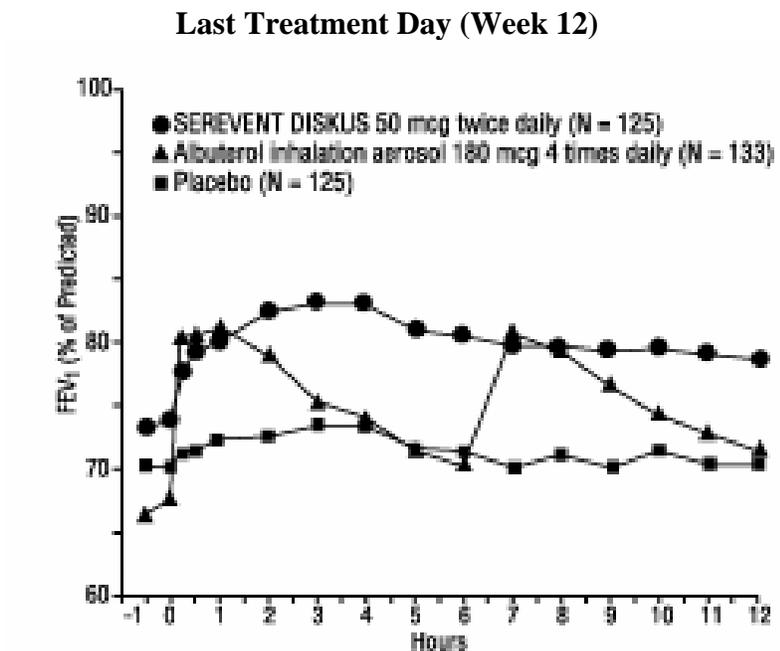
169

170 **Figure 1. Serial 12-Hour FEV<sub>1</sub> From Two 12-Week**  
 171 **Clinical Trials in Patients With Asthma**

172  
 173



174  
 175  
 176



177  
 178 Table 1 shows the treatment effects seen during daily treatment with SEREVENT DISKUS  
 179 for 12 weeks in adolescent and adult patients with mild-to-moderate asthma.

180

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

Parameter	Time	Placebo	SEREVENT DISKUS	Albuterol Inhalation Aerosol
No. of randomized subjects		152	149	148
Mean AM peak expiratory flow (L/min)	baseline	394	395	394
	12 weeks	396	427*	394
Mean % days with no asthma symptoms	baseline	14	13	12
	12 weeks	20	33	21
Mean % nights with no awakenings	baseline	70	63	68
	12 weeks	73	85*	71
Rescue medications (mean no. of inhalations per day)	baseline	4.2	4.3	4.3
	12 weeks	3.3	1.6†	2.2
Asthma exacerbations		14%	15%	16%

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

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

184

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

186 SEREVENT DISKUS and SEREVENT<sup>®</sup> (salmeterol xinafoate) Inhalation Aerosol were  
 187 compared to placebo in 2 additional randomized, double-blind clinical trials in adolescent and  
 188 adult patients with mild-to-moderate asthma. SEREVENT DISKUS 50 mcg and SEREVENT  
 189 Inhalation Aerosol 42 mcg, both administered twice daily, produced significant improvements in  
 190 pulmonary function compared with placebo over the 12-week period. While no statistically  
 191 significant differences were observed between the active treatments for any of the efficacy  
 192 assessments or safety evaluations performed, there were some efficacy measures on which the  
 193 metered-dose inhaler appeared to provide better results. Similar findings were noted in 2  
 194 randomized, single-dose, crossover comparisons of SEREVENT DISKUS and SEREVENT  
 195 Inhalation Aerosol for the prevention of exercise-induced bronchospasm (EIB). Therefore, while  
 196 SEREVENT DISKUS was comparable to SEREVENT Inhalation Aerosol in clinical trials in  
 197 mild-to-moderate patients with asthma, it should not be assumed that they will produce clinically  
 198 equivalent outcomes in all patients.

199 In a randomized, double-blind, controlled study (N = 449), 50 mcg of SEREVENT DISKUS  
 200 was administered twice daily to pediatric patients with asthma who did and who did not receive  
 201 concurrent inhaled corticosteroids. The efficacy of salmeterol inhalation powder was  
 202 demonstrated over the 12-week treatment period with respect to periodic serial peak expiratory  
 203 flow (PEF) (36% to 39% postdose increase from baseline) and FEV<sub>1</sub> (32% to 33% postdose  
 204 increase from baseline). Salmeterol was effective in demographic subgroup analyses (gender and  
 205 age) and was effective when coadministered with other inhaled asthma medications such as  
 206 short-acting bronchodilators and inhaled corticosteroids. A second randomized, double-blind,

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

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

215 Two randomized, double-blind, controlled, parallel-group clinical trials (N = 997) enrolled  
216 patients (ages 18 to 82 years) with persistent asthma who were previously maintained but not  
217 adequately controlled on inhaled corticosteroid therapy. During the 2-week run-in period, all  
218 patients were switched to beclomethasone dipropionate 168 mcg twice daily. Patients still not  
219 adequately controlled were randomized to either the addition of SEREVENT Inhalation Aerosol  
220 42 mcg twice daily or an increase of beclomethasone dipropionate to 336 mcg twice daily. As  
221 compared to the doubled dose of beclomethasone dipropionate, the addition of SEREVENT  
222 Inhalation Aerosol resulted in statistically significantly greater improvements in pulmonary  
223 function and asthma symptoms, and statistically significantly greater reduction in supplemental  
224 albuterol use. The percent of patients who experienced asthma exacerbations overall was not  
225 different between groups (i.e., 16.2% in the group receiving SEREVENT Inhalation Aerosol  
226 versus 17.9% in the higher-dose beclomethasone dipropionate group).

227 Two randomized, double-blind, parallel-group clinical trials (N = 925) enrolled patients (ages  
228 12 to 78 years) with persistent asthma who were previously maintained but not adequately  
229 controlled on prior therapy. During the 2- to 4-week run-in period, all patients were switched to  
230 fluticasone propionate 88 mcg twice daily. Patients still not adequately controlled were  
231 randomized to either the addition of SEREVENT Inhalation Aerosol 42 mcg twice daily or an  
232 increase of fluticasone propionate to 220 mcg twice daily. As compared to the increased (2.5  
233 times) dose of fluticasone propionate, the addition of SEREVENT Inhalation Aerosol resulted in  
234 statistically significantly greater improvements in pulmonary function and asthma symptoms,  
235 and statistically significantly greater reductions in supplemental albuterol use. Fewer patients  
236 receiving SEREVENT Inhalation Aerosol experienced asthma exacerbations than those  
237 receiving the higher dose of fluticasone propionate (8.8% versus 13.8%).

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

242

243

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

		Placebo (N = 52)		SEREVENT DISKUS (N = 52)	
		n	% Total	n	% Total
0.5-Hour postdose exercise challenge	<u>% Fall in FEV<sub>1</sub></u> <10%	15	29	31	60
	≥10%, <20%	3	6	11	21
	≥20%	34	65	10	19
Mean maximal % fall in FEV <sub>1</sub> (SE)		-25% (1.8)		-11% (1.9)	
8.5-Hour postdose exercise challenge	<u>% Fall in FEV<sub>1</sub></u> <10%	12	23	26	50
	≥10%, <20%	7	13	12	23
	≥20%	33	63	14	27
Mean maximal % fall in FEV <sub>1</sub> (SE)		-27% (1.5)		-16% (2.0)	

244

245 In 2 randomized studies in children 4 to 11 years old with asthma and EIB (N = 50), a single  
 246 50-mcg dose of SEREVENT DISKUS prevented EIB when dosed 30 minutes prior to exercise,  
 247 with protection lasting up to 11.5 hours in repeat testing following this single dose in many  
 248 patients.

249 **Salmeterol Multi-center Asthma Research Trial:** The Salmeterol Multi-center Asthma  
 250 Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta<sub>2</sub>-  
 251 agonist-naïve patients with asthma (average age of 39 years, 71% Caucasian, 18% African  
 252 American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol)  
 253 42 mcg twice daily over 28 weeks compared to placebo when added to usual asthma therapy.

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

260 Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death  
 261 occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo  
 262 (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also,  
 263 asthma-related death occurred at a higher rate in patients treated with salmeterol than those  
 264 treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the  
 265 relative risks of asthma-related death were similar in Caucasians and African Americans, the  
 266 estimate of excess deaths in patients treated with salmeterol was greater in African Americans  
 267 because there was a higher overall rate of asthma-related death in African American patients (see

268 Table 3).

269 The data from the SMART study are not adequate to determine whether concurrent use of  
270 inhaled corticosteroids or other asthma-controller therapy modifies the risk of asthma-related  
271 death.

272

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

	Salmeterol n (% <sup>*</sup> )	Placebo n (% <sup>*</sup> )	Relative Risk <sup>†</sup> (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients <sup>‡</sup> (95% Confidence Interval)
<b>Total Population<sup>§</sup></b> Salmeterol: N = 1,3176 Placebo: N = 1,3179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
<b>Caucasian</b> Salmeterol: N = 9,281 Placebo: N = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
<b>African American</b> Salmeterol: N = 2,366 Placebo: N = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

275 <sup>\*</sup> Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to  
276 study treatment to account for early withdrawal of patients from the study.

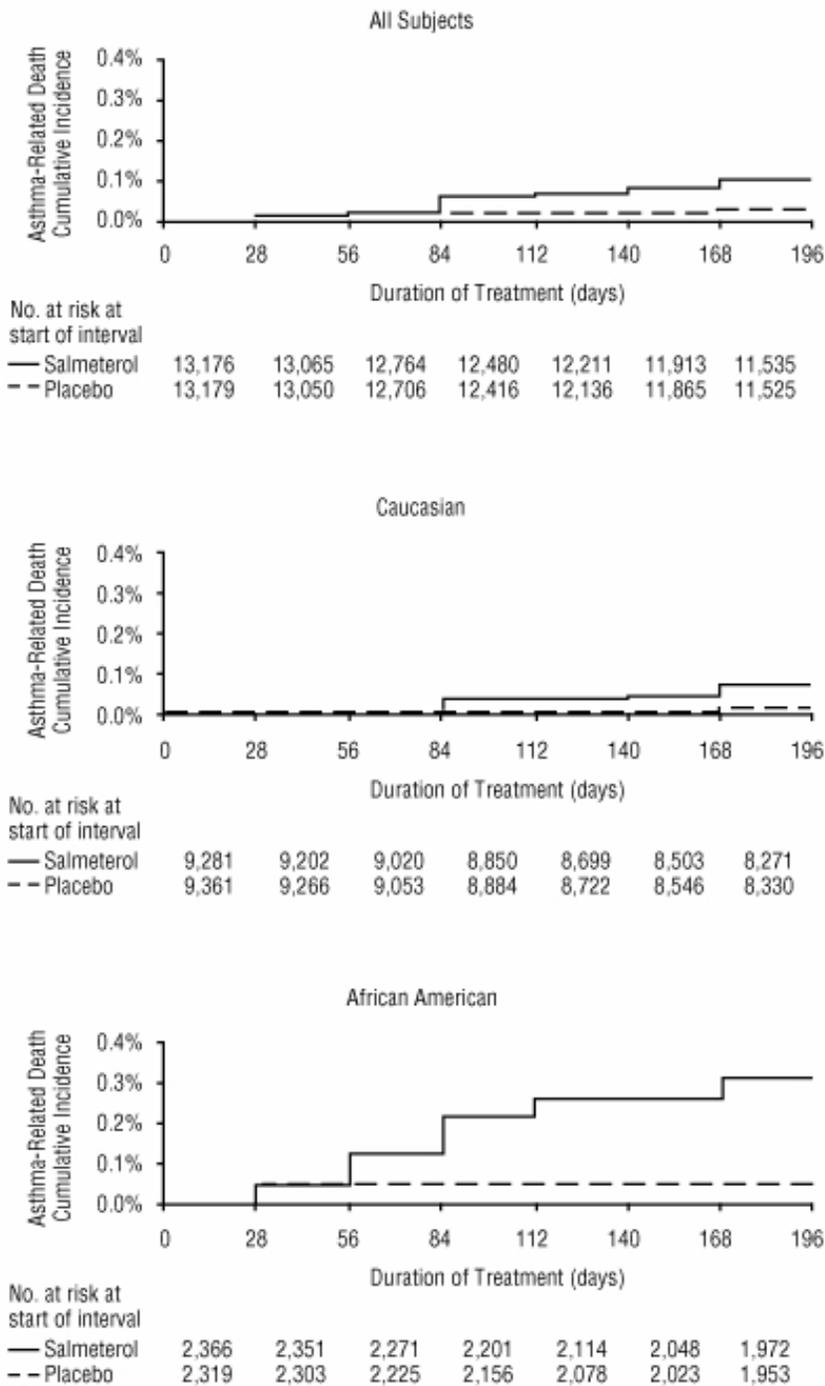
277 <sup>†</sup> Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the  
278 rate in the placebo group. The relative risk indicates how many more times likely an  
279 asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week  
280 treatment period.

281 <sup>‡</sup> Estimate of the number of additional asthma-related deaths in patients treated with salmeterol  
282 in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period.  
283 Estimate calculated as the difference between the salmeterol and placebo groups in the rates of  
284 asthma-related death multiplied by 10,000.

285 <sup>§</sup> The Total Population includes the following ethnic origins listed on the case report form:  
286 Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population  
287 includes those patients whose ethnic origin was not reported. The results for Caucasian and  
288 African American subpopulations are shown above. No asthma-related deaths occurred in the  
289 Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149),  
290 or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death  
291 occurred in the placebo group in the subpopulation whose ethnic origin was not reported  
292 (salmeterol n = 130, placebo n = 127).

293

294 **Figure 2. Cumulative Incidence of Asthma-Related Deaths**  
 295 **in the 28-Week Salmeterol Multi-center Asthma Research**  
 296 **Trial (SMART), by Duration of Treatment**  
 297



298  
 299  
 300 **Chronic Obstructive Pulmonary Disease:** In 2 clinical trials evaluating twice-daily

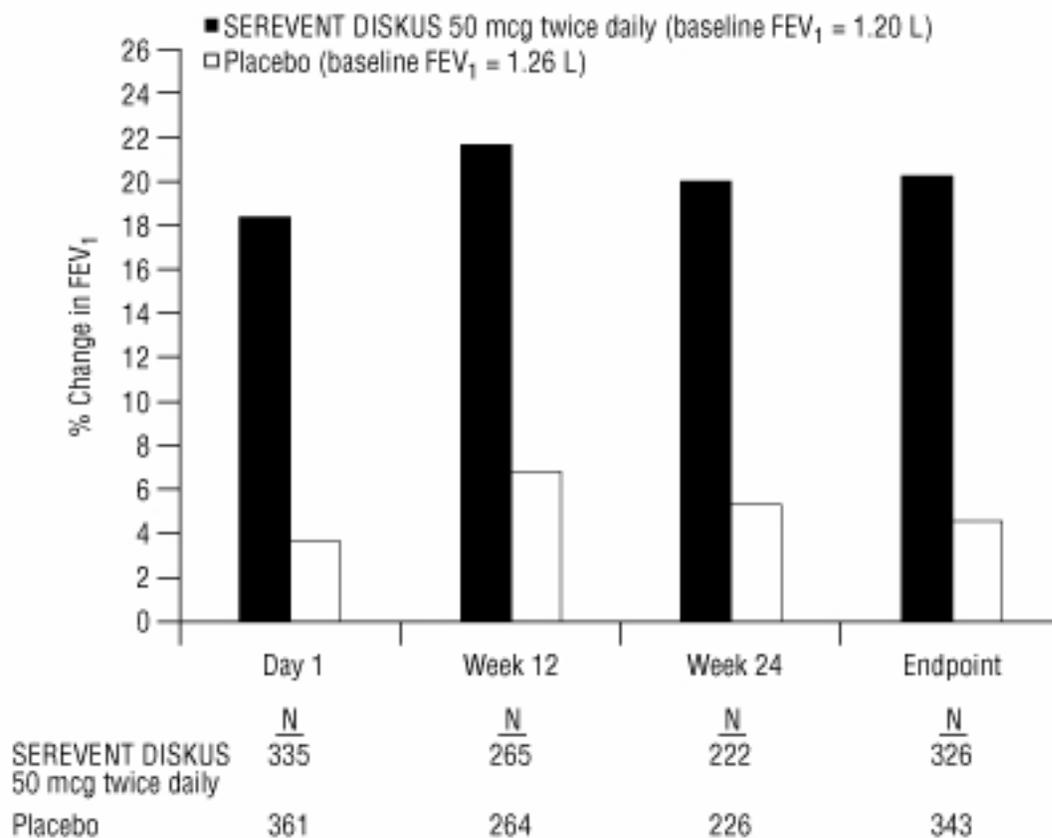
301 treatment with SEREVENT DISKUS 50 mcg (N = 336) compared to placebo (N = 366) in  
 302 patients with chronic bronchitis with airflow limitation, with or without emphysema,  
 303 improvements in pulmonary function endpoints were greater with salmeterol 50 mcg than with  
 304 placebo. Treatment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

308 Figure 3 displays the integrated 2-hour postdose FEV<sub>1</sub> results from the 2 clinical trials. The  
 309 percent change in FEV<sub>1</sub> refers to the change from baseline, defined as the predose value on  
 310 Treatment Day 1. To account for patient withdrawals during the study, Endpoint (last evaluable  
 311 FEV<sub>1</sub>) data are provided. Patients receiving SEREVENT DISKUS 50 mcg had significantly  
 312 greater improvements in 2-hour postdose FEV<sub>1</sub> at Endpoint (216 mL, 20%) compared to placebo  
 313 (43 mL, 5%). Improvement was apparent on the first day of treatment and maintained throughout  
 314 the 24 weeks of treatment.

315

316 **Figure 3. Mean Percent Change From Baseline in Postdose FEV<sub>1</sub> Integrated Data**  
 317 **From 2 Trials of Patients With Chronic Bronchitis and Airflow Limitation**

318

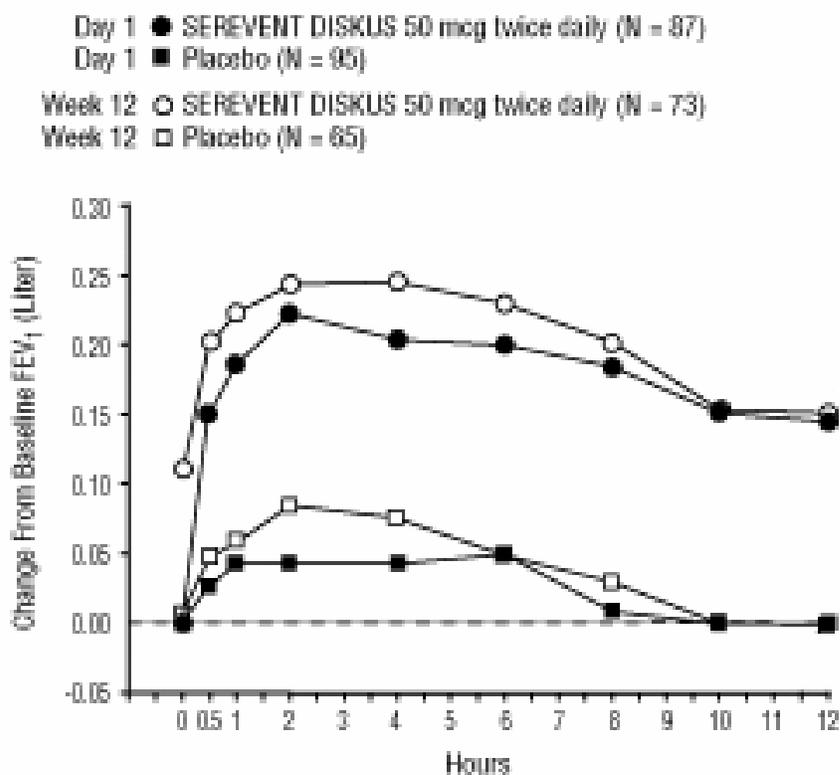


319

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

321 SEREVENT DISKUS were evaluated in a subset of patients (n = 87) from 1 of the 2 clinical  
 322 trials discussed above. Following the first 50-mcg dose, significant improvement in pulmonary  
 323 function (mean FEV<sub>1</sub> increase of 12% or more and at least 200 mL) occurred at 2 hours. The  
 324 mean time to peak bronchodilator effect was 4.75 hours. As seen in Figure 4, evidence of  
 325 bronchodilatation was seen throughout the 12-hour period. Figure 4 also demonstrates that the  
 326 bronchodilating effect after 12 weeks of treatment was similar to that observed after the first  
 327 dose. The mean time to peak bronchodilator effect after 12 weeks of treatment was 3.27 hours.  
 328

329 **Figure 4. Serial 12-Hour FEV<sub>1</sub> on the First Day and at Week 12**  
 330 **of Treatment**



331

332 **INDICATIONS AND USAGE**

333 **Asthma:** SEREVENT DISKUS is indicated for long-term, twice-daily (morning and evening)  
 334 administration in the maintenance treatment of asthma and in the prevention of bronchospasm in  
 335 patients 4 years of age and older with reversible obstructive airway disease, including patients  
 336 with symptoms of nocturnal asthma.

337 Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, the active ingredient in  
 338 SEREVENT DISKUS, may increase the risk of asthma-related death (see WARNINGS).  
 339 Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as  
 340 additional therapy for patients not adequately controlled on other asthma-controller medications

341 (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants  
342 initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. It is not  
343 indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting  
344 beta<sub>2</sub>-agonists or for patients whose asthma can be successfully managed by inhaled  
345 corticosteroids or other controller medications along with occasional use of inhaled, short-acting  
346 beta<sub>2</sub>-agonists.

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

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

## 352 **CONTRAINDICATIONS**

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

## 356 **WARNINGS**

- 357 • **Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, the active ingredient in**  
358 **SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when**  
359 **treating patients with asthma, SEREVENT DISKUS should only be used as additional**  
360 **therapy for patients not adequately controlled on other asthma-controller medications**  
361 **(e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly**  
362 **warrants initiation of treatment with 2 maintenance therapies, including SEREVENT**  
363 **DISKUS.**
- 364 • A large 28-week, placebo-controlled US study comparing the safety of salmeterol  
365 (SEREVENT Inhalation Aerosol) with placebo, each added to usual asthma therapy,  
366 showed an increase in asthma-related deaths in patients receiving salmeterol (see  
367 CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*). Given  
368 the similar basic mechanisms of action of beta<sub>2</sub>-agonists, it is possible that the findings  
369 seen in the SMART study represent a class effect.
- 370 • A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide  
371 Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study,  
372 the rate of asthma-related death was numerically, though not statistically significantly,  
373 greater in patients with asthma treated with salmeterol (42 mcg twice daily) than those  
374 treated with albuterol (180 mcg 4 times daily) added to usual asthma therapy.
- 375 • **The SNS and SMART studies enrolled patients with asthma. No studies have been**  
376 **conducted that were adequate to determine whether the rate of death in patients with**  
377 **COPD is increased by long-acting beta<sub>2</sub>-adrenergic agonists.**
- 378 • **It is important to watch for signs of worsening asthma, such as increasing use of**  
379 **inhaled, short-acting beta<sub>2</sub>-agonists or a significant decrease in PEF or lung function.**

- 380 Such findings require immediate evaluation. Patients should be advised to seek  
381 immediate medical attention should their condition deteriorate.
- 382 • **SEREVENT DISKUS should not be used to treat acute symptoms.** It is crucial to  
383 inform patients of this and prescribe an inhaled, short-acting beta<sub>2</sub>-agonist for this  
384 purpose and to warn them that increasing inhaled beta<sub>2</sub>-agonist use is a signal of  
385 deteriorating asthma that requires prompt consultation with a physician.
  - 386 • **SEREVENT DISKUS should not be initiated in patients with significantly worsening or**  
387 **acutely deteriorating asthma, which may be a life-threatening condition.** Serious acute  
388 respiratory events, including fatalities, have been reported both in the United States  
389 and worldwide when SEREVENT has been initiated in this situation. Although it is not  
390 possible from these reports to determine whether SEREVENT contributed to these  
391 adverse events or simply failed to relieve the deteriorating asthma, the use of  
392 SEREVENT DISKUS in this setting is inappropriate.
  - 393 • **SEREVENT DISKUS is not a substitute for inhaled or oral corticosteroids.**  
394 **Corticosteroids should not be stopped or reduced when SEREVENT DISKUS is**  
395 **initiated.**

396 **See PRECAUTIONS: Information for Patients and the Medication Guide accompanying**  
397 **the product.**

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

- 399 1. **SEREVENT DISKUS should not be used as a treatment for acutely deteriorating asthma.**  
400 SEREVENT DISKUS is intended for the maintenance treatment of asthma (see INDICATIONS  
401 AND USAGE) and should not be introduced in acutely deteriorating asthma, which is a  
402 potentially life-threatening condition. There are no data demonstrating that SEREVENT  
403 DISKUS provides greater efficacy than or additional efficacy to inhaled, short-acting  
404 beta<sub>2</sub>-agonists in patients with worsening asthma. Serious acute respiratory events, including  
405 fatalities, have been reported both in the United States and worldwide in patients receiving  
406 SEREVENT. In most cases, these have occurred in patients with severe asthma (e.g., patients  
407 with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical  
408 ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations)  
409 and/or in some patients in whom asthma has been acutely deteriorating (e.g., unresponsive to  
410 usual medications; increasing need for inhaled, short-acting beta<sub>2</sub>-agonists; increasing need for  
411 systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden  
412 or progressive deterioration in pulmonary function). However, they have occurred in a few  
413 patients with less severe asthma as well. It was not possible from these reports to determine  
414 whether SEREVENT contributed to these events.
- 415 2. **SEREVENT DISKUS should not be used to treat acute symptoms.** An inhaled, short-acting  
416 beta<sub>2</sub>-agonist, not SEREVENT DISKUS, should be used to relieve acute asthma or COPD  
417 symptoms. When prescribing SEREVENT DISKUS, the physician must also provide the patient  
418 with an inhaled, short-acting beta<sub>2</sub>-agonist (e.g., albuterol) for treatment of symptoms that occur  
419 acutely, despite regular twice-daily (morning and evening) use of SEREVENT DISKUS.

420 When beginning treatment with SEREVENT DISKUS, patients who have been taking  
421 inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., 4 times a day) should be instructed to  
422 discontinue the regular use of these drugs and use them only for symptomatic relief of acute  
423 asthma or COPD symptoms (see PRECAUTIONS: Information for Patients).

424 3. Increasing use of inhaled, short-acting beta<sub>2</sub>-agonists is a marker of deteriorating asthma or  
425 COPD. The physician and patient should be alert to such changes. The patient's condition may  
426 deteriorate acutely over a period of hours or chronically over several days or longer. If the  
427 patient's inhaled, short-acting beta<sub>2</sub>-agonist becomes less effective, the patient needs more  
428 inhalations than usual, or the patient develops a significant decrease in PEF or lung function,  
429 these may be markers of destabilization of their disease. In this setting, the patient requires  
430 immediate reevaluation with reassessment of the treatment regimen, giving special consideration  
431 to the possible need for corticosteroids. If the patient uses 4 or more inhalations per day of an  
432 inhaled, short-acting beta<sub>2</sub>-agonist for 2 or more consecutive days, or if more than 1 canister  
433 (200 inhalations per canister) of inhaled, short-acting beta<sub>2</sub>-agonist is used in an 8-week period in  
434 conjunction with SEREVENT DISKUS, then the patient should consult the physician for  
435 reevaluation. **Increasing the daily dosage of SEREVENT DISKUS in this situation is not**  
436 **appropriate. SEREVENT DISKUS should not be used more frequently than twice daily**  
437 **(morning and evening) at the recommended dose of 1 inhalation.**

438 4. SEREVENT DISKUS should not be used in conjunction with an inhaled, long-acting  
439 beta<sub>2</sub>-agonist. SEREVENT DISKUS should not be used with other medications containing  
440 long-acting beta<sub>2</sub>-agonists.

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

448 6. The recommended dosage should not be exceeded. As with other inhaled beta<sub>2</sub>-adrenergic  
449 drugs, SEREVENT DISKUS should not be used more often or at higher doses than  
450 recommended. Fatalities have been reported in association with excessive use of inhaled  
451 sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the  
452 recommended dose) have been associated with clinically significant prolongation of the QTc  
453 interval, which has the potential for producing ventricular arrhythmias.

454 7. Paradoxical bronchospasm. As with other inhaled asthma and COPD medications,  
455 SEREVENT DISKUS can produce paradoxical bronchospasm, which may be life threatening. If  
456 paradoxical bronchospasm occurs following dosing with SEREVENT DISKUS, it should be  
457 treated immediately with a short-acting, inhaled bronchodilator; SEREVENT DISKUS should be  
458 discontinued immediately; and alternative therapy should be instituted.

459 8. Immediate hypersensitivity reactions. Immediate hypersensitivity reactions may occur after

460 administration of SEREVENT DISKUS, as demonstrated by cases of urticaria, angioedema,  
461 rash, and bronchospasm.

462 9. Upper airway symptoms. Symptoms of laryngeal spasm, irritation, or swelling, such as stridor  
463 and choking, have been reported in patients receiving SEREVENT DISKUS.

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

473 11. Potential drug interactions. Because of the potential for drug interactions and the potential for  
474 increased risk of cardiovascular adverse events, the concomitant use of SEREVENT DISKUS  
475 with strong CYP 3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin,  
476 indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended  
477 (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Drug Interactions*).

## 478 **PRECAUTIONS**

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

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

491 **Metabolic Effects:** Doses of the related beta<sub>2</sub>-adrenoceptor agonist albuterol, when  
492 administered intravenously, have been reported to aggravate preexisting diabetes mellitus and  
493 ketoacidosis. Beta-adrenergic agonist medications may produce significant hypokalemia in some  
494 patients, possibly through intracellular shunting, which has the potential to produce adverse  
495 cardiovascular effects. The decrease in serum potassium is usually transient, not requiring  
496 supplementation.

497 Clinically significant changes in blood glucose and/or serum potassium were seen rarely  
498 during clinical studies with long-term administration of SEREVENT DISKUS at recommended

499 doses.

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

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

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

- 509 **1. Patients should be informed that salmeterol may increase the risk of asthma-related**  
510 **death.**
- 511 2. SEREVENT DISKUS is not meant to relieve acute asthma or COPD symptoms and extra  
512 doses should not be used for that purpose. Acute symptoms should be treated with an  
513 inhaled, short-acting bronchodilator (the physician should provide the patient with such  
514 medication and instruct the patient in how it should be used).
- 515 3. The physician should be notified immediately if any of the following signs of seriously  
516 worsening asthma or COPD occur:
  - 517 • decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonists;
  - 518 • need for more inhalations than usual of inhaled, short-acting beta<sub>2</sub>-agonists;
  - 519 • significant decrease in PEF or lung function as outlined by the physician;
  - 520 • use of 4 or more inhalations per day of a short-acting beta<sub>2</sub>-agonist for 2 or more days  
521 consecutively;
  - 522 • use of more than 1 canister (200 inhalations per canister) of an inhaled, short-acting  
523 beta<sub>2</sub>-agonist in an 8-week period.
- 524 4. Patients should not stop therapy with SEREVENT DISKUS for asthma or COPD without  
525 physician/provider guidance since symptoms may worsen after discontinuation.
- 526 5. SEREVENT DISKUS should not be used as a substitute for oral or inhaled corticosteroids.  
527 The dosage of these medications should not be changed and they should not be stopped  
528 without consulting the physician, even if the patient feels better after initiating treatment with  
529 SEREVENT DISKUS.
- 530 6. Patients should be cautioned regarding adverse effects associated with beta<sub>2</sub>-agonists, such as  
531 palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 532 7. When patients are prescribed SEREVENT DISKUS, other medications for asthma and  
533 COPD should be used only as directed by the physician.
- 534 8. SEREVENT DISKUS should not be used with a spacer device.
- 535 9. Patients who are pregnant or nursing should contact the physician about the use of  
536 SEREVENT DISKUS.
- 537 10. The action of SEREVENT DISKUS may last up to 12 hours or longer. The recommended  
538 dosage (1 inhalation twice daily, morning and evening) should not be exceeded.

- 539 11. When used for the treatment of EIB, 1 inhalation of SEREVENT DISKUS should be taken  
540 30 minutes before exercise.
- 541 • Additional doses of SEREVENT should not be used for 12 hours.
  - 542 • Patients who are receiving SEREVENT DISKUS twice daily should not use additional  
543 SEREVENT for prevention of EIB.
- 544 12. Effective and safe use of SEREVENT DISKUS includes an understanding of the way that it  
545 should be used:
- 546 • Never exhale into the DISKUS.
  - 547 • Never attempt to take the DISKUS apart.
  - 548 • Always activate and use the DISKUS in a level, horizontal position.
  - 549 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
  - 550 • Always keep the DISKUS in a dry place.
  - 551 • Discard **6 weeks** after removal from the moisture-protective foil overwrap pouch or after  
552 all blisters have been used (when the dose indicator reads “0”), whichever comes first.
- 553 13. For the proper use of SEREVENT DISKUS and to attain maximum benefit, the patient  
554 should read and follow carefully the Instructions for Using SEREVENT DISKUS in the  
555 Medication Guide accompanying the product.
- 556 14. Most patients are able to taste or feel a dose delivered from SEREVENT DISKUS. However,  
557 whether or not patients are able to sense delivery of a dose, they should not exceed the  
558 recommended dose of 1 inhalation twice daily, morning and evening. Patients should contact  
559 a physician or pharmacist if they have questions.

560 **Drug Interactions: Inhibitors of Cytochrome P450 3A4:** In a drug interaction study in 20  
561 healthy subjects, coadministration of salmeterol (50 mcg twice daily) and ketoconazole (400 mg  
562 once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-  
563 fold and C<sub>max</sub> increased 1.4-fold). Three (3) subjects were withdrawn due to beta<sub>2</sub>-agonist side  
564 effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there  
565 was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was  
566 associated with more frequent increases in QTc duration compared with salmeterol and placebo  
567 administration. Due to the potential increased risk of cardiovascular adverse events, the  
568 concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir,  
569 atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir,  
570 telithromycin) is not recommended.

571 **Short-Acting Beta<sub>2</sub>-Agonists:** In two 12-week, repetitive-dose adolescent and adult  
572 clinical trials in patients with asthma (N = 149), the mean daily need for additional beta<sub>2</sub>-agonist  
573 in patients using SEREVENT DISKUS was approximately 1½ inhalations/day. Twenty-six  
574 percent (26%) of the patients in these trials used between 8 and 24 inhalations of short-acting  
575 beta-agonist per day on 1 or more occasions. Nine percent (9%) of the patients in these trials  
576 averaged over 4 inhalations/day over the course of the 12-week trials. No increase in frequency  
577 of cardiovascular events was observed among the 3 patients who averaged 8 to 11  
578 inhalations/day; however, the safety of concomitant use of more than 8 inhalations/day of

579 short-acting beta<sub>2</sub>-agonist with SEREVENT DISKUS has not been established. In 29 patients  
580 who experienced worsening of asthma while receiving SEREVENT DISKUS during these trials,  
581 albuterol therapy administered via either nebulizer or inhalation aerosol (1 dose in most cases)  
582 led to improvement in FEV<sub>1</sub> and no increase in occurrence of cardiovascular adverse events.

583 In 2 clinical trials in patients with COPD, the mean daily need for additional beta<sub>2</sub>-agonist for  
584 patients using SEREVENT DISKUS was approximately 4 inhalations/day. Twenty-four percent  
585 (24%) of the patients using SEREVENT DISKUS in these trials averaged 6 or more inhalations  
586 of albuterol per day over the course of the 24-week trials. No increase in frequency of  
587 cardiovascular events was observed among patients who averaged 6 or more inhalations per day.

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

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

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

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

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

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

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

628 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol  
629 caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at  
630 doses of 0.68 mg/kg and above (approximately 55 times the maximum recommended daily  
631 inhalation dose in adults and approximately 25 times the maximum recommended daily  
632 inhalation dose in children on a mg/m<sup>2</sup> basis). No tumors were seen at 0.21 mg/kg  
633 (approximately 15 times the maximum recommended daily inhalation dose in adults and  
634 approximately 8 times the maximum recommended daily inhalation dose in children on a mg/m<sup>2</sup>  
635 basis). These findings in rodents are similar to those reported previously for other  
636 beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

637 Salmeterol produced no detectable or reproducible increases in microbial and mammalian  
638 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo  
639 in a rat micronucleus test. No effects on fertility were identified in male and female rats treated  
640 with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum  
641 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis).

642 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. No teratogenic effects occurred in  
643 rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily  
644 inhalation dose in adults on a mg/m<sup>2</sup> basis). In pregnant Dutch rabbits administered oral doses of  
645 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in  
646 adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects  
647 characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid  
648 openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the  
649 frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately  
650 20 times the maximum recommended daily inhalation dose in adults based on comparison of the  
651 AUCs).

652 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal  
653 bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the maximum  
654 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Extensive use of other  
655 beta-agonists has provided no evidence that these class effects in animals are relevant to their use  
656 in humans. There are no adequate and well-controlled studies with SEREVENT DISKUS in  
657 pregnant women. SEREVENT DISKUS should be used during pregnancy only if the potential  
658 benefit justifies the potential risk to the fetus.

659 Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice  
660 and rats (approximately 410 and 810 times, respectively, the maximum recommended daily  
661 inhalation dose in adults on a mg/m<sup>2</sup> basis).

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

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

672 **Pediatric Use:** The safety and efficacy of SEREVENT DISKUS has been evaluated in over  
673 2,500 patients aged 4 to 11 years with asthma, 346 of whom were administered SEREVENT  
674 DISKUS for 1 year. Based on available data, no adjustment of dosage of SEREVENT DISKUS  
675 in pediatric patients is warranted for either asthma or EIB (see DOSAGE AND  
676 ADMINISTRATION).

677 In 2 randomized, double-blind, controlled clinical trials of 12 weeks' duration, SEREVENT  
678 DISKUS 50 mcg was administered to 211 pediatric patients with asthma who did and who did  
679 not receive concurrent inhaled corticosteroids. The efficacy of SEREVENT DISKUS was  
680 demonstrated over the 12-week treatment period with respect to PEF and FEV<sub>1</sub>. SEREVENT  
681 DISKUS was effective in demographic subgroups (gender and age) of the population.  
682 SEREVENT DISKUS was effective when coadministered with other inhaled asthma  
683 medications, such as short-acting bronchodilators and inhaled corticosteroids. SEREVENT  
684 DISKUS was well tolerated in the pediatric population, and there were no safety issues identified  
685 specific to the administration of SEREVENT DISKUS to pediatric patients.

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

689 **Geriatric Use:** Of the total number of adolescent and adult patients with asthma who received  
690 SEREVENT DISKUS in chronic dosing clinical trials, 209 were 65 years of age and older. Of  
691 the total number of patients with COPD who received SEREVENT DISKUS in chronic dosing  
692 clinical trials, 167 were 65 years of age or older and 45 were 75 years of age or older. No  
693 apparent differences in the safety of SEREVENT DISKUS were observed when geriatric patients  
694 were compared with younger patients in clinical trials. As with other beta<sub>2</sub>-agonists, however,  
695 special caution should be observed when using SEREVENT DISKUS in geriatric patients who  
696 have concomitant cardiovascular disease that could be adversely affected by this class of drug.  
697 Data from the trials in patients with COPD suggested a greater effect on FEV<sub>1</sub> of SEREVENT  
698 DISKUS in the <65 years age-group, as compared with the ≥65 years age-group. However,

699 based on available data, no adjustment of dosage of SEREVENT DISKUS in geriatric patients is  
700 warranted.

701 **ADVERSE REACTIONS**

702 **Data from a large, 28-week, placebo-controlled US study that compared the safety of**  
703 **salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy**  
704 **showed an increase in asthma-related deaths in patients receiving salmeterol (see**  
705 **WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research***  
706 ***Trial*).**

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

710

711 **Table 4. Adverse Event Incidence in Two 12-Week Adolescent and Adult Clinical Trials in**  
712 **Patients With Asthma**

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

713

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

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

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

723 **Ear, Nose, and Throat:** Sinus headache.  
 724 **Gastrointestinal:** Nausea.  
 725 **Mouth and Teeth:** Oral mucosal abnormality.  
 726 **Musculoskeletal:** Pain in joint.  
 727 **Neurological:** Sleep disturbance, paresthesia.  
 728 **Skin:** Contact dermatitis, eczema.  
 729 **Miscellaneous:** Localized aches and pains, pyrexia of unknown origin.

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

735  
 736 **Table 5. Adverse Event Incidence in Two 12-Week Pediatric Clinical Trials in Patients**  
 737 **With Asthma**

Adverse Event	Percent of Patients		
	Placebo (N = 215)	SEREVENT DISKUS 50 mcg Twice Daily (N = 211)	Albuterol Inhalation Powder 200 mcg 4 Times Daily (N = 115)
Ear, nose, and throat			
Ear signs and symptoms	3	4	9
Pharyngitis	3	6	3
Neurological			
Headache	14	17	20
Respiratory			
Asthma	2	4	<1
Skin			
Skin rashes	3	4	2
Urticaria	0	3	2

738  
 739 The following events were reported at an incidence of 1% to 2% (3 to 4 patients) in the  
 740 salmeterol group and with a higher incidence than in the albuterol and placebo groups:  
 741 gastrointestinal signs and symptoms, lower respiratory signs and symptoms, photodermatitis, and  
 742 arthralgia and articular rheumatism.

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

746 **Chronic Obstructive Pulmonary Disease:** Two multicenter, 24-week, controlled studies

747 have evaluated twice-daily doses of SEREVENT DISKUS in patients with COPD. For  
 748 presentation (Table 6), the placebo data from a third trial, identical in design, patient entrance  
 749 criteria, and overall conduct but comparing fluticasone propionate with placebo, were integrated  
 750 with the placebo data from these 2 studies (total N = 341 for salmeterol and 576 for placebo).

751

752 **Table 6. Adverse Events With ≥3% Incidence in US Controlled Clinical Trials With**  
 753 **SEREVENT DISKUS in Patients With Chronic Obstructive Pulmonary Disease\***

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

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

758

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

761 **Endocrine and Metabolic:** Hyperglycemia.

762 **Eye:** Keratitis and conjunctivitis.

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

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

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

768 **Neurology:** Migraines.

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

770 **Psychiatry:** Anxiety.

771 **Skin:** Skin rashes.

772 Adverse reactions to salmeterol are similar in nature to those seen with other selective  
773 beta<sub>2</sub>-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions,  
774 including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor;  
775 nervousness; and paradoxical bronchospasm (see WARNINGS).

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

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

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

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

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

## 793 **OVERDOSAGE**

794 The expected signs and symptoms with overdosage of SEREVENT DISKUS are those of  
795 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and  
796 symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or  
797 hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache,  
798 tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.  
799 Overdosage with SEREVENT DISKUS may be expected to result in exaggeration of the  
800 pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia

801 and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with SEREVENT  
802 DISKUS can lead to clinically significant prolongation of the QTc interval, which can produce  
803 ventricular arrhythmias. Other signs of overdosage may include hypokalemia and  
804 hyperglycemia.

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

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

812 No deaths were seen in rats at an inhalation dose of 2.9 mg/kg (approximately 240 times the  
813 maximum recommended daily inhalation dose in adults and approximately 110 times the  
814 maximum recommended daily inhalation dose in children on a mg/m<sup>2</sup> basis) and in dogs at an  
815 inhalation dose of 0.7 mg/kg (approximately 190 times the maximum recommended daily  
816 inhalation dose in adults and approximately 90 times the maximum recommended daily  
817 inhalation dose in children on a mg/m<sup>2</sup> basis). By the oral route, no deaths occurred in mice at  
818 150 mg/kg (approximately 6,100 times the maximum recommended daily inhalation dose in  
819 adults and approximately 2,900 times the maximum recommended daily inhalation dose in  
820 children on a mg/m<sup>2</sup> basis) and in rats at 1,000 mg/kg (approximately 81,000 times the maximum  
821 recommended daily inhalation dose in adults and approximately 38,000 times the maximum  
822 recommended daily inhalation dose in children on a mg/m<sup>2</sup> basis).

## 823 **DOSAGE AND ADMINISTRATION**

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

828 **Asthma:** Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, the active ingredient in  
829 SEREVENT DISKUS, may increase the risk of asthma-related death (see WARNINGS).

830 Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as  
831 additional therapy for patients not adequately controlled on other asthma-controller medications  
832 (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants  
833 initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. It is not  
834 indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting  
835 beta<sub>2</sub>-agonists or for patients whose asthma can be successfully managed by inhaled  
836 corticosteroids or other controller medications along with occasional use of inhaled, short-acting  
837 beta<sub>2</sub>-agonists.

838 For maintenance of bronchodilatation and prevention of symptoms of asthma, including the  
839 symptoms of nocturnal asthma, the usual dosage for adults and children 4 years of age and older

840 is 1 inhalation (50 mcg) twice daily (morning and evening, approximately 12 hours apart). If a  
841 previously effective dosage regimen fails to provide the usual response, medical advice should  
842 be sought immediately as this is often a sign of destabilization of asthma. Under these  
843 circumstances, the therapeutic regimen should be reevaluated. If symptoms arise in the period  
844 between doses, an inhaled, short-acting beta<sub>2</sub>-agonist should be taken for immediate relief.

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

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

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

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

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

## 863 HOW SUPPLIED

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

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

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

875  
876



877

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880  
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## 886 MEDICATION GUIDE

### 887 888 SEREVENT<sup>®</sup> [*ser' uh-vent*] DISKUS<sup>®</sup> 889 (salmeterol xinafoate inhalation powder) 890

891 Read the Medication Guide that comes with SEREVENT DISKUS before you start using it and  
892 each time you get a refill. There may be new information. This Medication Guide does not take  
893 the place of talking to your healthcare provider about your medical condition or treatment.  
894

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

896 SEREVENT DISKUS is a medicine called a long-acting beta<sub>2</sub>-agonist or LABA. LABA  
897 medicines are used in patients with asthma, exercise-induced bronchospasm (EIB), and chronic  
898 obstructive pulmonary disease (COPD). LABA medicines help the muscles around the airways  
899 in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These  
900 symptoms can happen when the muscles around the airways tighten. This makes it hard to  
901 breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right  
902 away.  
903

- 904 • **In patients with asthma, LABA medicines, such as SEREVENT DISKUS, may increase**  
905 **the chance of death from asthma problems.** In a large asthma study, more patients who  
906 used salmeterol (SEREVENT) died from asthma problems compared with patients who did  
907 not use salmeterol (SEREVENT). Talk with your healthcare provider about this risk and the  
908 benefits of treating your asthma with SEREVENT DISKUS.  
909
- 910 • **SEREVENT DISKUS does not relieve sudden symptoms. Always have a short-acting**  
911 **beta<sub>2</sub>-agonist medicine with you to treat sudden symptoms. If you do not have an**  
912 **inhaled, short-acting bronchodilator, contact your healthcare provider to have one**  
913 **prescribed for you.**  
914
- 915 • **Do not stop using SEREVENT DISKUS unless told to do so by your healthcare**  
916 **provider because your symptoms might get worse.**

- 917
- 918 • **SEREVENT DISKUS:**
- 919 • **should not be the only medicine prescribed for your asthma**
- 920 • **should be used only if your healthcare provider decides that another**
- 921 **asthma-controller medicine alone does not control your asthma or that you need 2**
- 922 **asthma-controller medicines**
- 923
- 924 • **Call your healthcare provider if breathing problems worsen over time while using**
- 925 **SEREVENT DISKUS. You may need different treatment.**
- 926
- 927 • **Get emergency medical care if:**
- 928 • **breathing problems worsen quickly, and**
- 929 • **you use your short-acting beta<sub>2</sub>-agonist medicine, but it does not relieve your**
- 930 **breathing problems**
- 931

932 **What is SEREVENT DISKUS?**

933 SEREVENT DISKUS is a long-acting beta<sub>2</sub>-agonist medicine (LABA). SEREVENT DISKUS is

934 used for asthma, exercise-induced bronchospasm (EIB), and chronic obstructive pulmonary

935 disease (COPD) as follows:

936

937 **Asthma**

938 SEREVENT DISKUS is used long term, twice a day, to control symptoms of asthma, and

939 prevent symptoms such as wheezing in adults and children ages 4 and older.

940

941 **Because LABA medicines, such as SEREVENT DISKUS, may increase the chance of death**

942 **from asthma problems, SEREVENT DISKUS is not for adults and children with asthma**

943 **who:**

- 944 • are well controlled with another asthma-controller medicine, such as a low to medium
- 945 dose of an inhaled corticosteroid medicine
- 946 • only need short-acting beta<sub>2</sub>-agonist medicines once in awhile
- 947

948 **Exercise-Induced Bronchospasm (EIB)**

949 SEREVENT DISKUS is used for the prevention of wheezing caused by exercise in adults and

950 children 4 years of age and older.

951

952 **Chronic Obstructive Pulmonary Disease (COPD)**

953 SEREVENT DISKUS is used long term, twice a day in controlling symptoms of COPD and

954 preventing wheezing in adults with COPD.

955

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

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

- 958 • **have heart problems**
- 959 • **have high blood pressure**
- 960 • **have seizures**
- 961 • **have thyroid problems**
- 962 • **have diabetes**
- 963 • **have liver problems**
- 964 • **are pregnant or planning to become pregnant.** It is not known if SEREVENT DISKUS  
965 may harm your unborn baby.
- 966 • **are breastfeeding.** It is not known if SEREVENT DISKUS passes into your milk and if it  
967 can harm your baby.
- 968 • **are allergic to SEREVENT DISKUS, any other medicines, or food products**

969

970 Tell your healthcare provider about all the medicines you take including prescription and  
971 non-prescription medicines, vitamins, and herbal supplements. SEREVENT DISKUS and certain  
972 other medicines may interact with each other. This may cause serious side effects.

973

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

976

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

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

982

983 • Children should use SEREVENT DISKUS with an adult's help, as instructed by the child's  
984 healthcare provider.

985

986 • Use SEREVENT DISKUS exactly as prescribed. **Do not use SEREVENT DISKUS more**  
987 **often than prescribed.**

988

989 • For asthma and COPD, the usual dose is 1 inhalation twice a day (morning and evening). The  
990 2 doses should be about 12 hours apart.

991

992 • For preventing exercise-induced bronchospasm, take 1 inhalation at least 30 minutes before  
993 exercise. Do not use SEREVENT DISKUS more often than every 12 hours. Do not use extra  
994 SEREVENT DISKUS before exercise if you already use it twice a day.

995

996 • If you miss a dose of SEREVENT DISKUS, just skip that dose. Take your next dose at your

- 997 usual time. Do not take 2 doses at one time.
- 998
- 999 • Do not use a spacer device with SEREVENT DISKUS.
- 1000
- 1001 • Do not breathe into SEREVENT DISKUS.
- 1002
- 1003 • **While you are using SEREVENT DISKUS twice a day, do not use other medicines that**
- 1004 **contain a long-acting beta<sub>2</sub>-agonist or LABA for any reason. Other LABA medicines**
- 1005 **include ADVAIR DISKUS<sup>®</sup> (fluticasone propionate and salmeterol inhalation powder),**
- 1006 **ADVAIR<sup>®</sup> HFA (fluticasone propionate and salmeterol) Inhalation Aerosol,**
- 1007 **FORADIL<sup>®</sup> AEROLIZER<sup>®</sup> (formoterol fumarate inhalation powder), SYMBICORT<sup>®</sup>**
- 1008 **(budesonide and formoterol fumarate dihydrate) Inhalation Aerosol,**
- 1009 **PERFOROMIST<sup>™</sup> (formoterol fumarate) Inhalation Solution, and BROVANA<sup>™</sup>**
- 1010 **(arformoterol tartrate) Inhalation Solution.**
- 1011
- 1012 • Do not change or stop any of your medicines used to control or treat your breathing
- 1013 problems. Your healthcare provider will adjust your medicines as needed.
- 1014
- 1015 • Make sure you always have a short-acting beta<sub>2</sub>-agonist medicine with you. Use your
- 1016 short-acting beta<sub>2</sub>-agonist medicine if you have breathing problems between doses of
- 1017 SEREVENT DISKUS.
- 1018
- 1019 • **Call your healthcare provider or get medical care right away if:**
- 1020 • your breathing problems worsen with SEREVENT DISKUS
- 1021 • you need to use your short-acting beta<sub>2</sub>-agonist medicine more often than usual
- 1022 • your short-acting beta<sub>2</sub>-agonist medicine does not work as well for you at relieving
- 1023 symptoms
- 1024 • you need to use 4 or more inhalations of your short-acting beta<sub>2</sub>-agonist medicine for 2 or
- 1025 more days in a row
- 1026 • you use 1 whole canister of your short-acting beta<sub>2</sub>-agonist medicine in 8 weeks' time
- 1027 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers
- 1028 that are right for you.
- 1029 • you have asthma and your symptoms do not improve after using SEREVENT DISKUS
- 1030 regularly for 1 week.
- 1031

1032 **What are the possible side effects with SEREVENT DISKUS?**

- 1033 • **In patients with asthma, LABA medicines, such as SEREVENT, may increase the**
- 1034 **chance of death from asthma problems. See “What is the most important information I**
- 1035 **should know about SEREVENT DISKUS?”**
- 1036

1037 **Other possible side effects with SEREVENT DISKUS include:**

- 1038 • **serious allergic reactions including rash; hives; swelling of the face, mouth, and**
- 1039 **tongue; and breathing problems.** Call your healthcare provider or get emergency
- 1040 medical care if you get any symptoms of a serious allergic reaction.
- 1041 • **increased blood pressure**
- 1042 • **a fast and irregular heartbeat**
- 1043 • **chest pain**
- 1044 • **headache**
- 1045 • **tremor**
- 1046 • **nervousness**
- 1047 • **throat irritation**

1048

1049 Tell your healthcare provider about any side effect that bothers you or that does not go away.

1050

1051 These are not all the side effects with SEREVENT DISKUS. Ask your healthcare provider or

1052 pharmacist for more information.

1053

1054 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-

1055 800-FDA-1088.

1056

1057 **How do I store SEREVENT DISKUS?**

- 1058 • Store SEREVENT DISKUS at room temperature between 68° to 77° F (20° to 25° C).
- 1059 Keep in a dry place away from heat and sunlight.
- 1060 • Safely discard SEREVENT DISKUS 6 weeks after you remove it from the foil pouch, or
- 1061 after the dose indicator reads “0”, whichever comes first.
- 1062 • **Keep SEREVENT DISKUS and all medicines out of the reach of children.**

1063

1064 **General Information about SEREVENT DISKUS**

1065 Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not

1066 use SEREVENT DISKUS for a condition for which it was not prescribed. Do not give your

1067 SEREVENT DISKUS to other people, even if they have the same condition. It may harm them.

1068

1069 This Medication Guide summarizes the most important information about SEREVENT

1070 DISKUS. If you would like more information, talk with your healthcare provider or pharmacist.

1071 You can ask your healthcare provider or pharmacist for information about SEREVENT DISKUS

1072 that was written for healthcare professionals. You can also contact the company that makes

1073 SEREVENT DISKUS (toll free) at 1-888-825-5249 or at [www.serevent.com](http://www.serevent.com).

1074

1075

#### **Instructions for Using SEREVENT DISKUS**

1076 Follow the instructions below for using your SEREVENT DISKUS. **You will breathe in**

1077 (inhale) the medicine from the DISKUS. If you have any questions, ask your healthcare  
1078 provider or pharmacist.



1079  
1080 Take the SEREVENT DISKUS out of the box and foil pouch. Write the “Pouch opened” and  
1081 “Use by” dates on the label on top of the DISKUS. The “Use by” date is 6 weeks from date of  
1082 opening the pouch.

- 1083
- 1084 • The DISKUS will be in the closed position when the pouch is opened.
- 1085
- 1086 • The **dose indicator** on the top of the DISKUS tells you how many doses are left. The  
1087 dose indicator number will decrease each time you use the DISKUS. After you have used  
1088 55 doses from the DISKUS, the numbers 5 to 0 will appear in **red** to warn you that there  
1089 are only a few doses left (*see Figure 1*).

1090



1091

1092

1093

1094 Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.

1095

Figure 1

1096  
1097  
1098  
1099  
1100

**1. OPEN**

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



1101  
1102  
1103  
1104

Figure 2

**2. CLICK**

1105  
1106  
1107  
1108

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



1109  
1110  
1111  
1112  
1113  
1114

Figure 3

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

- 1115 • **Do not close the DISKUS.**
- 1116 • **Do not tilt the DISKUS.**
- 1117 • **Do not play with the lever.**
- 1118 • **Do not move the lever more than once.**

1120 **3. INHALE**

1121 Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the  
1122 DISKUS level and away from your mouth (*see Figure 4*). **Remember, never breathe**  
1123 **out into the DISKUS mouthpiece.**



1125 Figure 4

1126 Put the mouthpiece to your lips (*see Figure 5*). Breathe in quickly and deeply through the  
1127 DISKUS. Do not breathe in through your nose.



1128 Figure 5

1131 Remove the DISKUS from your mouth. Hold your breath for about 10 seconds, or for as  
1132  
1133  
1134

1135 long as is comfortable. Breathe out slowly.

1136

1137 The DISKUS delivers your dose of medicine as a very fine powder. Most patients can  
1138 taste or feel the powder. Do not use another dose from the DISKUS if you do not feel or  
1139 taste the medicine.

1140

1141 **4. Close the DISKUS when you are finished taking a dose so that the DISKUS will be**  
1142 **ready for you to take your next dose.** Put your thumb on the thumbgrip and slide the  
1143 thumbgrip back towards you as far as it will go (*see Figure 6*). The DISKUS will click  
1144 shut. The lever will automatically return to its original position. The DISKUS is now  
1145 ready for you to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to  
1146 4.)

1147



1148

1149

Figure 6

1150

1151 **Remember:**

- 1152 • Never breathe into the DISKUS.
- 1153 • Never take the DISKUS apart.
- 1154 • Always ready and use the DISKUS in a level, flat position.
- 1155 • Do not use the DISKUS with a spacer device.
- 1156 • Never wash the mouthpiece or any part of the DISKUS. **Keep it dry.**
- 1157 • Always keep the DISKUS in a dry place.
- 1158 • Never take an extra dose, even if you did not taste or feel the medicine.

1159

1160 **Rx only**

1161

1162



1163  
1164 GlaxoSmithKline  
1165 Research Triangle Park, NC 27709

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1175  
1176 Month Year

1177  
1178 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**