

1 **PRESCRIBING INFORMATION**

2 **ADVAIR[®] HFA 45/21**

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

4 **Inhalation Aerosol**

5
6 **ADVAIR[®] HFA 115/21**

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

8 **Inhalation Aerosol**

9
10 **ADVAIR[®] 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**

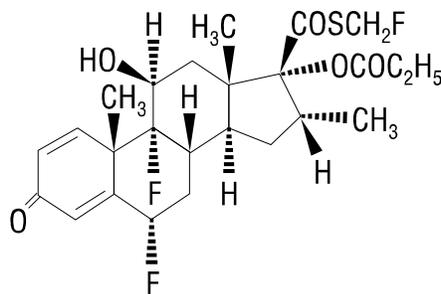
17 **WARNING**

18 Long-acting beta₂-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[®] 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 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-oxoandrosta-
34 1,4-diene-17 β -carbothioate, 17-propionate and the following chemical structure:
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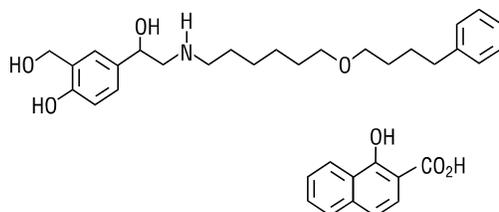


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38 Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical
39 formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide
40 and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

41 The other active component of ADVAIR HFA is salmeterol xinafoate, a beta₂-adrenergic
42 bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt
43 of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy- α^1 -[[[6-(4-
44 phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-
45 naphthalenecarboxylate, and it has the following chemical structure:

46



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

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

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

64 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 releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before
69 each spray.

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 beta₂-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 beta₂-adrenergic agonist. In vitro studies
90 and in vivo pharmacologic studies demonstrate that salmeterol is selective for
91 beta₂-adrenoceptors compared with isoproterenol, which has approximately equal agonist
92 activity on beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least 50 times
93 more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the
94 predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the
95 predominant receptors in the heart, there are also beta₂-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 beta₂-agonists may have cardiac effects.

99 The pharmacologic effects of beta₂-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 D₂, 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_{max}) 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 beta₂-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[®] 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 with 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 with
151 ADVAIR 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 β -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 dosages (42 mcg of salmeterol inhalation
227 aerosol twice daily). Following chronic administration of an inhaled dosage of 42 mcg twice
228 daily, salmeterol was detected in plasma within 5 to 10 minutes in 6 patients with asthma;
229 plasma 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 α -hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4).
239 Ketoconazole, a strong inhibitor of CYP3A4, essentially completely inhibited the formation of
240 α -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 13 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; $p = 0.12$), a 3.6-beat/min increase in heart rate (95% CI: 0.19, 7.03;
269 $p < 0.04$), a 5.8-msec increase in QTc interval (95% CI: -6.14, 17.77; $p = 0.34$), and no change in
270 plasma potassium.

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

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

298 A 4-way crossover study in 13 patients with asthma compared pharmacodynamics at steady
299 state following 4 weeks of twice-daily treatment with 2 inhalations of ADVAIR HFA 115/21,
300 1 inhalation of ADVAIR DISKUS 250/50 mcg, 2 inhalations of fluticasone propionate HFA

301 inhalation aerosol 110 mcg, and placebo. No significant differences in serum cortisol AUC were
302 observed between active treatments and placebo. Mean 12-hour serum cortisol AUC ratios
303 comparing active treatment with placebo ranged from 0.9 to 1.2. No statistically or clinically
304 significant increases in heart rate or QTc interval were observed for any active treatment
305 compared with placebo.

306 In a 12-week study (see CLINICAL TRIALS: Studies Comparing ADVAIR HFA With
307 Fluticasone Propionate Alone or Salmeterol Alone: *Study 3*) in patients with asthma,
308 ADVAIR HFA 115/21 was compared with the individual components, fluticasone propionate
309 CFC inhalation aerosol 110 mcg and salmeterol CFC inhalation aerosol 21 mcg, and placebo. All
310 treatments were administered as 2 inhalations twice daily. After 12 weeks of treatment with these
311 therapeutic doses, the geometric mean ratio of urinary cortisol excretion compared with baseline
312 was 0.9 for ADVAIR HFA and fluticasone propionate and 1.0 for placebo and salmeterol. In
313 addition, the ability to increase cortisol production in response to stress, as assessed by
314 30-minute cosyntropin stimulation in 23 to 32 patients per treatment group, remained intact for
315 the majority of patients and was similar across treatments. Three patients who received
316 ADVAIR HFA 115/21 had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing,
317 compared with 1 patient who received placebo, 2 patients who received fluticasone propionate
318 110 mcg, and 1 patient who received salmeterol.

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

325 **Fluticasone Propionate:** In clinical trials with fluticasone propionate inhalation powder
326 using dosages up to and including 250 mcg twice daily, occasional abnormal short cosyntropin
327 tests (peak serum cortisol <18 mcg/dL) were noted both in patients receiving fluticasone
328 propionate and in patients receiving placebo. The incidence of abnormal tests at 500 mcg twice
329 daily was greater than placebo. In a 2-year study carried out in 64 patients with mild, persistent
330 asthma (mean FEV₁ 91% of predicted) randomized to fluticasone propionate 500 mcg twice
331 daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6-hour
332 cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of
333 <35 mcg/dL, 1 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year;
334 repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone
335 propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal
336 response at 1 or 2 years.

337 **Salmeterol Xinafoate:** Inhaled salmeterol, like other beta-adrenergic agonist drugs, can
338 produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium
339 in some patients (see PRECAUTIONS). The cardiovascular effects (heart rate, blood pressure)

340 associated with salmeterol occur with similar frequency, and are of similar type and severity, as
341 those noted following albuterol administration.

342 The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol were
343 studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg resulted in
344 heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by
345 inhalation aerosol (4 to 10 beats/min). In 2 double-blind asthma studies, patients receiving either
346 42 mcg of salmeterol inhalation aerosol twice daily (n = 81) or 180 mcg of albuterol inhalation
347 aerosol 4 times daily (n = 80) underwent continuous electrocardiographic monitoring during four
348 24-hour periods; no clinically significant dysrhythmias were noted.

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

353 **CLINICAL TRIALS**

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

361 **Studies Comparing ADVAIR HFA With Fluticasone Propionate Alone or**
362 **Salmeterol Alone:** Four (4) double-blind, parallel-group clinical trials were conducted with
363 ADVAIR HFA in 1,517 adolescent and adult patients (≥ 12 years, mean baseline forced
364 expiratory volume in 1 second [FEV₁] 65% to 75% of predicted normal) with asthma that was
365 not optimally controlled on their current therapy. All metered-dose inhaler treatments were
366 inhalation aerosols given as 2 inhalations twice daily, and other maintenance therapies were
367 discontinued.

368 **Study 1: Clinical Trial With ADVAIR HFA 45/21 Inhalation Aerosol:** This
369 placebo-controlled, 12-week, US study compared ADVAIR HFA 45/21 with fluticasone
370 propionate CFC inhalation aerosol 44 mcg or salmeterol CFC inhalation aerosol 21 mcg, each
371 given as 2 inhalations twice daily. The primary efficacy endpoints were predose FEV₁ and
372 withdrawals due to worsening asthma. This study was stratified according to baseline asthma
373 therapy: patients using beta-agonists (albuterol alone [n = 142], salmeterol [n = 84], or inhaled
374 corticosteroids [n = 134] [daily doses of beclomethasone dipropionate 252 to 336 mcg;
375 budesonide 400 to 600 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol
376 176 mcg; fluticasone propionate inhalation powder 200 mcg; or triamcinolone acetonide 600 to
377 800 mcg]). Baseline FEV₁ measurements were similar across treatments: ADVAIR HFA 45/21,
378 2.29 L; fluticasone propionate 44 mcg, 2.20 L; salmeterol, 2.33 L; and placebo, 2.27 L.

379 Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were
 380 utilized for this placebo-controlled study. Worsening asthma was defined as a clinically
 381 important decrease in FEV₁ or peak expiratory flow (PEF), increase in use of VENTOLIN[®]
 382 (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency
 383 intervention or hospitalization due to asthma, or requirement for asthma medication not allowed
 384 by the protocol. As shown in Table 1, statistically significantly fewer patients receiving
 385 ADVAIR HFA 45/21 were withdrawn due to worsening asthma compared with salmeterol and
 386 placebo. Fewer patients receiving ADVAIR HFA 45/21 were withdrawn due to worsening
 387 asthma compared with fluticasone propionate 44 mcg; however, the difference was not
 388 statistically significant.

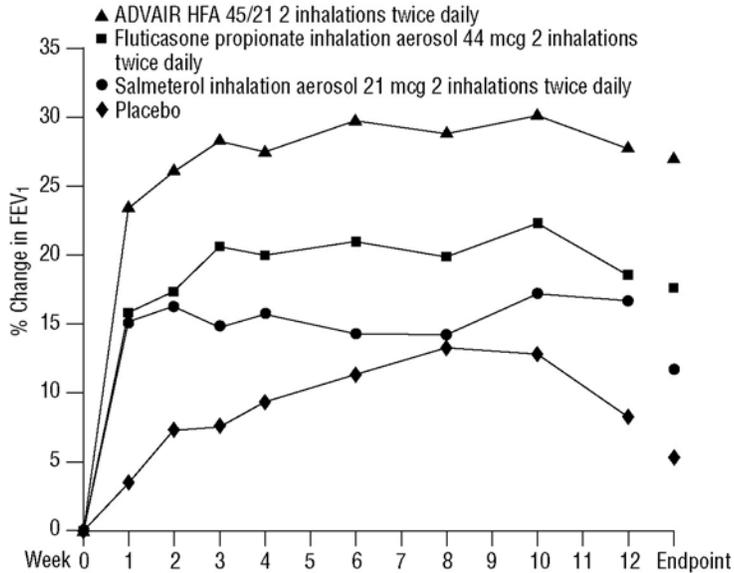
389
 390 **Table 1. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously**
 391 **Treated With Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids**
 392 **(Study 1)**

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%

393
 394 The FEV₁ results are displayed in Figure 1. Because this trial used predetermined criteria for
 395 worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV₁
 396 results at Endpoint (last available FEV₁ result) are also provided. Patients receiving ADVAIR
 397 HFA 45/21 had significantly greater improvements in FEV₁ (0.58 L, 27%) compared with
 398 fluticasone propionate 44 mcg (0.36 L, 18%), salmeterol (0.25 L, 12%), and placebo (0.14 L,
 399 5%). These improvements in FEV₁ with ADVAIR HFA 45/21 were achieved regardless of
 400 baseline asthma therapy (albuterol alone, salmeterol, or inhaled corticosteroids).

401

402 **Figure 1. Mean Percent Change From Baseline in FEV₁ in Patients**
 403 **Previously Treated With Either Beta₂-Agonists (Albuterol or**
 404 **Salmeterol) or Inhaled Corticosteroids (Study 1)**
 405



	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

406
 407

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

411

412 **Table 2. Secondary Efficacy Variable Results for Patients Previously Treated With**
 413 **Beta₂-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

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

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

422 **Study 2: Clinical Trial With ADVAIR HFA 45/21 Inhalation Aerosol:** This
 423 active-controlled, 12-week, US study compared ADVAIR HFA 45/21 with fluticasone
 424 propionate CFC inhalation aerosol 44 mcg and salmeterol CFC inhalation aerosol 21 mcg, each
 425 given as 2 inhalations twice daily, in 283 patients using as-needed albuterol alone. The primary
 426 efficacy endpoint was predose FEV₁. Baseline FEV₁ measurements were similar across
 427 treatments: ADVAIR HFA 45/21, 2.37 L; fluticasone propionate 44 mcg, 2.31 L; and salmeterol,
 428 2.34 L.

429 Efficacy results in this study were similar to those observed in Study 1. Patients receiving
430 ADVAIR HFA 45/21 had significantly greater improvements in FEV₁ (0.69 L, 33%) compared
431 with fluticasone propionate 44 mcg (0.51 L, 25%) and salmeterol (0.47 L, 22%).

432 **Study 3: Clinical Trial With ADVAIR HFA 115/21 Inhalation Aerosol:** This
433 placebo-controlled, 12-week, US study compared ADVAIR HFA 115/21 with fluticasone
434 propionate CFC inhalation aerosol 110 mcg or salmeterol CFC inhalation aerosol 21 mcg, each
435 given as 2 inhalations twice daily, in 365 patients using inhaled corticosteroids (daily doses of
436 beclomethasone dipropionate 378 to 840 mcg; budesonide 800 to 1,200 mcg; flunisolide 1,250 to
437 2,000 mcg; fluticasone propionate inhalation aerosol 440 to 660 mcg; fluticasone propionate
438 inhalation powder 400 to 600 mcg; or triamcinolone acetonide 900 to 1,600 mcg). The primary
439 efficacy endpoints were predose FEV₁ and withdrawals due to worsening asthma. Baseline FEV₁
440 measurements were similar across treatments: ADVAIR HFA 115/21, 2.23 L; fluticasone
441 propionate 110 mcg, 2.18 L; salmeterol, 2.22 L; and placebo, 2.17 L.

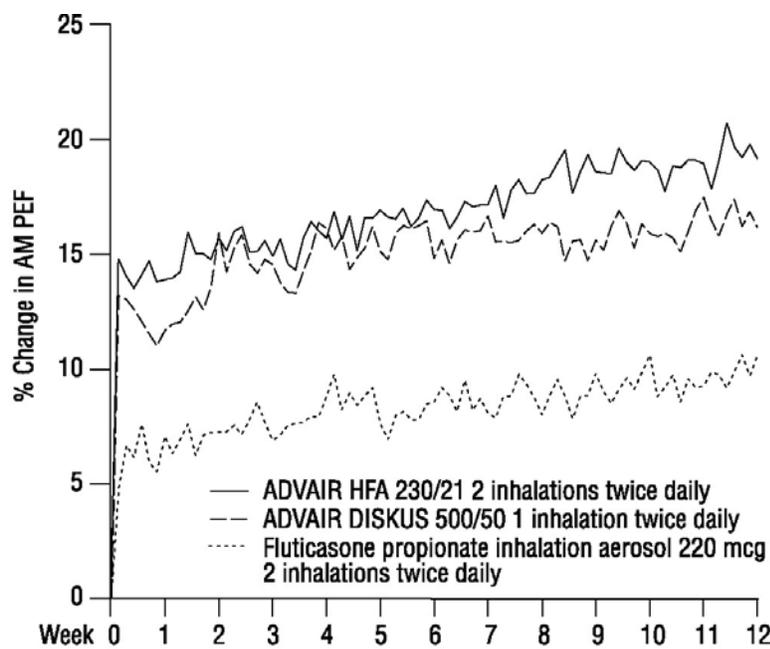
442 Efficacy results in this study were similar to those observed in Studies 1 and 2. Patients
443 receiving ADVAIR HFA 115/21 had significantly greater improvements in FEV₁ (0.41 L, 20%)
444 compared with fluticasone propionate 110 mcg (0.19 L, 9%), salmeterol (0.15 L, 8%), and
445 placebo (-0.12 L, -6%). Significantly fewer patients receiving ADVAIR HFA 115/21 were
446 withdrawn from this study for worsening asthma (7%) compared with salmeterol (24%) and
447 placebo (54%). Fewer patients receiving ADVAIR HFA 115/21 were withdrawn due to
448 worsening asthma (7%) compared with fluticasone propionate 110 mcg (11%); however, the
449 difference was not statistically significant.

450 **Study 4: Clinical Trial With ADVAIR HFA 230/21 Inhalation Aerosol:** This
451 active-controlled, 12-week, non-US study compared ADVAIR HFA 230/21 with fluticasone
452 propionate CFC inhalation aerosol 220 mcg, each given as 2 inhalations twice daily, and with
453 ADVAIR DISKUS 500/50 given as 1 inhalation twice daily in 509 patients using inhaled
454 corticosteroids (daily doses of beclomethasone dipropionate CFC inhalation aerosol 1,500 to
455 2,000 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; fluticasone
456 propionate inhalation aerosol 660 to 880 mcg; or fluticasone propionate inhalation powder 750 to
457 1,000 mcg). The primary efficacy endpoint was morning PEF.

458 Baseline morning PEF measurements were similar across treatments: ADVAIR HFA 230/21,
459 327 L/min; ADVAIR DISKUS 500/50, 341 L/min; and fluticasone propionate 220 mcg,
460 345 L/min. As shown in Figure 2, morning PEF improved significantly with ADVAIR HFA
461 230/21 compared with fluticasone propionate 220 mcg over the 12-week treatment period.
462 Improvements in morning PEF observed with ADVAIR HFA 230/21 were similar to
463 improvements observed with ADVAIR DISKUS 500/50.

464

465 **Figure 2. Mean Percent Change From Baseline in Morning Peak**
 466 **Expiratory Flow in Patients Previously Treated With Inhaled**
 467 **Corticosteroids (Study 4)**
 468



	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

469
470

471 **One-Year Safety Study: Clinical Trial With ADVAIR HFA 45/21, 115/21, and 230/21**

472 **Inhalation Aerosol:** This 1-year, open-label, non-US study evaluated the safety of ADVAIR
 473 HFA 45/21, 115/21, and 230/21 given as 2 inhalations twice daily in 325 patients. This study
 474 was stratified into 3 groups according to baseline asthma therapy: patients using short-acting
 475 beta₂-agonists alone (n = 42), salmeterol (n = 91), or inhaled corticosteroids (n = 277). Patients
 476 treated with short-acting beta₂-agonists alone, salmeterol, or low doses of inhaled corticosteroids
 477 with or without concurrent salmeterol received ADVAIR HFA 45/21. Patients treated with
 478 moderate doses of inhaled corticosteroids with or without concurrent salmeterol received
 479 ADVAIR HFA 115/21. Patients treated with high doses of inhaled corticosteroids with or
 480 without concurrent salmeterol received ADVAIR HFA 230/21. Baseline FEV₁ measurements
 481 ranged from 2.3 to 2.6 L.

482 Improvements in FEV₁ (0.17 to 0.35 L at 4 weeks) were seen across all 3 treatments and were
 483 sustained throughout the 52-week treatment period. Few patients (3%) were withdrawn due to
 484 worsening asthma over 1 year.

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

487 US trials and 1 active-controlled US trial. Following the first dose, the median time to onset of
488 clinically significant bronchodilatation ($\geq 15\%$ improvement in FEV₁) in most patients was seen
489 within 30 to 60 minutes. Maximum improvement in FEV₁ occurred within 4 hours, and clinically
490 significant improvement was maintained for 12 hours (see Figure 3).

491 Following the initial dose, predose FEV₁ relative to day 1 baseline improved markedly over
492 the first week of treatment and continued to improve over the 12 weeks of treatment in all
493 3 studies.

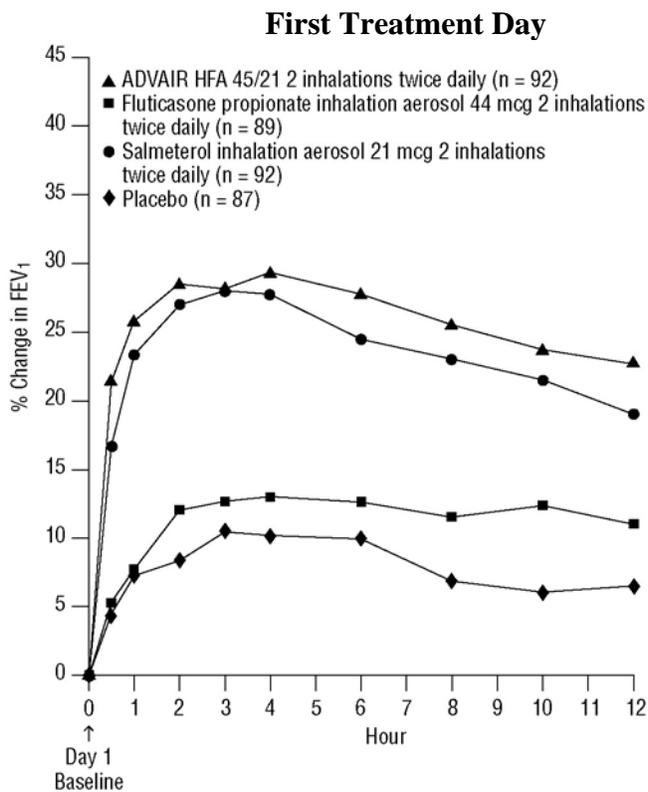
494 No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR HFA
495 45/21 (Figures 3 and 4) or ADVAIR HFA 230/21 as assessed by FEV₁ following 12 weeks of
496 therapy.

497

498 **Figure 3. Percent Change in Serial 12-Hour FEV₁ in**
499 **Patients Previously Using Either Beta₂-Agonists (Albuterol**
500 **or Salmeterol) or Inhaled Corticosteroids (Study 1)**

501

502

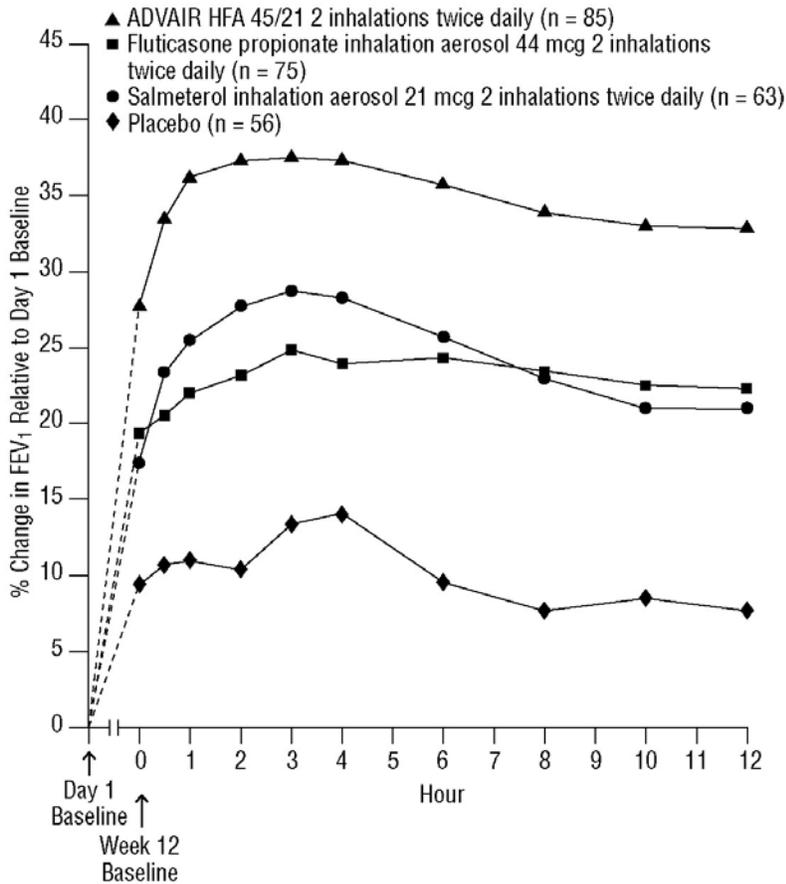


503

504

505 **Figure 4. Percent Change in Serial 12-Hour FEV₁ in**
 506 **Patients Previously Using Either Beta₂-Agonists (Albuterol**
 507 **or Salmeterol) or Inhaled Corticosteroids (Study 1)**

508
 509 **Last Treatment Day (Week 12)**
 510



511
 512

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

516 **INDICATIONS AND USAGE**

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

519 Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in
 520 ADVAIR HFA, may increase the risk of asthma-related death (see WARNINGS). Therefore,
 521 when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients
 522 not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose
 523 inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2

524 maintenance therapies. ADVAIR HFA is not indicated in patients whose asthma can be
525 successfully managed by inhaled corticosteroids along with occasional use of inhaled,
526 short-acting beta₂-agonists.

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

528 **CONTRAINDICATIONS**

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

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

532 **WARNINGS**

533 **Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients**
534 **in ADVAIR HFA, may increase the risk of asthma-related death. Therefore, when treating**
535 **patients with asthma, physicians should only prescribe ADVAIR HFA for patients not**
536 **adequately controlled on other asthma-controller medications (e.g., low- to medium-dose**
537 **inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment**
538 **with 2 maintenance therapies.**

539 A large placebo-controlled US study that compared the safety of salmeterol with placebo,
540 each added to usual asthma therapy, showed an increase in asthma-related deaths in patients
541 receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a
542 randomized, double-blind study that enrolled long-acting beta₂-agonist-naïve patients with
543 asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily
544 over 28 weeks compared with placebo when added to usual asthma therapy. A planned interim
545 analysis was conducted when approximately half of the intended number of patients had been
546 enrolled (N = 26,355), which led to premature termination of the study. The results of the interim
547 analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events
548 (see Table 3 and Figure 5). In the total population, a higher rate of asthma-related death occurred
549 in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%; relative risk
550 4.37 [95% CI 1.25, 15.34]).

551 Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death
552 occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo
553 (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also,
554 asthma-related death occurred at a higher rate in patients treated with salmeterol than those
555 treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the
556 relative risks of asthma-related death were similar in Caucasians and African Americans, the
557 estimate of excess deaths in patients treated with salmeterol was greater in African Americans
558 because there was a higher overall rate of asthma-related death in African American patients (see
559 Table 3). Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the
560 findings seen in the SMART study represent a class effect.

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

564

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

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

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

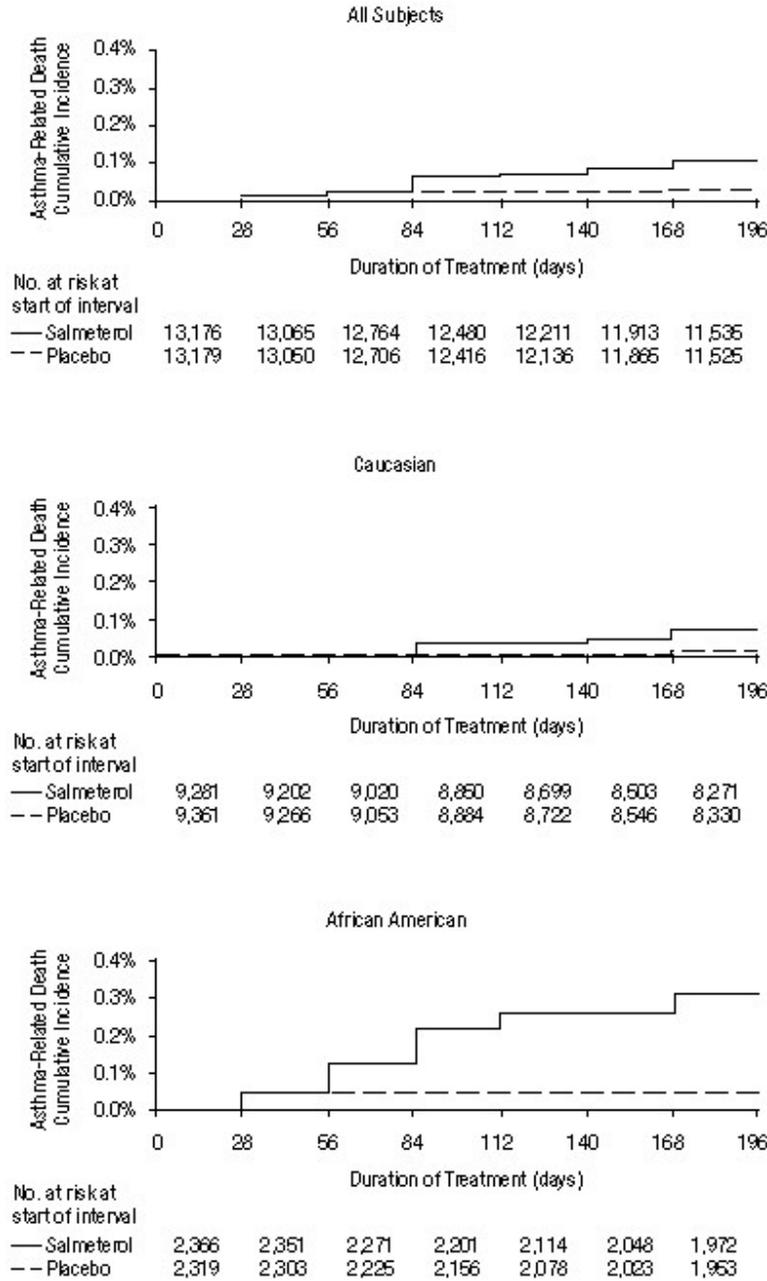
569 † Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the
 570 rate in the placebo group. The relative risk indicates how many more times likely an
 571 asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week
 572 treatment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

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

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

585

586 **Figure 5. Cumulative Incidence of Asthma-Related**
 587 **Deaths in the 28-Week Salmeterol Multi-center Asthma**
 588 **Research Trial (SMART), by Duration of Treatment**
 589



590
 591
 592 A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide
 593 Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate
 594 of asthma-related death was numerically, though not statistically significantly, greater in patients
 595 with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol
 596 (180 mcg 4 times daily) added to usual asthma therapy.

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

598 1. ADVAIR HFA should not be initiated in patients during rapidly deteriorating or potentially
599 life-threatening episodes of asthma. Serious acute respiratory events, including fatalities, have
600 been reported both in the United States and worldwide when salmeterol, a component of
601 ADVAIR HFA, has been initiated in patients with significantly worsening or acutely
602 deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g.,
603 patients with a history of corticosteroid dependence, low pulmonary function, intubation,
604 mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma
605 exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g.,
606 unresponsive to usual medications; increasing need for inhaled, short-acting beta₂-agonists;
607 increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency
608 room visits; sudden or progressive deterioration in pulmonary function). However, they have
609 occurred in a few patients with less severe asthma as well. It was not possible from these reports
610 to determine whether salmeterol contributed to these events.

611 2. ADVAIR HFA should not be used to treat acute symptoms. An inhaled, short-acting
612 beta₂-agonist, not ADVAIR HFA, should be used to relieve acute symptoms of shortness of
613 breath. When prescribing ADVAIR HFA, the physician must also provide the patient with an
614 inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of shortness of breath that
615 occurs acutely, despite regular twice-daily (morning and evening) use of ADVAIR HFA.

616 When beginning treatment with ADVAIR HFA, patients who have been taking oral or
617 inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to
618 discontinue the regular use of these drugs. For patients taking ADVAIR HFA, inhaled,
619 short-acting beta₂-agonists should only be used for symptomatic relief of acute symptoms of
620 shortness of breath (see PRECAUTIONS: Information for Patients).

621 3. Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma. The
622 physician and patient should be alert to such changes. The patient's condition may deteriorate
623 acutely over a period of hours or chronically over several days or longer. If the patient's inhaled,
624 short-acting beta₂-agonist becomes less effective, the patient needs more inhalations than usual,
625 or the patient develops a significant decrease in lung function, this may be a marker of
626 destabilization of the disease. In this setting, the patient requires immediate reevaluation with
627 reassessment of the treatment regimen, giving special consideration to the possible need for
628 replacing the current strength of ADVAIR HFA with a higher strength, adding additional inhaled
629 corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2
630 inhalations twice daily (morning and evening) of ADVAIR HFA.

631 4. ADVAIR HFA should not be used for transferring patients from systemic corticosteroid
632 therapy. Particular care is needed for patients who have been transferred from systemically active
633 corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have
634 occurred in patients with asthma during and after transfer from systemic corticosteroids to less
635 systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a
636 number of months are required for recovery of HPA function.

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

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

651 5. ADVAIR HFA should not be used in conjunction with an inhaled, long-acting beta₂-agonist.
652 Patients who are receiving ADVAIR HFA twice daily should not use additional salmeterol or
653 other long-acting beta₂-agonists (e.g., formoterol) for prevention of exercise-induced
654 bronchospasm (EIB) or the maintenance treatment of asthma. Additional benefit would not be
655 gained from using supplemental salmeterol or formoterol for prevention of EIB since ADVAIR
656 HFA already contains an inhaled, long-acting beta₂-agonist.

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

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

667 8. Immediate hypersensitivity reactions. Immediate hypersensitivity reactions may occur after
668 administration of ADVAIR HFA, as demonstrated by cases of urticaria, angioedema, rash, and
669 bronchospasm.

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

673 10. Cardiovascular disorders. ADVAIR HFA, like all products containing sympathomimetic
674 amines, should be used with caution in patients with cardiovascular disorders, especially
675 coronary insufficiency, cardiac arrhythmias, and hypertension. Salmeterol, a component of
676 ADVAIR HFA, can produce a clinically significant cardiovascular effect in some patients as

677 measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon
678 after administration of salmeterol at recommended doses, if they occur, the drug may need to be
679 discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG)
680 changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment
681 depression. The clinical significance of these findings is unknown.

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

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

696 13. Pneumonia. Lower respiratory tract infections, including pneumonia, have been reported in
697 patients with COPD following the inhaled administration of corticosteroids, including
698 fluticasone propionate and ADVAIR DISKUS. In 2 replicate 12-month studies of 1,579 patients
699 with COPD, there was a higher incidence of pneumonia reported in patients receiving ADVAIR
700 DISKUS 250/50 (7%) than in those receiving salmeterol 50 mcg (3%). The incidence of
701 pneumonia in the patients treated with ADVAIR DISKUS was higher in patients over 65 years
702 of age (9%) compared with the incidence in patients less than 65 years of age (4%).

703 In a 3-year study of 6,184 patients with COPD, there was a higher incidence of pneumonia
704 reported in patients receiving ADVAIR DISKUS 500/50 compared with placebo (16% with
705 ADVAIR DISKUS 500/50, 14% with fluticasone propionate 500 mcg, 11% with salmeterol 50
706 mcg, and 9% with placebo). Similar to what was seen in the 1-year studies with ADVAIR
707 DISKUS 250/50, the incidence of pneumonia was higher in patients over 65 years of age (18%
708 with ADVAIR DISKUS 500/50 versus 10% with placebo) compared with patients less than 65
709 years of age (14% with ADVAIR DISKUS 500/50 versus 8% with placebo).

710 14. Potential drug interactions with CYP 3A4 inhibitors. Both fluticasone propionate and
711 salmeterol are substrates of CYP 3A4.

712 Fluticasone Propionate: A drug interaction study in healthy subjects has shown that ritonavir
713 (a strong cytochrome P450 3A4 inhibitor) can significantly increase systemic fluticasone
714 propionate exposure (AUC), resulting in significantly reduced serum cortisol concentrations (see
715 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug Interactions*
716 and PRECAUTIONS: Drug Interactions: *Inhibitors of Cytochrome P450*). During postmarketing

717 use, there have been reports of clinically significant drug interactions in patients receiving
718 fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including
719 Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone
720 propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs
721 the risk of systemic corticosteroid side effects.

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

727 **PRECAUTIONS**

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

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

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

746 Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously,
747 have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic
748 agonist medications may produce significant hypokalemia in some patients, possibly through
749 intracellular shunting, which has the potential to produce adverse cardiovascular effects. The
750 decrease in serum potassium is usually transient, not requiring supplementation.

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

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

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

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

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

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

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

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

792 Lower respiratory tract infections, including pneumonia, have been reported following the
793 inhaled administration of corticosteroids, including fluticasone propionate, a component of
794 ADVAIR HFA.

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

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

802 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a
803 component of ADVAIR HFA, may present with systemic eosinophilic conditions, with some
804 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a
805 condition that is often treated with systemic corticosteroid therapy. These events usually, but not
806 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy
807 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions
808 have also been reported with other inhaled corticosteroids in this clinical setting. Physicians
809 should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac
810 complications, and/or neuropathy presenting in their patients. A causal relationship between
811 fluticasone propionate and these underlying conditions has not been established (see ADVERSE
812 REACTIONS: Observed During Clinical Practice: *Eosinophilic Conditions*).

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

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

- 821 1. **Patients should be informed that salmeterol, one of the active ingredients in ADVAIR**
822 **HFA, may increase the risk of asthma-related death.** They should also be informed that
823 data are not adequate to determine whether the concurrent use of inhaled corticosteroids,
824 such as fluticasone propionate, the other component of ADVAIR HFA, or other
825 asthma-controller therapy modifies this risk.
- 826 2. ADVAIR HFA is not meant to relieve acute asthma symptoms and extra doses should not be
827 used for that purpose. Acute symptoms should be treated with an inhaled, short-acting
828 beta₂-agonist such as albuterol (the physician should provide the patient with such
829 medication and instruct the patient in how it should be used).
- 830 3. The physician should be notified immediately if any of the following signs of seriously
831 worsening asthma occur:
 - 832 • decreasing effectiveness of inhaled, short-acting beta₂-agonists;
 - 833 • need for more inhalations than usual of inhaled, short-acting beta₂-agonists;
 - 834 • significant decrease in lung function as outlined by the physician.

- 835 4. Patients should not stop therapy with ADVAIR HFA without physician/provider guidance
836 since symptoms may recur after discontinuation.
- 837 5. Patients should be cautioned regarding common adverse effects associated with
838 beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 839 6. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of
840 ADVAIR HFA, may increase the risk of some eye problems (cataracts or glaucoma). Regular
841 eye examinations should be considered.
- 842 7. When patients are prescribed ADVAIR HFA, other medications for asthma should be used
843 only as directed by the physician.
- 844 8. Patients who are pregnant or nursing should contact the physician about the use of ADVAIR
845 HFA.
- 846 9. Patients should use ADVAIR HFA at regular intervals as directed. Results of clinical trials
847 indicated significant improvement may occur within the first 30 minutes of taking the first
848 dose; however, the full benefit may not be achieved until treatment has been administered for
849 1 week or longer. The patient should not use more than the prescribed dosage but should
850 contact the physician if symptoms do not improve or if the condition worsens.
- 851 10. The bronchodilation from a single dose of ADVAIR HFA may last up to 12 hours or longer.
852 The recommended dosage (2 inhalations twice daily, morning and evening) should not be
853 exceeded. Patients who are receiving ADVAIR HFA twice daily should not use salmeterol or
854 other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of EIB or
855 maintenance treatment of asthma.
- 856 11. Patients should be warned to avoid exposure to chickenpox or measles and, if they are
857 exposed to consult the physician without delay.
- 858 12. Prime the inhaler before using for the first time by releasing 4 test sprays into the air away
859 from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has
860 not been used for more than 4 weeks or when it has been dropped, prime the inhaler again by
861 releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before each
862 spray.
- 863 13. After inhalation, rinse the mouth with water and spit out. Do not swallow.
- 864 14. Clean the inhaler at least once a week after the evening dose. Keeping the canister and plastic
865 actuator clean is important to prevent medicine buildup. (See the cleaning instructions in the
866 “How to use your ADVAIR HFA” section of the Medication Guide accompanying the
867 product.)
- 868 15. Use ADVAIR HFA only with the actuator supplied with the product. When the counter reads
869 020, contact the pharmacist for a refill of medication or consult the physician to determine
870 whether a prescription refill is needed. Discard the inhaler when the counter reads 000. Never
871 try to alter the numbers or remove the counter from the metal canister.
- 872 16. For important summary information and instructions for the proper use of ADVAIR HFA,
873 the patient should carefully read and follow the Medication Guide accompanying the
874 product.

875 **Drug Interactions:** ADVAIR HFA has been used concomitantly with other drugs, including
876 short-acting beta₂-agonists, methylxanthines, and intranasal corticosteroids, commonly used in
877 patients with asthma, without adverse drug reactions. No formal drug interaction studies have
878 been performed with ADVAIR HFA.

879 **Short-Acting Beta₂-Agonists:** In three 12-week US clinical trials, the mean daily need for
880 additional beta₂-agonist use in 277 patients receiving ADVAIR HFA was approximately
881 1.2 inhalations/day and ranged from 0 to 9 inhalations/day. Two percent (2%) of patients
882 receiving ADVAIR HFA in these trials averaged 6 or more inhalations per day over the course of
883 the 12-week trials. No increase in frequency of cardiovascular events was observed among
884 patients who averaged 6 or more inhalations per day.

885 **Methylxanthines:** The concurrent use of intravenously or orally administered
886 methylxanthines (e.g., aminophylline, theophylline) by patients receiving ADVAIR HFA has not
887 been completely evaluated. In five 12-week clinical trials (3 US and 2 non-US), 45 patients
888 receiving ADVAIR HFA 45/21, 115/21, or 230/21 twice daily concurrently with a theophylline
889 product had adverse event rates similar to those in 577 patients receiving ADVAIR HFA without
890 theophylline.

891 **Fluticasone Propionate Nasal Spray:** In patients receiving ADVAIR HFA in three
892 12-week US clinical trials, no difference in the profile of adverse events or HPA axis effects was
893 noted between patients receiving FLONASE[®] (fluticasone propionate) Nasal Spray, 50 mcg
894 concurrently (n = 89) and those who were not (n = 192).

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

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

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

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

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

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

928 **Salmeterol:** In a drug interaction study in 20 healthy subjects, coadministration of inhaled
929 salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in
930 greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold).
931 Three (3) subjects were withdrawn due to beta₂-agonist side effects (2 with prolonged QTc and 1
932 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean
933 QTc, coadministration of salmeterol and ketoconazole was associated with more frequent
934 increases in QTc duration compared with salmeterol and placebo administration. Due to the
935 potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with
936 strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir,
937 itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) is not recommended (see
938 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Salmeterol Xinafoate: Drug Interactions*).

939 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate:**
940 Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to
941 1,000 mcg/kg (approximately 4 times the maximum recommended human daily inhalation dose
942 on a mcg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than the
943 maximum recommended human daily inhalation dose on a mcg/m² basis) for 104 weeks.

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

947 No evidence of impairment of fertility was observed in reproductive studies conducted in
948 male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum
949 recommended human daily inhalation dose on a mcg/m² basis). Prostate weight was significantly
950 reduced at a subcutaneous dose of 50 mcg/kg.

951 **Salmeterol:** In an 18-month oral carcinogenicity study in CD-mice, salmeterol at oral doses
952 of 1.4 mg/kg and above (approximately 10 times the maximum recommended human daily
953 inhalation dose based on comparison of the AUCs) caused a dose-related increase in the

954 incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus,
955 and ovarian cysts. The incidence of leiomyosarcomas was not statistically significant. No tumors
956 were seen at 0.2 mg/kg (approximately 2 times the maximum recommended human daily
957 inhalation dose in adults based on comparison of the AUCs).

958 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol
959 caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at
960 doses of 0.68 mg/kg and above (approximately 65 times the maximum recommended human
961 daily inhalation dose on a mg/m² basis). No tumors were seen at 0.21 mg/kg (approximately
962 20 times the maximum recommended human daily inhalation dose on a mg/m² basis). These
963 findings in rodents are similar to those reported previously for other beta-adrenergic agonist
964 drugs. The relevance of these findings to human use is unknown.

965 Salmeterol produced no detectable or reproducible increases in microbial and mammalian
966 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo
967 in a rat micronucleus test. No effects on fertility were identified in male and female rats treated
968 with salmeterol at oral doses up to 2 mg/kg (approximately 190 times the maximum
969 recommended human daily inhalation dose on a mg/m² basis).

970 **Pregnancy: Teratogenic Effects: ADVAIR HFA Inhalation Aerosol:** Pregnancy
971 Category C. From the reproduction toxicity studies in mice and rats, no evidence of enhanced
972 toxicity was seen using combinations of fluticasone propionate and salmeterol compared with
973 toxicity data from the components administered separately. In mice combining 150 mcg/kg
974 subcutaneously of fluticasone propionate (less than the maximum recommended human daily
975 inhalation dose on a mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 480 times
976 the maximum recommended human daily inhalation dose on a mg/m² basis) were teratogenic.
977 Cleft palate, fetal death, increased implantation loss and delayed ossification was seen. These
978 observations are characteristic of glucocorticoids. No developmental toxicity was observed at
979 combination doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the
980 maximum recommended human daily inhalation dose on a mcg/m² basis) and up to 1.4 mg/kg
981 orally of salmeterol (approximately 70 times the maximum recommended human daily
982 inhalation dose on a mg/m² basis). In rats, no teratogenicity was observed at combination doses
983 up to 30 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended
984 human daily inhalation dose on a mcg/m² basis) and up to 1 mg/kg of salmeterol (approximately
985 95 times the maximum recommended human daily inhalation dose on a mg/m² basis).
986 Combining 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum
987 recommended human daily inhalation dose on a mcg/m² basis) with 10 mg/kg orally of
988 salmeterol (approximately 970 times the maximum recommended human daily inhalation dose
989 on a mg/m² basis) produced maternal toxicity, decreased placental weight, decreased fetal
990 weight, umbilical hernia, delayed ossification, and changes in the occipital bone.

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

994 **Fluticasone Propionate:** Pregnancy Category C. Subcutaneous studies in the mouse
995 and rat at 45 and 100 mcg/kg, respectively (less than and equivalent to, respectively, the
996 maximum recommended human daily inhalation dose on a mcg/m² basis), revealed fetal toxicity
997 characteristic of potent corticosteroid compounds, including embryonic growth retardation,
998 omphalocele, cleft palate, and retarded cranial ossification. No teratogenicity was seen in the rat
999 at inhalation doses up to 68.7 mcg/kg (less than the maximum recommended human daily
1000 inhalation dose on a mcg/m² basis).

1001 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of
1002 4 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m²
1003 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg
1004 (approximately 5 times the maximum recommended human daily inhalation dose on a mcg/m²
1005 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this
1006 study, consistent with the established low bioavailability following oral administration (see
1007 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Absorption*).

1008 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose
1009 of 100 mcg/kg to mice (less than the maximum recommended human daily inhalation dose on a
1010 mcg/m² basis), a subcutaneous or an oral dose of 100 mcg/kg to rats (equivalent to the maximum
1011 recommended human daily inhalation dose on a mcg/m² basis), and an oral dose of 300 mcg/kg
1012 to rabbits (approximately 5 times the maximum recommended human daily inhalation dose on a
1013 mcg/m² basis).

1014 There are no adequate and well-controlled studies in pregnant women. ADVAIR HFA should
1015 be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

1016 Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to
1017 physiologic, doses suggests that rodents are more prone to teratogenic effects from
1018 corticosteroids than humans. In addition, because there is a natural increase in corticosteroid
1019 production during pregnancy, most women will require a lower exogenous corticosteroid dose
1020 and many will not need corticosteroid treatment during pregnancy.

1021 **Salmeterol:** Pregnancy Category C. No teratogenic effects occurred in the rat at oral
1022 doses up to 2 mg/kg (approximately 190 times the maximum recommended human daily
1023 inhalation dose on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg
1024 and above (approximately 25 times the maximum recommended human daily inhalation dose
1025 based on the comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically
1026 resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft
1027 palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial
1028 bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 10 times the
1029 maximum recommended human daily inhalation dose based on comparison of the AUCs).

1030 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal
1031 cranial bones was seen at an oral dose of 10 mg/kg (approximately 1,900 times the maximum
1032 recommended human daily inhalation dose on a mg/m² basis). Extensive use of other

1033 beta-agonists has provided no evidence that these class effects in animals are relevant to their use
1034 in humans.

1035 Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice
1036 and rats (approximately 480 and 970 times, respectively, the maximum recommended human
1037 daily inhalation dose on a mg/m² basis).

1038 There are no adequate and well-controlled studies with salmeterol in pregnant women.
1039 Salmeterol should be used during pregnancy only if the potential benefit justifies the potential
1040 risk to the fetus.

1041 **Use in Labor and Delivery:** There are no well-controlled human studies that have
1042 investigated effects of ADVAIR HFA on preterm labor or labor at term. Because of the potential
1043 for beta-agonist interference with uterine contractility, use of ADVAIR HFA for management of
1044 asthma during labor should be restricted to those patients in whom the benefits clearly outweigh
1045 the risks.

1046 **Nursing Mothers:** Plasma levels of salmeterol, a component of ADVAIR HFA, after inhaled
1047 therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There are no
1048 data from controlled trials on the use of salmeterol by nursing mothers. It is not known whether
1049 fluticasone propionate, a component of ADVAIR HFA, is excreted in human breast milk.
1050 However, other corticosteroids have been detected in human milk. Subcutaneous administration
1051 to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the maximum
1052 recommended human daily inhalation dose on a mcg/m² basis) resulted in measurable
1053 radioactivity in milk.

1054 Since there are no data from controlled trials on the use of ADVAIR HFA by nursing mothers,
1055 a decision should be made whether to discontinue nursing or to discontinue ADVAIR HFA,
1056 taking into account the importance of ADVAIR HFA to the mother.

1057 Caution should be exercised when ADVAIR HFA is administered to a nursing woman.

1058 **Pediatric Use:** Thirty-eight (38) patients 12 to 17 years of age were treated with ADVAIR
1059 HFA in US pivotal clinical trials. Patients in this age-group demonstrated efficacy results similar
1060 to those observed in patients 18 years of age and older. There were no obvious differences in the
1061 type or frequency of adverse events reported in this age-group compared with patients 18 years
1062 of age and older.

1063 The safety and effectiveness of ADVAIR HFA in children under 12 years have not been
1064 established.

1065 Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in
1066 growth in pediatric patients. In these studies, the mean reduction in growth velocity was
1067 approximately 1 cm/year (range, 0.3 to 1.8 cm/year) and appears to depend upon dose and
1068 duration of exposure. This effect was observed in the absence of laboratory evidence of HPA
1069 axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic
1070 corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis
1071 function. The long-term effects of this reduction in growth velocity associated with orally
1072 inhaled corticosteroids, including the impact on final adult height, are unknown. The potential

1073 for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids
1074 has not been adequately studied. The effects on growth velocity of treatment with orally inhaled
1075 corticosteroids for over 1 year, including the impact on final adult height, are unknown. The
1076 growth of children and adolescents receiving orally inhaled corticosteroids, including ADVAIR
1077 HFA, should be monitored. If a child or adolescent on any corticosteroid appears to have growth
1078 suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids
1079 should be considered. The potential growth effects of prolonged treatment should be weighed
1080 against the clinical benefits obtained and the risks associated with alternative therapies. To
1081 minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR HFA, each
1082 patient should be titrated to the lowest strength that effectively controls his/her asthma (see
1083 DOSAGE AND ADMINISTRATION).

1084 **Geriatric Use:** Of the total number of patients in clinical studies treated with ADVAIR HFA,
1085 41 were 65 years of age or older and 21 were 75 years of age or older. No overall differences in
1086 safety were observed between these patients and younger patients, and other reported clinical
1087 experience, including studies of the individual components, has not identified differences in
1088 responses between the elderly and younger patients, but greater sensitivity of some older
1089 individuals cannot be ruled out. As with other products containing beta₂-agonists, special caution
1090 should be observed when using ADVAIR HFA in geriatric patients who have concomitant
1091 cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available
1092 data for ADVAIR HFA or its active components, no adjustment of dosage of ADVAIR HFA in
1093 geriatric patients is warranted.

1094 **ADVERSE REACTIONS**

1095 **Long-acting beta₂-adrenergic agonists, such as salmeterol, may increase the risk of**
1096 **asthma-related death. Data from a large, placebo-controlled US study that compared the**
1097 **safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma**
1098 **therapy showed an increase in asthma-related deaths in patients receiving salmeterol (see**
1099 **WARNINGS). Salmeterol is a component of ADVAIR HFA. However, the data from this**
1100 **study are not adequate to determine whether concurrent use of inhaled corticosteroids,**
1101 **such as fluticasone propionate, the other component of ADVAIR HFA, or other asthma**
1102 **controller therapy modifies the risk of asthma-related death.**

1103 The incidence of common adverse events in Table 4 is based upon 2 placebo-controlled,
1104 12-week, US clinical studies (Studies 1 and 3) and 1 active-controlled, 12-week, US clinical
1105 study (Study 2). A total of 1,008 adolescent and adult patients with asthma (556 females and 452
1106 males) previously treated with albuterol alone, salmeterol, or inhaled corticosteroids were treated
1107 twice daily with 2 inhalations of ADVAIR HFA 45/21 or ADVAIR HFA 115/21, fluticasone
1108 propionate CFC inhalation aerosol (44- or 110-mcg doses), salmeterol CFC inhalation aerosol
1109 21 mcg, or placebo HFA inhalation aerosol.

1110

1111 **Table 4. Overall Adverse Events With $\geq 3\%$ Incidence in US Controlled Clinical Trials**
 1112 **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	21	15	24	16	20	11
Dizziness	4	1	1	0	<1	0
Gastrointestinal						
Nausea & vomiting	5	3	4	2	2	3
Viral gastrointestinal infections	4	2	2	0	1	2
Gastrointestinal signs & symptoms	3	2	2	1	1	1
Non-site specific						
Pain	3	1	2	1	2	2
Musculoskeletal						
Musculoskeletal pain	5	7	8	2	4	4
Muscle pain	4	1	1	1	3	<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

1113

1114 Table 4 includes all events (whether considered drug-related or nondrug-related by the
1115 investigator) that occurred at a rate of 3% or greater in any of the groups receiving ADVAIR
1116 HFA and were more common than in the placebo group. In considering these data, differences in
1117 average duration of exposure should be taken into account. These adverse reactions were mostly
1118 mild to moderate in severity.

1119 Other adverse events that occurred in the groups receiving ADVAIR HFA in these studies
1120 with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1121 **Cardiovascular:** Tachycardia, arrhythmias, myocardial infarction.

1122 **Drug Interaction, Overdose, and Trauma:** Postoperative complications, wounds and
1123 lacerations, soft tissue injuries, poisoning and toxicity, pressure-induced disorder.

1124 **Ear, Nose, and Throat:** Ear, nose, and throat infection; ear signs and symptoms;
1125 rhinorrhea/postnasal drip; epistaxis; nasal congestion/blockage; laryngitis; unspecified
1126 oropharyngeal plaques; dryness of nose.

1127 **Endocrine and Metabolic:** Weight gain.

1128 **Eye:** Allergic eye disorders, eye edema and swelling.

1129 **Gastrointestinal:** Gastrointestinal discomfort and pain, dental discomfort and pain,
1130 candidiasis mouth/throat, hyposalivation, gastrointestinal infections, disorders of hard tissue of
1131 teeth, hemorrhoids, gastrointestinal gaseous symptoms, abdominal discomfort and pain,
1132 constipation, oral abnormalities.

1133 **Musculoskeletal:** Arthralgia and articular rheumatism, muscle cramps and spasms,
1134 musculoskeletal inflammation, bone and skeletal pain.

1135 **Neurology:** Sleep disorders, migraines.

1136 **Non-Site Specific:** Allergies and allergic reactions, viral infections, bacterial infections,
1137 candidiasis unspecified site, congestion, inflammation.

1138 **Reproduction:** Bacterial reproductive infections.

1139 **Respiratory:** Lower respiratory signs and symptoms, lower respiratory infections, lower
1140 respiratory hemorrhage.

1141 **Skin:** Eczema, dermatitis and dermatosis.

1142 **Urology:** Urinary infections.

1143 Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare
1144 events of angioedema and bronchospasm, have been reported.

1145 The incidence of common adverse events reported in Study 4, a 12-week, non-US clinical
1146 study of 509 patients previously treated with inhaled corticosteroids who were treated twice daily
1147 with 2 inhalations of ADVAIR HFA 230/21, fluticasone propionate CFC inhalation aerosol

1148 220 mcg, or 1 inhalation of ADVAIR DISKUS 500/50 was similar to the incidences reported in
1149 Table 4.

1150 **Observed During Clinical Practice:** In addition to adverse events reported from clinical
1151 trials, the following events have been identified during worldwide use of any formulation of
1152 ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are
1153 reported voluntarily from a population of unknown size, estimates of frequency cannot be made.
1154 These events have been chosen for inclusion due to either their seriousness, frequency of
1155 reporting, or causal connection to ADVAIR, fluticasone propionate, and/or salmeterol or a
1156 combination of these factors.

1157 In extensive US and worldwide postmarketing experience with salmeterol, a component of
1158 ADVAIR HFA, serious exacerbations of asthma, including some that have been fatal, have been
1159 reported. In most cases, these have occurred in patients with severe asthma and/or in some
1160 patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also
1161 occurred in a few patients with less severe asthma. It was not possible from these reports to
1162 determine whether salmeterol contributed to these events.

1163 **Cardiovascular:** Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular
1164 tachycardia), hypertension, ventricular tachycardia.

1165 **Ear, Nose, and Throat:** Aphonia, earache, facial and oropharyngeal edema, paranasal sinus
1166 pain, rhinitis, throat soreness and irritation, tonsillitis.

1167 **Endocrine and Metabolic:** Cushing syndrome, Cushingoid features, growth velocity
1168 reduction in children/adolescents, hypercorticism, hyperglycemia, osteoporosis.

1169 **Eye:** Cataracts, glaucoma.

1170 **Gastrointestinal:** Dyspepsia, xerostomia.

1171 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1172 **Musculoskeletal:** Back pain, myositis.

1173 **Neurology:** Paresthesia, restlessness.

1174 **Non-Site Specific:** Fever, immediate and delayed hypersensitivity reaction, pallor.

1175 **Psychiatry:** Agitation, aggression, anxiety, depression. Behavioral changes, including
1176 hyperactivity and irritability, have been reported very rarely and primarily in children.

1177 **Respiratory:** Asthma; asthma exacerbation; chest congestion; chest tightness; cough;
1178 dyspnea; immediate bronchospasm; influenza; paradoxical bronchospasm; tracheitis; wheezing;
1179 pneumonia; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling;
1180 stridor; choking.

1181 **Skin:** Contact dermatitis, contusions, ecchymoses, photodermatitis, pruritus.

1182 **Urogenital:** Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal
1183 candidiasis, vaginitis, vulvovaginitis.

1184 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a
1185 component of ADVAIR HFA, may present with systemic eosinophilic conditions, with some
1186 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a
1187 condition that is often treated with systemic corticosteroid therapy. These events usually, but not

1188 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy
1189 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions
1190 have also been reported with other inhaled corticosteroids in this clinical setting. While
1191 ADVAIR HFA should not be used for transferring patients from systemic corticosteroid therapy,
1192 physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms,
1193 cardiac complications, and/or neuropathy presenting in their patients. A causal relationship
1194 between fluticasone propionate and these underlying conditions has not been established (see
1195 PRECAUTIONS: General: *Eosinophilic Conditions*).

1196 **OVERDOSAGE**

1197 **ADVAIR HFA Inhalation Aerosol:** No deaths occurred in rats given a single-dose
1198 combination of salmeterol 3.6 mg/kg and fluticasone propionate 1.9 mg/kg given as the
1199 inhalation powder (approximately 290 and 15 times, respectively, the maximum recommended
1200 human daily inhalation dose on a mg/m² basis).

1201 **Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in
1202 signs/symptoms of hypercorticism (see PRECAUTIONS: General: *Metabolic and Other Effects*).
1203 Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate
1204 inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate CFC
1205 inhalation aerosol were well tolerated. Fluticasone propionate given by inhalation aerosol at
1206 dosages of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well
1207 tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral
1208 doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of
1209 mild or moderate severity, and incidences were similar in active and placebo treatment groups. In
1210 mice the oral median lethal dose was >1,000 mg/kg (>4,400 times the maximum recommended
1211 human daily inhalation dose on a mg/m² basis). In rats the subcutaneous median lethal dose was
1212 >1,000 mg/kg (>8,800 times the maximum recommended human daily inhalation dose on a
1213 mg/m² basis).

1214 **Salmeterol:** The expected signs and symptoms with overdosage of salmeterol are those of
1215 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and
1216 symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or
1217 hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache,
1218 tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.
1219 Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic
1220 adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or
1221 arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to
1222 clinically significant prolongation of the QTc interval, which can produce ventricular
1223 arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

1224 As with all sympathomimetic medications, cardiac arrest and even death may be associated
1225 with abuse of salmeterol.

1226 Treatment consists of discontinuation of salmeterol together with appropriate symptomatic
1227 therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing
1228 in mind that such medication can produce bronchospasm. There is insufficient evidence to
1229 determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is
1230 recommended in cases of overdosage.

1231 No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg
1232 (approximately 280 times the maximum recommended human daily inhalation dose on a mg/m²
1233 basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 230 times the maximum
1234 recommended human daily inhalation dose on a mg/m² basis). By the oral route, no deaths
1235 occurred in mice at 150 mg/kg (approximately 7,200 times the maximum recommended human
1236 daily inhalation dose on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 97,000 times
1237 the maximum recommended human daily inhalation dose on a mg/m² basis).

1238 **DOSAGE AND ADMINISTRATION**

1239 ADVAIR HFA should be administered by the orally inhaled route only in patients 12 years of
1240 age and older. ADVAIR HFA should not be used for transferring patients from systemic
1241 corticosteroid therapy. ADVAIR HFA has not been studied in patients under 12 years of age or
1242 in patients with COPD.

1243 Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in
1244 ADVAIR HFA, may increase the risk of asthma-related death (see WARNINGS). Therefore,
1245 when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients
1246 not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose
1247 inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2
1248 maintenance therapies. ADVAIR HFA is not indicated in patients whose asthma can be
1249 successfully managed by inhaled corticosteroids along with occasional use of inhaled,
1250 short-acting beta₂-agonists.

1251 ADVAIR HFA is available in 3 strengths, ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR
1252 HFA 115/21 Inhalation Aerosol, and ADVAIR HFA 230/21 Inhalation Aerosol, containing 45,
1253 115, and 230 mcg of fluticasone propionate, respectively, and 21 mcg of salmeterol per
1254 inhalation.

1255 ADVAIR HFA should be administered as 2 inhalations twice daily every day. More frequent
1256 administration (more than twice daily) or a higher number of inhalations (more than 2 inhalations
1257 twice daily) of the prescribed strength of ADVAIR HFA is not recommended as some patients
1258 are more likely to experience adverse effects with higher doses of salmeterol. The safety and
1259 efficacy of ADVAIR HFA when administered in excess of recommended doses have not been
1260 established.

1261 If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should
1262 be taken for immediate relief.

1263 Patients who are receiving ADVAIR HFA twice daily should not use additional salmeterol or
1264 other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of EIB or for any other
1265 reason.

1266 For patients 12 years of age and older, the dosage is 2 inhalations twice daily (morning and
1267 evening, approximately 12 hours apart).

1268 The recommended starting dosages for ADVAIR HFA are based upon patients' current
1269 asthma therapy.

- 1270 • For patients not adequately controlled on an inhaled corticosteroid, Table 5 provides the
1271 recommended starting dosage.
- 1272 • For patients not currently on inhaled corticosteroids, whose disease severity clearly warrants
1273 initiation of treatment with 2 maintenance therapies, the recommended starting dosage is 2
1274 inhalations of ADVAIR HFA 45/21 or ADVAIR HFA 115/21 twice daily (see
1275 INDICATIONS AND USAGE).

1276 The maximum recommended dosage is 2 inhalations of ADVAIR HFA 230/21 twice daily.

1277 **For all patients it is desirable to titrate to the lowest effective strength after adequate**
1278 **asthma stability is achieved.**

1279

1280 **Table 5. Recommended Dosages of ADVAIR HFA Inhalation Aerosol for Patients Not**
 1281 **Adequately Controlled on Inhaled Corticosteroids**

Current Daily Dose 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

1282 * ADVAIR HFA should not be used for transferring patients from systemic corticosteroid
 1283 therapy.

1284
 1285 Improvement in asthma control following inhaled administration of ADVAIR HFA can occur
 1286 within 30 minutes of beginning treatment, although maximum benefit may not be achieved for
 1287 1 week or longer after starting treatment. Individual patients will experience a variable time to
 1288 onset and degree of symptom relief.

1289 For patients who do not respond adequately to the starting dosage after 2 weeks of therapy,
 1290 replacing the current strength of ADVAIR HFA with a higher strength may provide additional
 1291 improvement in asthma control.

1292 If a previously effective dosage regimen of ADVAIR HFA fails to provide adequate
 1293 improvement in asthma control, the therapeutic regimen should be reevaluated and additional
 1294 therapeutic options, e.g., replacing the current strength of ADVAIR HFA with a higher strength,
 1295 adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be considered.

1296 ADVAIR HFA should be primed before using for the first time by releasing 4 test sprays into
1297 the air away from the face, shaking well for 5 seconds before each spray. In cases where the
1298 inhaler has not been used for more than 4 weeks or when it has been dropped, prime the inhaler
1299 again by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before
1300 each spray.

1301 **Geriatric Use:** In studies where geriatric patients (65 years of age or older, see
1302 PRECAUTIONS: Geriatric Use) have been treated with ADVAIR HFA, efficacy and safety did
1303 not differ from that in younger patients. Based on available data for ADVAIR HFA and its active
1304 components, no dosage adjustment is recommended.

1305 **HOW SUPPLIED**

1306 Each strength of ADVAIR HFA Inhalation Aerosol is supplied in a 12-g pressurized
1307 aluminum canister containing 120 metered actuations in a box of 1.* Each canister is fitted with a
1308 counter, supplied with a purple actuator with a light purple strapcap, and sealed in a
1309 plastic-coated, moisture-protective foil pouch with a desiccant that should be discarded when the
1310 pouch is opened. Each canister is packaged with a Medication Guide leaflet.

1311 *NDC 0173-0715-20 ADVAIR HFA 45/21 Inhalation Aerosol

1312 *NDC 0173-0716-20 ADVAIR HFA 115/21 Inhalation Aerosol

1313 *NDC 0173-0717-20 ADVAIR HFA 230/21 Inhalation Aerosol

1314 **The purple actuator supplied with ADVAIR HFA Inhalation Aerosol should not be used**
1315 **with any other product canisters, and actuators from other products should not be used**
1316 **with an ADVAIR HFA Inhalation Aerosol canister.**

1317 **The correct amount of medication in each actuation cannot be assured after the counter**
1318 **reads 000, even though the canister is not completely empty and will continue to operate.**

1319 **The inhaler should be discarded when the counter reads 000.**

1320 **Keep out of reach of children. Avoid spraying in eyes.**

1321 **Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame.**
1322 **Exposure to temperatures above 120°F may cause bursting. Never throw container into fire**
1323 **or incinerator.**

1324 **Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Store the inhaler with**
1325 **the mouthpiece down. For best results, the inhaler should be at room temperature before**
1326 **use. SHAKE WELL FOR 5 SECONDS BEFORE USING.**

1327 ADVAIR HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the
1328 propellant.

1329 **PATIENT INFORMATION**

1330 **MEDICATION GUIDE**

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1332 **ADVAIR® HFA [*ad' vair*] 45/21 Inhalation Aerosol**
1333 **(fluticasone propionate 45 mcg and salmeterol 21 mcg)**

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ADVAIR[®] HFA 115/21 Inhalation Aerosol
(fluticasone propionate 115 mcg and salmeterol 21 mcg)

ADVAIR[®] HFA 230/21 Inhalation Aerosol
(fluticasone propionate 230 mcg and salmeterol 21 mcg)

Read this Medication Guide carefully before you start to use ADVAIR HFA Inhalation Aerosol.

Keep this Medication Guide because it has important summary information about ADVAIR HFA. This Medication Guide does not contain all the information about your medicine. If you have any questions or are not sure about something, you should ask your doctor or pharmacist.

Read the new Medication Guide that comes with each refill of your prescription because there may be new information.

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

- **ADVAIR HFA contains 2 medicines:**
 - **fluticasone propionate (the same medicine found in FLOVENT[®]),** 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[®]),** a long-acting beta₂-agonist (LABA) medicine. 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 around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.
- **In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in ADVAIR HFA), may increase the chance of death from asthma problems.** In a large asthma study, more patients who used salmeterol died from asthma problems compared with patients who did not use salmeterol. It is not known whether fluticasone propionate, the other medicine in ADVAIR HFA, changes your chance of death from asthma problems seen with salmeterol. Talk with your healthcare provider about this risk and the benefits of treating your asthma with ADVAIR HFA.
- **ADVAIR HFA does not relieve sudden symptoms. Always have a short-acting beta₂-agonist medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.**
- **Do not stop using ADVAIR HFA unless told to do so by your healthcare provider because your symptoms might get worse.**

- 1373 • **ADVAIR HFA should be used only if your healthcare provider decides that another**
1374 **asthma-controller medicine alone does not control your asthma or that you need 2**
1375 **asthma-controller medicines.**
- 1376 • **Call your healthcare provider if breathing problems worsen over time while using**
1377 **ADVAIR HFA. You may need different treatment.**
- 1378 • **Get emergency medical care if:**
- 1379 • **breathing problems worsen quickly, and**
 - 1380 • **you use your short-acting beta₂-agonist medicine, but it does not relieve your**
1381 **breathing problems.**
- 1382

What is ADVAIR HFA?

1384 ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate (the same
1385 medicine found in FLOVENT) and a LABA medicine, salmeterol (the same medicine found in
1386 SEREVENT).

1387 ADVAIR HFA is used long term, twice a day to control symptoms of asthma, and prevent
1388 symptoms such as wheezing in adults and adolescents 12 years of age and older.

1389 **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). Because**
1390 **LABA medicines, such as salmeterol, may increase the chance of death from asthma**
1391 **problems, ADVAIR HFA is not for adults and children with asthma who:**

- 1392 • are well controlled with another asthma-controller medicine, such as a low to medium dose
1393 of an inhaled corticosteroid medicine
 - 1394 • only need short-acting beta₂-agonist medicines once in awhile
- 1395

Who should not use ADVAIR HFA?

1396 Do not use ADVAIR HFA:

- 1397 • to treat sudden severe symptoms of asthma
 - 1398 • if you are allergic to any of the ingredients in ADVAIR HFA. See the end of this Medication
1399 Guide for a list of ingredients in ADVAIR HFA.
- 1400
1401

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

1402 **Tell your healthcare provider about all of your health conditions, including if you:**

- 1403 • **have heart problems**
 - 1404 • **have high blood pressure**
 - 1405 • **have seizures**
 - 1406 • **have thyroid problems**
 - 1407 • **have diabetes**
 - 1408 • **have liver problems**
 - 1409 • **have osteoporosis**
 - 1410 • **have an immune system problem**
- 1411

1412 • **are pregnant or planning to become pregnant.** It is not known if ADVAIR HFA may harm
1413 your unborn baby.

1414 • **are breastfeeding.** It is not known if ADVAIR HFA passes into your milk and if it can harm
1415 your baby.

1416 • **are allergic to ADVAIR HFA or any other medicines**

1417 • **are exposed to chickenpox or measles**

1418 Tell your healthcare provider about all the medicines you take including prescription and
1419 non-prescription medicines, vitamins, and herbal supplements. ADVAIR HFA and certain other
1420 medicines may interact with each other. This may cause serious side effects. Especially, tell your
1421 healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR[®] (ritonavir capsules)
1422 Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA[®] (lopinavir/ritonavir) Tablets
1423 contain ritonavir.

1424 Know the medicines you take. Keep a list and show it to your healthcare provider and
1425 pharmacist each time you get a new medicine.

1426

1427 **How do I use ADVAIR HFA?**

1428 **See the step-by-step instructions for using ADVAIR HFA at the end of this Medication**

1429 **Guide.** Do not use ADVAIR HFA unless your healthcare provider has taught you and you
1430 understand everything. Ask your healthcare provider or pharmacist if you have any questions.

1431 • Use ADVAIR HFA exactly as prescribed. **Do not use ADVAIR HFA more often than**
1432 **prescribed.** ADVAIR HFA comes in 3 strengths. Your healthcare provider has prescribed the
1433 one that is best for your condition.

1434 • The usual dose of ADVAIR HFA is 2 inhalations twice a day (morning and evening). The 2
1435 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR
1436 HFA.

1437 • If you miss a dose of ADVAIR HFA, just skip that dose. Take your next dose at your usual
1438 time. Do not take 2 doses at one time.

1439 • **While you are using ADVAIR HFA twice a day, do not use other medicines that contain**
1440 **a LABA for any reason. Other LABA-containing medicines include ADVAIR DISKUS[®]**
1441 **(fluticasone propionate and salmeterol inhalation powder), SEREVENT[®] DISKUS[®]**
1442 **(salmeterol xinafoate inhalation powder), FORADIL[®] AEROLIZER[®] (formoterol**
1443 **fumarate inhalation powder), SYMBICORT[®] (budesonide and formoterol fumarate**
1444 **dihydrate) Inhalation Aerosol, PERFOROMIST[™] (formoterol fumarate) Inhalation**
1445 **Solution, and BROVANA[™] (arformoterol tartrate) Inhalation Solution.**

1446 • Do not change or stop any of your medicines used to control or treat your breathing problems.
1447 Your healthcare provider will adjust your medicines as needed.

- 1448 • Make sure you always have a short-acting beta₂-agonist medicine with you. Use your
1449 short-acting beta₂-agonist medicine if you have breathing problems between doses of
1450 ADVAIR HFA.
- 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 beta₂-agonist medicine more often than usual
 - 1454 • your short-acting beta₂-agonist medicine does not work as well for you at relieving
1455 symptoms
 - 1456 • you need to use your short-acting beta₂-agonist medicine more than twice in 1 week
 - 1457 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers
1458 that are right for you.
 - 1459 • you have asthma and your symptoms do not improve after using ADVAIR HFA regularly
1460 for 1 week
- 1461

1462 **What are the possible side effects with ADVAIR HFA?**

1463 **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). In**
1464 **patients with asthma, LABA medicines, such as salmeterol, may increase the chance of**
1465 **death from asthma problems.** See “What is the most important information I should know
1466 about ADVAIR HFA?”

1467 **Other possible side effects with ADVAIR HFA include:**

- 1468 • **serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue;**
1469 **and breathing problems.** Call your healthcare provider or get emergency medical care if you
1470 get any symptoms of a serious allergic reaction.
- 1471 • **increased blood pressure**
- 1472 • **a fast and irregular heartbeat**
- 1473 • **chest pain**
- 1474 • **headache**
- 1475 • **tremor**
- 1476 • **nervousness**
- 1477 • **immune system effects and a higher chance for infections**
- 1478 • **lower bone mineral density.** This may be a problem for people who already have a higher
1479 chance for low bone density (osteoporosis).
- 1480 • **eye problems including glaucoma and cataracts.** You should have regular eye exams while
1481 using ADVAIR HFA.
- 1482 • **slowed growth in children.** A child’s growth should be checked often.
- 1483 • **throat irritation**
- 1484 • **pneumonia.** ADVAIR HFA contains the same medicine found in ADVAIR DISKUS.
1485 ADVAIR DISKUS is used to treat people with asthma and people with chronic obstructive
1486 pulmonary disease (COPD). People with COPD have a higher chance of getting pneumonia.

1487 ADVAIR DISKUS may increase the chance of getting pneumonia. ADVAIR HFA has not
1488 been studied in people with COPD.

1489 Common side effects of ADVAIR HFA include upper respiratory tract infection and
1490 headache.

1491 Tell your healthcare provider about any side effect that bothers you or that does not go away.

1492 These are not all the side effects with ADVAIR HFA. Ask your healthcare provider or
1493 pharmacist for more information.

1494 Call your doctor for medical advice about side effects. You may report side effects to FDA at
1495 1-800-FDA-1088.

1496

How should I store ADVAIR HFA?

1498 Store at room temperature with the mouthpiece down.

1499 **Contents Under Pressure:** Do not puncture. Do not use or store near heat or open flame.

1500 Exposure to temperatures above 120°F may cause bursting.

1501 Do not throw into fire or an incinerator.

1502 **Keep ADVAIR HFA and all medicines out of the reach of children.**

1503

General information about ADVAIR HFA

1505 Medicines are sometimes prescribed for purposes other than those listed in a Medication
1506 Guide. Do not use ADVAIR HFA for a condition for which it was not prescribed. Do not give
1507 your ADVAIR HFA to other people, even if they have the same condition that you have. It may
1508 harm them.

1509 This Medication Guide summarizes the most important information about ADVAIR HFA. If
1510 you would like more information, talk with your healthcare provider or pharmacist. You can ask
1511 your healthcare provider or pharmacist for information about ADVAIR HFA that was written for
1512 healthcare professionals. You can also contact the company that makes ADVAIR HFA (toll free)
1513 at 1-888-825-5249 or at www.advair.com.

1514

What are the ingredients in ADVAIR HFA?

1516 Active ingredients: fluticasone propionate, salmeterol xinafoate

1517 Inactive ingredient: propellant HFA-134a

1518

How to use your ADVAIR HFA

1520 **The parts of your ADVAIR HFA:**

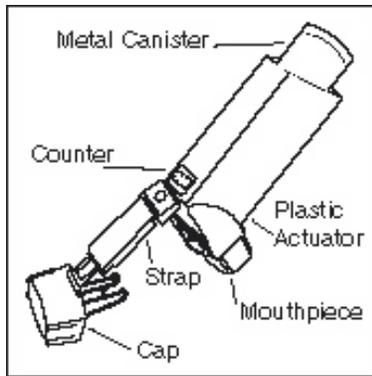


Figure 1

1523 There are 2 main parts to your ADVAIR HFA inhaler—
 1524 the metal canister that holds the medicine and the purple
 1525 plastic actuator that sprays the medicine from the canister
 1526 (see Figure 1).

1527 The inhaler also has a cap that covers the mouthpiece of
 1528 the actuator. The strap on the cap will stay attached to the
 1529 actuator.

1530 **Do not use the actuator with a canister of medicine**
 1531 **from any other inhaler. Do not use an ADVAIR HFA**
 1532 **canister with an actuator from any other inhaler.**

1521
 1522

1533 The canister has a counter to show how many sprays of medicine you have left. The number
 1534 shows through a window in the back of the actuator.

1535 The counter starts at 124, or at 64 if you have a sample canister. The number will count down
 1536 by 1 each time you spray the inhaler. The counter will stop counting at 000.

1537 **Never try to change the numbers or take the counter off the metal canister.** The counter
 1538 cannot be reset, and it is permanently attached to the canister.

1539 **Before using your ADVAIR HFA:**

1540 Take the inhaler out of the foil pouch. Safely throw away the foil pouch and the drying packet
 1541 that comes inside the pouch. The counter should read 124, or 64 if you have a sample canister.

1542 The inhaler should be at room temperature before you use it.

1543 Check each time to make sure the canister fits firmly in the plastic actuator. Also look into the
 1544 mouthpiece to make sure there are no foreign objects there, especially if the strap is no longer
 1545 attached to the actuator or if the cap is not being used to cover the mouthpiece.

1546 **Priming your ADVAIR HFA:**

1547 Before you use ADVAIR HFA for the first time, you must prime the inhaler so that you will
 1548 get the right amount of medicine when you use it. To prime the inhaler, take the cap off the
 1549 mouthpiece and shake the inhaler well for 5 seconds. Then spray it 1 time into the air away from
 1550 your face. Shake and spray the inhaler like this 3 more times to finish priming it. **Avoid**
 1551 **spraying in eyes.** The counter should now read 120, or 60 if you have a sample canister.

1552 You must prime your inhaler again if you have not used it in more than 4 weeks or if you have
 1553 dropped it. Take the cap off the mouthpiece, shake the inhaler well for 5 seconds, and spray it
 1554 into the air away from your face. Shake and spray the inhaler like this 1 more time to finish
 1555 priming it.

1556 **Instructions for taking a dose from your ADVAIR HFA:**

1557 Read through the 7 steps below before using ADVAIR HFA. If you have any questions, ask
 1558 your doctor or pharmacist.

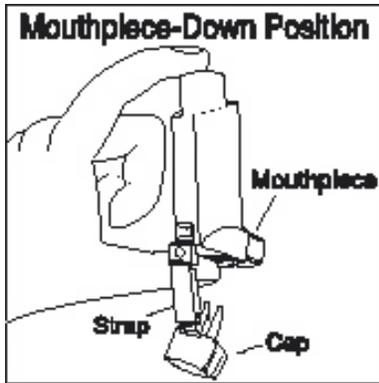


Figure 2

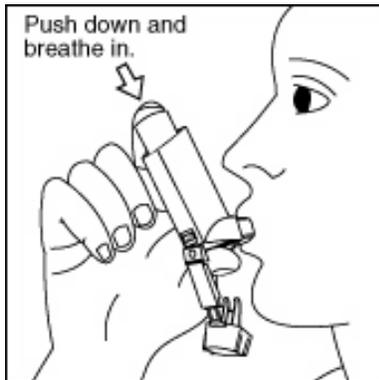


Figure 3

- 1564 1. Take the cap off the mouthpiece of the actuator. **Shake**
- 1565 **the inhaler well** for 5 seconds before each spray.
- 1566 2. Hold the inhaler with the mouthpiece down (see Figure
- 1567 2). **Breathe out through your mouth** and push as much
- 1568 air from your lungs as you can. Put the mouthpiece in
- 1569 your mouth and close your lips around it.
- 1570 3. **Push the top of the canister all the way down while**
- 1571 **you breathe in deeply and slowly through your**
- 1572 **mouth** (see Figure 3). Right after the spray comes out,
- 1573 take your finger off the canister. After you have breathed
- 1574 in all the way, take the inhaler out of your mouth and
- 1575 close your mouth.
- 1576 4. **Hold your breath as long as you can**, up to 10 seconds,
- 1577 then breathe normally.
- 1578 5. Wait about 30 seconds and **shake** the inhaler again for 5
- 1579 seconds. Repeat steps 2 through 4.
- 1580 6. After you finish taking this medicine, rinse your mouth
- 1581 with water. Spit out the water. Do not swallow it.
- 1582 7. Put the cap back on the mouthpiece after every time you
- 1583 use the inhaler, and make sure it snaps firmly into place.

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1584 **When to replace your ADVAIR HFA:**

- 1585 • **When the counter reads 020**, you should refill your prescription or ask your doctor if you
- 1586 need another prescription for ADVAIR HFA.
- 1587 • **Throw the inhaler away** when the counter reads 000. You should not keep using the inhaler
- 1588 when the counter reads 000 because you will not receive the right amount of medicine.
- 1589 • **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.

1590 **How to clean your ADVAIR HFA:**

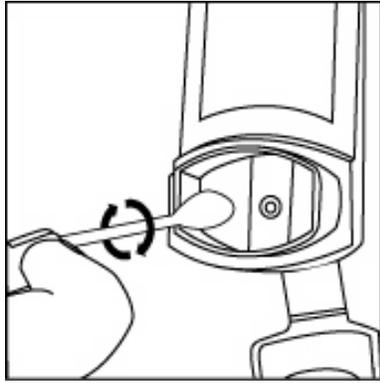


Figure 4

1593 Clean the inhaler at least once a week after your evening
1594 dose. It is important to keep the canister and plastic actuator
1595 clean so the medicine will not build-up and block the spray.

- 1596 1. Take the cap off the mouthpiece. The strap on the cap
1597 will stay attached to the actuator. Do not take the
1598 canister out of the plastic actuator.
1599 2. Use a dry cotton swab to clean the small circular
1600 opening where the medicine sprays out of the canister.
1601 Carefully twist the swab in a circular motion to take off
1602 any medicine (see Figure 4).
1603 3. Wipe the inside of the mouthpiece with a clean tissue
1604 dampened with water. Let the actuator air-dry overnight.
1605 4. Put the cap back on the mouthpiece after the actuator has
1606 dried.

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1592

1607

1608 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

1609

1610 April 2009

ADH:4MG

1611

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1613 VENTOLIN are registered trademarks of GlaxoSmithKline.

1614 The other brands listed are trademarks of their respective owners and are not trademarks of
1615 GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse
1616 GlaxoSmithKline or its products.

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1620 GlaxoSmithKline

1621 Research Triangle Park, NC 27709

1622

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1624

1625 April 2009

ADH:4PI

1626

PHARMACIST—DETACH HERE AND GIVE MEDICATION GUIDE TO PATIENT

1627

MEDICATION GUIDE

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

**ADVAIR[®] HFA 115/21 Inhalation Aerosol
(fluticasone propionate 115 mcg and salmeterol 21 mcg)**

**ADVAIR[®] HFA 230/21 Inhalation Aerosol
(fluticasone propionate 230 mcg and salmeterol 21 mcg)**

Read this Medication Guide carefully before you start to use ADVAIR HFA Inhalation Aerosol.

Keep this Medication Guide because it has important summary information about ADVAIR HFA. This Medication Guide does not contain all the information about your medicine. If you have any questions or are not sure about something, you should ask your doctor or pharmacist.

Read the new Medication Guide that comes with each refill of your prescription because there may be new information.

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

- **ADVAIR HFA contains 2 medicines:**
 - **fluticasone propionate (the same medicine found in FLOVENT[®]),** 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[®]),** a long-acting beta₂-agonist (LABA) medicine. 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 around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.
- **In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in ADVAIR HFA), may increase the chance of death from asthma problems.** In a large asthma study, more patients who used salmeterol died from asthma problems compared with patients who did not use salmeterol. It is not known whether fluticasone propionate, the other medicine in ADVAIR HFA, changes your chance of death from asthma problems seen with salmeterol. Talk with your healthcare provider about this risk and the benefits of treating your asthma with ADVAIR HFA.
- **ADVAIR HFA does not relieve sudden symptoms. Always have a short-acting beta₂-agonist medicine with you to treat sudden symptoms. If you do not have an**

1667 inhaled, short-acting bronchodilator, contact your healthcare provider to have one
1668 prescribed for you.

- 1669 • Do not stop using ADVAIR HFA unless told to do so by your healthcare provider
1670 because your symptoms might get worse.
- 1671 • ADVAIR HFA should be used only if your healthcare provider decides that another
1672 asthma-controller medicine alone does not control your asthma or that you need 2
1673 asthma-controller medicines.
- 1674 • Call your healthcare provider if breathing problems worsen over time while using
1675 ADVAIR HFA. You may need different treatment.
- 1676 • Get emergency medical care if:
 - 1677 • breathing problems worsen quickly, and
 - 1678 • you use your short-acting beta₂-agonist medicine, but it does not relieve your
1679 breathing problems.

1680

1681 **What is ADVAIR HFA?**

1682 ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate (the same
1683 medicine found in FLOVENT) and a LABA medicine, salmeterol (the same medicine found in
1684 SEREVENT).

1685 ADVAIR HFA is used long term, twice a day to control symptoms of asthma, and prevent
1686 symptoms such as wheezing in adults and adolescents 12 years of age and older.

1687 **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). Because**
1688 **LABA medicines, such as salmeterol, may increase the chance of death from asthma**
1689 **problems, ADVAIR HFA is not for adults and children with asthma who:**

- 1690 • are well controlled with another asthma-controller medicine, such as a low to medium dose
1691 of an inhaled corticosteroid medicine
- 1692 • only need short-acting beta₂-agonist medicines once in awhile

1693

1694 **Who should not use ADVAIR HFA?**

1695 Do not use ADVAIR HFA:

- 1696 • to treat sudden severe symptoms of asthma
- 1697 • if you are allergic to any of the ingredients in ADVAIR HFA. See the end of this Medication
1698 Guide for a list of ingredients in ADVAIR HFA.

1699

1700 **What should I tell my healthcare provider before using ADVAIR HFA?**

1701 **Tell your healthcare provider about all of your health conditions, including if you:**

- 1702 • have heart problems
- 1703 • have high blood pressure
- 1704 • have seizures
- 1705 • have thyroid problems

- 1706 • **have diabetes**
- 1707 • **have liver problems**
- 1708 • **have osteoporosis**
- 1709 • **have an immune system problem**
- 1710 • **are pregnant or planning to become pregnant.** It is not known if ADVAIR HFA may harm
- 1711 your unborn baby.
- 1712 • **are breastfeeding.** It is not known if ADVAIR HFA passes into your milk and if it can harm
- 1713 your baby.
- 1714 • **are allergic to ADVAIR HFA or any other medicines**
- 1715 • **are exposed to chickenpox or measles**
- 1716 Tell your healthcare provider about all the medicines you take including prescription and
- 1717 non-prescription medicines, vitamins, and herbal supplements. ADVAIR HFA and certain other
- 1718 medicines may interact with each other. This may cause serious side effects. Especially, tell your
- 1719 healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR[®] (ritonavir capsules)
- 1720 Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA[®] (lopinavir/ritonavir) Tablets
- 1721 contain ritonavir.
- 1722 Know the medicines you take. Keep a list and show it to your healthcare provider and
- 1723 pharmacist each time you get a new medicine.
- 1724

How do I use ADVAIR HFA?

- 1726 **See the step-by-step instructions for using ADVAIR HFA at the end of this Medication**
- 1727 **Guide.** Do not use ADVAIR HFA unless your healthcare provider has taught you and you
- 1728 understand everything. Ask your healthcare provider or pharmacist if you have any questions.
- 1729 • Use ADVAIR HFA exactly as prescribed. **Do not use ADVAIR HFA more often than**
- 1730 **prescribed.** ADVAIR HFA comes in 3 strengths. Your healthcare provider has prescribed the
- 1731 one that is best for your condition.
- 1732 • The usual dose of ADVAIR HFA is 2 inhalations twice a day (morning and evening). The 2
- 1733 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR
- 1734 HFA.
- 1735 • If you miss a dose of ADVAIR HFA, just skip that dose. Take your next dose at your usual
- 1736 time. Do not take 2 doses at one time.
- 1737 • **While you are using ADVAIR HFA twice a day, do not use other medicines that contain**
- 1738 **a LABA for any reason. Other LABA-containing medicines include ADVAIR DISKUS[®]**
- 1739 **(fluticasone propionate and salmeterol inhalation powder), SEREVENT[®] DISKUS[®]**
- 1740 **(salmeterol xinafoate inhalation powder), FORADIL[®] AEROLIZER[®] (formoterol**
- 1741 **fumarate inhalation powder), SYMBICORT[®] (budesonide and formoterol fumarate**
- 1742 **dihydrate) Inhalation Aerosol, PERFOROMIST[™] (formoterol fumarate) Inhalation**
- 1743 **Solution, and BROVANA[™] (arformoterol tartrate) Inhalation Solution.**

- 1744 • Do not change or stop any of your medicines used to control or treat your breathing problems.
1745 Your healthcare provider will adjust your medicines as needed.
- 1746 • Make sure you always have a short-acting beta₂-agonist medicine with you. Use your
1747 short-acting beta₂-agonist medicine if you have breathing problems between doses of
1748 ADVAIR HFA.
- 1749 • **Call your healthcare provider or get medical care right away if:**
- 1750 • your breathing problems worsen with ADVAIR HFA
 - 1751 • you need to use your short-acting beta₂-agonist medicine more often than usual
 - 1752 • your short-acting beta₂-agonist medicine does not work as well for you at relieving
1753 symptoms
 - 1754 • you need to use your short-acting beta₂-agonist medicine more than twice in 1 week
 - 1755 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers
1756 that are right for you.
 - 1757 • you have asthma and your symptoms do not improve after using ADVAIR HFA regularly
1758 for 1 week
 - 1759

What are the possible side effects with ADVAIR HFA?

1761 **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). In**
1762 **patients with asthma, LABA medicines, such as salmeterol, may increase the chance of**
1763 **death from asthma problems.** See “What is the most important information I should know
1764 about ADVAIR HFA?”

Other possible side effects with ADVAIR HFA include:

- 1766 • **serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue;**
1767 **and breathing problems.** Call your healthcare provider or get emergency medical care if you
1768 get any symptoms of a serious allergic reaction.
- 1769 • **increased blood pressure**
- 1770 • **a fast and irregular heartbeat**
- 1771 • **chest pain**
- 1772 • **headache**
- 1773 • **tremor**
- 1774 • **nervousness**
- 1775 • **immune system effects and a higher chance for infections**
- 1776 • **lower bone mineral density.** This may be a problem for people who already have a higher
1777 chance for low bone density (osteoporosis).
- 1778 • **eye problems including glaucoma and cataracts.** You should have regular eye exams while
1779 using ADVAIR HFA.
- 1780 • **slowed growth in children.** A child’s growth should be checked often.
- 1781 • **throat irritation**

1782 • **pneumonia.** ADVAIR HFA contains the same medicine found in ADVAIR DISKUS.
1783 ADVAIR DISKUS is used to treat people with asthma and people with chronic obstructive
1784 pulmonary disease (COPD). People with COPD have a higher chance of getting pneumonia.
1785 ADVAIR DISKUS may increase the chance of getting pneumonia. ADVAIR HFA has not
1786 been studied in people with COPD.
1787 Common side effects of ADVAIR HFA include upper respiratory tract infection and
1788 headache.
1789 Tell your healthcare provider about any side effect that bothers you or that does not go away.
1790 These are not all the side effects with ADVAIR HFA. Ask your healthcare provider or
1791 pharmacist for more information.
1792 Call your doctor for medical advice about side effects. You may report side effects to FDA at
1793 1-800-FDA-1088.

1794

How should I store ADVAIR HFA?

1796 Store at room temperature with the mouthpiece down.
1797 **Contents Under Pressure:** Do not puncture. Do not use or store near heat or open flame.
1798 Exposure to temperatures above 120°F may cause bursting.
1799 Do not throw into fire or an incinerator.
1800 **Keep ADVAIR HFA and all medicines out of the reach of children.**

1801

General information about ADVAIR HFA

1803 Medicines are sometimes prescribed for purposes other than those listed in a Medication
1804 Guide. Do not use ADVAIR HFA for a condition for which it was not prescribed. Do not give
1805 your ADVAIR HFA to other people, even if they have the same condition that you have. It may
1806 harm them.
1807 This Medication Guide summarizes the most important information about ADVAIR HFA. If
1808 you would like more information, talk with your healthcare provider or pharmacist. You can ask
1809 your healthcare provider or pharmacist for information about ADVAIR HFA that was written for
1810 healthcare professionals. You can also contact the company that makes ADVAIR HFA (toll free)
1811 at 1-888-825-5249 or at www.advair.com.

1812

What are the ingredients in ADVAIR HFA?

1814 Active ingredients: fluticasone propionate, salmeterol xinafoate
1815 Inactive ingredient: propellant HFA-134a

1816

How to use your ADVAIR HFA

1818 **The parts of your ADVAIR HFA:**

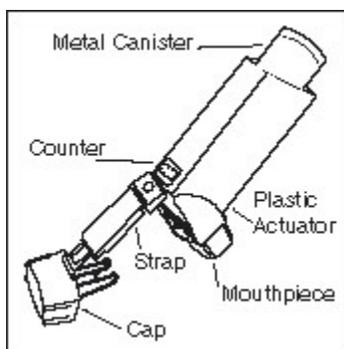


Figure 1

1821 There are 2 main parts to your ADVAIR HFA inhaler—
 1822 the metal canister that holds the medicine and the purple
 1823 plastic actuator that sprays the medicine from the canister
 1824 (see Figure 1).

1825 The inhaler also has a cap that covers the mouthpiece of
 1826 the actuator. The strap on the cap will stay attached to the
 1827 actuator.

1828 **Do not use the actuator with a canister of medicine**
 1829 **from any other inhaler. Do not use an ADVAIR HFA**
 1830 **canister with an actuator from any other inhaler.**

1819

1820

1831 The canister has a counter to show how many sprays of medicine you have left. The number
 1832 shows through a window in the back of the actuator.

1833 The counter starts at 124, or at 64 if you have a sample canister. The number will count down
 1834 by 1 each time you spray the inhaler. The counter will stop counting at 000.

1835 **Never try to change the numbers or take the counter off the metal canister.** The counter
 1836 cannot be reset, and it is permanently attached to the canister.

1837 **Before using your ADVAIR HFA:**

1838 Take the inhaler out of the foil pouch. Safely throw away the foil pouch and the drying packet
 1839 that comes inside the pouch. The counter should read 124, or 64 if you have a sample canister.

1840 The inhaler should be at room temperature before you use it.

1841 Check each time to make sure the canister fits firmly in the plastic actuator. Also look into the
 1842 mouthpiece to make sure there are no foreign objects there, especially if the strap is no longer
 1843 attached to the actuator or if the cap is not being used to cover the mouthpiece.

1844 **Priming your ADVAIR HFA:**

1845 Before you use ADVAIR HFA for the first time, you must prime the inhaler so that you will
 1846 get the right amount of medicine when you use it. To prime the inhaler, take the cap off the
 1847 mouthpiece and shake the inhaler well for 5 seconds. Then spray it 1 time into the air away from
 1848 your face. Shake and spray the inhaler like this 3 more times to finish priming it. **Avoid**
 1849 **spraying in eyes.** The counter should now read 120, or 60 if you have a sample canister.

1850 You must prime your inhaler again if you have not used it in more than 4 weeks or if you have
 1851 dropped it. Take the cap off the mouthpiece, shake the inhaler well for 5 seconds, and spray it
 1852 into the air away from your face. Shake and spray the inhaler like this 1 more time to finish
 1853 priming it.

1854 **Instructions for taking a dose from your ADVAIR HFA:**

1855 Read through the 7 steps below before using ADVAIR HFA. If you have any questions, ask
 1856 your doctor or pharmacist.

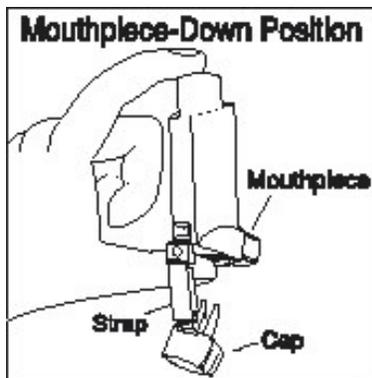


Figure 2

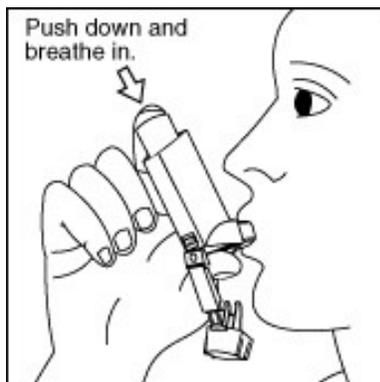


Figure 3

- 1862 1. Take the cap off the mouthpiece of the actuator. **Shake**
- 1863 **the inhaler well** for 5 seconds before each spray.
- 1864 2. Hold the inhaler with the mouthpiece down (see Figure
- 1865 2). **Breathe out through your mouth** and push as much
- 1866 air from your lungs as you can. Put the mouthpiece in
- 1867 your mouth and close your lips around it.
- 1868 3. **Push the top of the canister all the way down while**
- 1869 **you breathe in deeply and slowly through your**
- 1870 **mouth** (see Figure 3). Right after the spray comes out,
- 1871 take your finger off the canister. After you have breathed
- 1872 in all the way, take the inhaler out of your mouth and
- 1873 close your mouth.
- 1874 4. **Hold your breath as long as you can**, up to 10 seconds,
- 1875 then breathe normally.
- 1876 5. Wait about 30 seconds and **shake** the inhaler again for 5
- 1877 seconds. Repeat steps 2 through 4.
- 1878 6. After you finish taking this medicine, rinse your mouth
- 1879 with water. Spit out the water. Do not swallow it.
- 1880 7. Put the cap back on the mouthpiece after every time you
- 1881 use the inhaler, and make sure it snaps firmly into place.

When to replace your ADVAIR HFA:

- 1882 • **When the counter reads 020**, you should refill your prescription or ask your doctor if you
- 1883 need another prescription for ADVAIR HFA.
- 1884 • **Throw the inhaler away** when the counter reads **000**. You should not keep using the inhaler
- 1885 when the counter reads 000 because you will not receive the right amount of medicine.
- 1886 • **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.

How to clean your ADVAIR HFA:

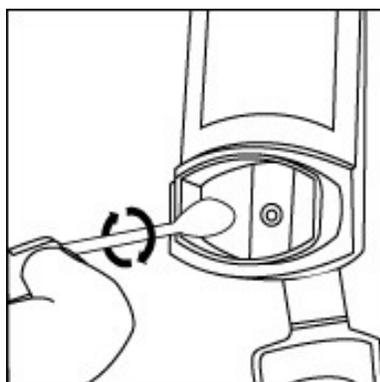


Figure 4

- 1891 Clean the inhaler at least once a week after your evening
- 1892 dose. It is important to keep the canister and plastic actuator
- 1893 clean so the medicine will not build-up and block the spray.
- 1894 1. Take the cap off the mouthpiece. The strap on the cap
- 1895 will stay attached to the actuator. Do not take the
- 1896 canister out of the plastic actuator.
- 1897 2. Use a dry cotton swab to clean the small circular
- 1898 opening where the medicine sprays out of the canister.
- 1899 Carefully twist the swab in a circular motion to take off
- 1900 any medicine (see Figure 4).

- 1901 3. Wipe the inside of the mouthpiece with a clean tissue
1902 dampened with water. Let the actuator air-dry overnight.
1903 4. Put the cap back on the mouthpiece after the actuator has
1904 dried.

1905

1906 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

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