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RESEARCH**

APPLICATION NUMBER:

NDA 21-254

LABELING

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**

13
14 *As salmeterol xinafoate salt 30.45 mcg, equivalent to salmeterol base 21 mcg

15
16 **For Oral Inhalation Only**

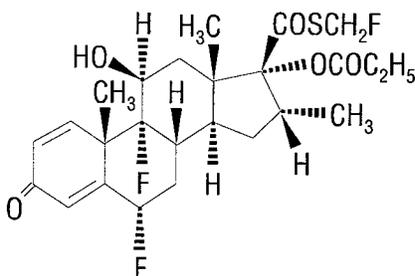
17 **WARNING**

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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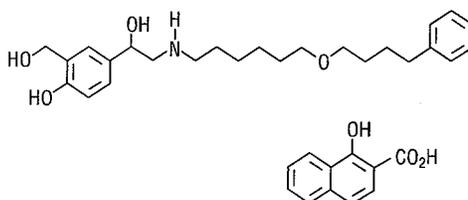


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38 Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and
39 the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in
40 dimethyl sulfoxide and dimethylformamide, and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



47
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49 Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8, and the
50 empirical formula is $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in
51 ethanol, 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 intended
54 for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone
55 propionate (micronized) and salmeterol xinafoate (micronized) in propellant HFA-134a
56 (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 and 45, 115, or 230 mcg, ~~respectively,~~ of fluticasone propionate and 21 mcg of
60 salmeterol from the actuator in 75 mg of suspension from the actuator. Twenty-one micrograms
61 (21 mcg) of salmeterol base is equivalent to 30.45 mcg of salmeterol xinafoate. The actual
62 amount of drug delivered to the lung may depend on patient factors, such as the coordination
63 between the actuation of the device and inspiration through the 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 shaking well before each spray and releasing 2 test sprays into the air away from the
69 face.

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

71 CLINICAL PHARMACOLOGY

72 **Mechanism of Action: ADVAIR HFA Inhalation Aerosol:** Since ADVAIR HFA contains
73 both fluticasone propionate and salmeterol, the mechanisms of action described below for the
74 individual components apply to ADVAIR HFA. These drugs represent 2 classes of medications
75 (a synthetic corticosteroid and a selective, long-acting 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 adenyl 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 to individual inhalers.

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

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

152 Absolute bioavailability of fluticasone propionate from ADVAIR HFA in 15 healthy subjects
153 was 5.3%. Terminal half-life estimates of fluticasone propionate for ADVAIR HFA, ADVAIR
154 DISKUS, and fluticasone propionate CFC inhalation aerosol were similar and averaged
155 5.9 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 highly potent 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 potent cytochrome P450 3A4 inhibitors are
214 coadministered with fluticasone propionate. In a drug interaction study, coadministration of
215 orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted
216 in increased systemic fluticasone propionate exposure and reduced plasma cortisol AUC, but had
217 no effect on urinary excretion of cortisol.

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

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

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

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

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

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

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

243 **Pharmacodynamics: ADVAIR HFA Inhalation Aerosol:** Since systemic
244 pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher
245 doses were used to produce measurable effects. Four placebo-controlled, crossover studies were
246 conducted in healthy subjects: (1) a cumulative-dose study using 42 to 336 mcg of salmeterol
247 CFC inhalation aerosol given alone or as ADVAIR HFA 115/21, (2) a single-dose study using
248 4 inhalations of ADVAIR HFA 230/21, salmeterol CFC inhalation aerosol 21 mcg, or
249 fluticasone propionate CFC inhalation aerosol 220 mcg, (3) a single-dose study using
250 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, or ADVAIR HFA 230/21, and (4)
251 a single-dose study using 4 inhalations of ADVAIR HFA 230/21; 2 inhalations of ADVAIR
252 DISKUS 500/50; 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg; or
253 1,010 mcg of fluticasone propionate given intravenously. In these studies pulse rate, blood
254 pressure, QTc interval, glucose, and/or potassium were measured. Comparable or lower effects
255 were observed for ADVAIR HFA compared to ADVAIR DISKUS or salmeterol alone. The
256 effect of salmeterol on pulse rate and potassium was not altered by the presence of different
257 amounts of fluticasone propionate in ADVAIR HFA. The potential effect of salmeterol on the
258 effects of fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis was also
259 evaluated in 3 of these studies. Compared with fluticasone propionate CFC inhalation aerosol,
260 ADVAIR HFA had less effect on 24-hour urinary cortisol excretion and less or comparable

261 effect on 24-hour serum cortisol. In these crossover studies in healthy subjects, ADVAIR HFA
262 and ADVAIR DISKUS had similar effects on urinary and serum cortisol.

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

270 A 4-way crossover study in 13 patients with asthma compared pharmacodynamics at steady
271 state following 4 weeks of twice-daily treatment with 2 inhalations of ADVAIR HFA 115/21,
272 1 inhalation of ADVAIR DISKUS 250/50 mcg, 2 inhalations of fluticasone propionate HFA
273 inhalation aerosol 110 mcg, and placebo. No significant differences in serum cortisol AUC were
274 observed between active treatments and placebo. Mean 12-hour serum cortisol AUC ratios
275 comparing active treatment with placebo ranged from 0.9 to 1.2. No statistically or clinically
276 significant increases in heart rate or QTc interval were observed for any active treatment
277 compared with placebo.

278 In a 12-week study (see CLINICAL TRIALS: Studies Comparing ADVAIR HFA to
279 Fluticasone Propionate Alone or Salmeterol Alone: *Study 3*) in patients with asthma,
280 ADVAIR HFA 115/21 was compared with the individual components, fluticasone propionate
281 CFC inhalation aerosol 110 mcg and salmeterol CFC inhalation aerosol 21 mcg, and placebo. All
282 treatments were administered as 2 inhalations twice daily. After 12 weeks of treatment with these
283 therapeutic doses, the geometric mean ratio of urinary cortisol excretion compared with baseline
284 was 0.9 for ADVAIR HFA and fluticasone propionate and 1.0 for placebo and salmeterol. In
285 addition, the ability to increase cortisol production in response to stress, as assessed by
286 30-minute cosyntropin stimulation in 23 to 32 patients per treatment group, remained intact for
287 the majority of patients and was similar across treatments. Three patients who received
288 ADVAIR HFA 115/21 had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing,
289 compared with 1 patient who received placebo, 2 patients who received fluticasone propionate
290 110 mcg, and 1 patient who received salmeterol.

291 In another 12-week study (see CLINICAL TRIALS: Studies Comparing ADVAIR HFA to
292 Fluticasone Propionate Alone or Salmeterol Alone: *Study 4*) in patients with asthma,
293 ADVAIR HFA 230/21 (2 inhalations twice daily) was compared with ADVAIR DISKUS 500/50
294 (1 inhalation twice daily) and fluticasone propionate CFC inhalation aerosol 220 mcg
295 (2 inhalations twice daily). The geometric mean ratio of 24-hour urinary cortisol excretion at
296 week 12 compared with baseline was 0.9 for all 3 treatment groups.

297 **Fluticasone Propionate:** In clinical trials with fluticasone propionate inhalation powder
298 using doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin
299 tests (peak serum cortisol <18 mcg/dL) were noted both in patients receiving fluticasone
300 propionate and in patients receiving placebo. The incidence of abnormal tests at 500 mcg twice

301 daily was greater than placebo. In a 2-year study carried out in 64 patients with mild, persistent
302 asthma (mean FEV1 91% of predicted) randomized to fluticasone propionate 500 mcg twice
303 daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6-hour
304 cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of
305 <35 mcg/dL, 1 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year,
306 repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone
307 propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal
308 response at 1 or 2 years.

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

314 The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol were
315 studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg resulted in
316 heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by
317 inhalation aerosol (4 to 10 beats/min). In 2 double-blind asthma studies, patients receiving either
318 42 mcg of salmeterol inhalation aerosol twice daily (n = 81) or 180 mcg of albuterol inhalation
319 aerosol 4 times daily (n = 80) underwent continuous electrocardiographic monitoring during four
320 24-hour periods; no clinically significant dysrhythmias were noted.

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

325 **CLINICAL TRIALS**

326 ADVAIR HFA has been studied in patients with asthma 12 years of age and older.

327 ADVAIR HFA has not been studied in patients under 12 years of age or in patients with COPD.

328 In clinical trials comparing ADVAIR HFA Inhalation Aerosol with the individual components,
329 improvements in most efficacy endpoints were greater with ADVAIR HFA than with the use of
330 either fluticasone propionate or salmeterol alone. In addition, clinical trials showed comparable
331 results between ADVAIR HFA and ADVAIR DISKUS.

332 **Studies Comparing ADVAIR HFA to Fluticasone Propionate Alone or Salmeterol**
333 **Alone:** Four (4) double-blind, parallel-group clinical trials were conducted with ADVAIR HFA
334 in 1,517 adolescent and adult patients (≥12 years, mean baseline forced expiratory volume in
335 1 second [FEV₁] 65% to 75% of predicted normal) with asthma that was not optimally controlled
336 on their current therapy. All metered-dose inhaler treatments were inhalation aerosols given as
337 2 inhalations twice daily, and other maintenance therapies were discontinued.

338 **Study 1: Clinical Trial With ADVAIR HFA 45/21 Inhalation Aerosol:** This
339 placebo-controlled, 12-week, US study compared ADVAIR HFA 45/21 with fluticasone

340 propionate CFC inhalation aerosol 44 mcg or salmeterol CFC inhalation aerosol 21 mcg, each
 341 given as 2 inhalations twice daily. The primary efficacy endpoints were predose FEV₁ and
 342 withdrawals due to worsening asthma. This study was stratified according to baseline asthma
 343 therapy: patients using beta-agonists (albuterol alone [n = 142], salmeterol [n = 84], or inhaled
 344 corticosteroids [n = 134] [daily doses of beclomethasone dipropionate 252 to 336 mcg;
 345 budesonide 400 to 600 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol
 346 176 mcg; fluticasone propionate inhalation powder 200 mcg; or triamcinolone acetonide 600 to
 347 800 mcg]). Baseline FEV₁ measurements were similar across treatments: ADVAIR HFA 45/21,
 348 2.29 L; fluticasone propionate 44 mcg, 2.20 L; salmeterol, 2.33 L; and placebo, 2.27 L.

349 Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were
 350 utilized for this placebo-controlled study. Worsening asthma was defined as a clinically
 351 important decrease in FEV₁ or peak expiratory flow (PEF), increase in use of VENTOLIN®
 352 (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency
 353 intervention or hospitalization due to asthma, or requirement for asthma medication not allowed
 354 by the protocol. As shown in Table 1, statistically significantly fewer patients receiving
 355 ADVAIR HFA 45/21 were withdrawn due to worsening asthma compared with salmeterol and
 356 placebo. Fewer patients receiving ADVAIR HFA 45/21 were withdrawn due to worsening
 357 asthma compared to fluticasone propionate 44 mcg; however, the difference was not statistically
 358 significant.

359

360 **Table 1. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously**
 361 **Treated With Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids**
 362 **(Study 1)**

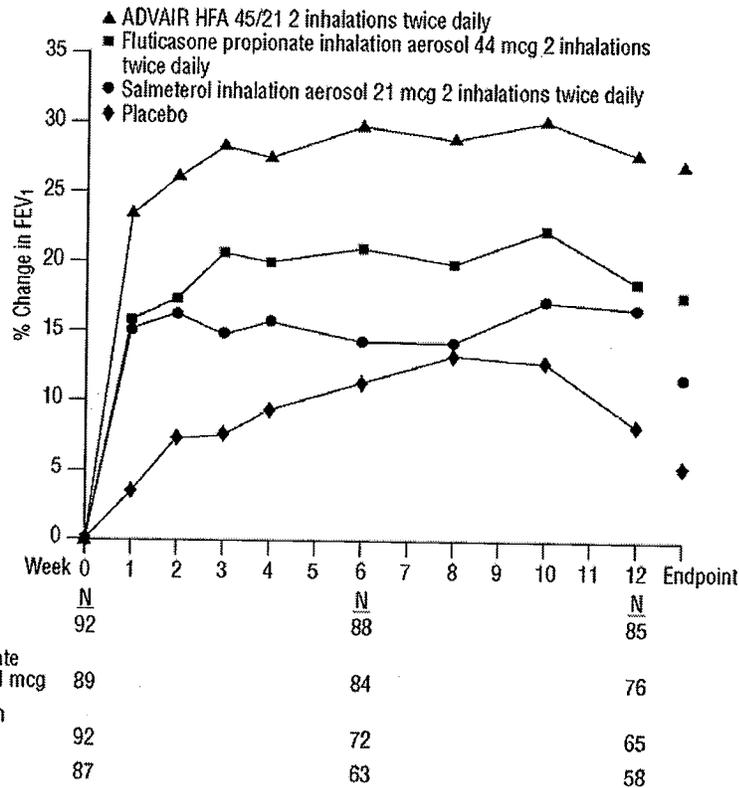
ADVAIR HFA 45/21 (n = 92)	Fluticasone Propionate CFC Inhalation Aerosol 44 mcg (n = 89)	Salmeterol CFC Inhalation Aerosol 21 mcg (n = 92)	Placebo HFA Inhalation Aerosol (n = 87)
2%	8%	25%	28%

363

364 The FEV₁ results are displayed in Figure 1. Because this trial used predetermined criteria for
 365 worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV₁
 366 results at Endpoint (last available FEV₁ result) are also provided. Patients receiving ADVAIR
 367 HFA 45/21 had significantly greater improvements in FEV₁ (0.58 L, 27%) compared with
 368 fluticasone propionate 44 mcg (0.36 L, 18%), salmeterol (0.25 L, 12%), and placebo (0.14 L,
 369 5%). These improvements in FEV₁ with ADVAIR HFA 45/21 were achieved regardless of
 370 baseline asthma therapy (albuterol alone, salmeterol, or inhaled corticosteroids).

371

372 **Figure 1. Mean Percent Change From Baseline in FEV₁ in Patients**
 373 **Previously Treated With Either Beta₂-Agonists (Albuterol or**
 374 **Salmeterol) or Inhaled Corticosteroids (Study 1)**
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The effect of ADVAIR HFA 45/21 on the secondary efficacy parameters, including morning and evening PEF, usage of VENTOLIN Inhalation Aerosol, and asthma symptoms over 24 hours on a scale of 0 to 5 is shown in Table 2.

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Table 2. Secondary Efficacy Variable Results for Patients Previously Treated With 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

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

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

388

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

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

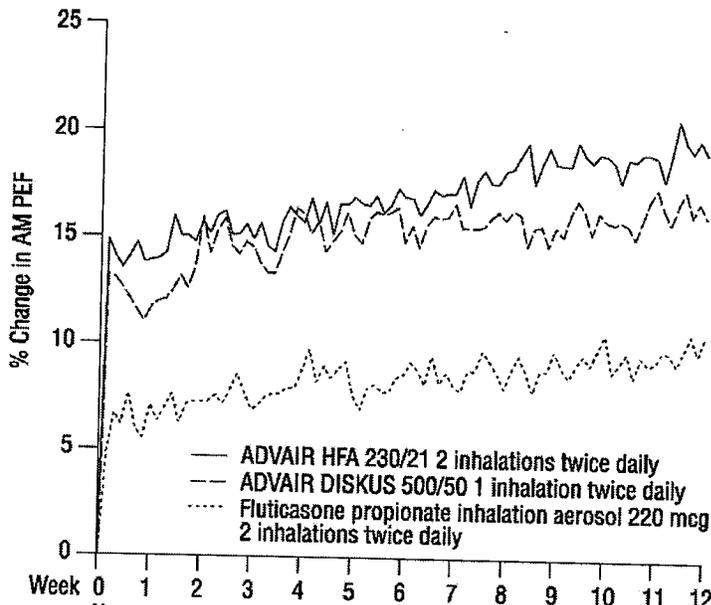
403 **Study 3: Clinical Trial With ADVAIR HFA 115/21 Inhalation Aerosol:** This
404 placebo-controlled, 12-week, US study compared ADVAIR HFA 115/21 with fluticasone
405 propionate CFC inhalation aerosol 110 mcg or salmeterol CFC inhalation aerosol 21 mcg, each
406 given as 2 inhalations twice daily, in 365 patients using inhaled corticosteroids (daily doses of
407 beclomethasone dipropionate 378 to 840 mcg; budesonide 800 to 1,200 mcg; flunisolide 1,250 to
408 2,000 mcg; fluticasone propionate inhalation aerosol 440 to 660 mcg; fluticasone propionate
409 inhalation powder 400 to 600 mcg; or triamcinolone acetonide 900 to 1,600 mcg). The primary
410 efficacy endpoints were predose FEV₁ and withdrawals due to worsening asthma. Baseline FEV₁
411 measurements were similar across treatments: ADVAIR HFA 115/21, 2.23 L; fluticasone
412 propionate 110 mcg, 2.18 L; salmeterol, 2.22 L; and placebo, 2.17 L.

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

421 **Study 4: Clinical Trial With ADVAIR HFA 230/21 Inhalation Aerosol:** This
422 active-controlled, 12-week, non-US study compared ADVAIR HFA 230/21 with fluticasone
423 propionate CFC inhalation aerosol 220 mcg, each given as 2 inhalations twice daily, and with
424 ADVAIR DISKUS 500/50 given as 1 inhalation twice daily in 509 patients using inhaled
425 corticosteroids (daily doses of beclomethasone dipropionate CFC inhalation aerosol 1,500 to
426 2,000 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; fluticasone
427 propionate inhalation aerosol 660 to 880 mcg; or fluticasone propionate inhalation powder 750 to
428 1,000 mcg). The primary efficacy endpoint was morning PEF.

429 Baseline morning PEF measurements (~~primary efficacy parameter~~) were similar across
430 treatments: ADVAIR HFA 230/21, 327 L/min; ADVAIR DISKUS 500/50, 341 L/min; and
431 fluticasone propionate 220 mcg, 345 L/min. As shown in Figure 2, morning PEF improved
432 significantly with ADVAIR HFA 230/21 compared with fluticasone propionate 220 mcg over
433 the 12-week treatment period. Improvements in morning PEF observed with ADVAIR HFA
434 230/21 were similar to improvements observed with ADVAIR DISKUS 500/50.
435

436 **Figure 2. Mean Percent Change From Baseline in Morning Peak**
 437 **Expiratory Flow in Patients Previously Treated With Inhaled**
 438 **Corticosteroids (Study 4)**
 439



	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

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

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

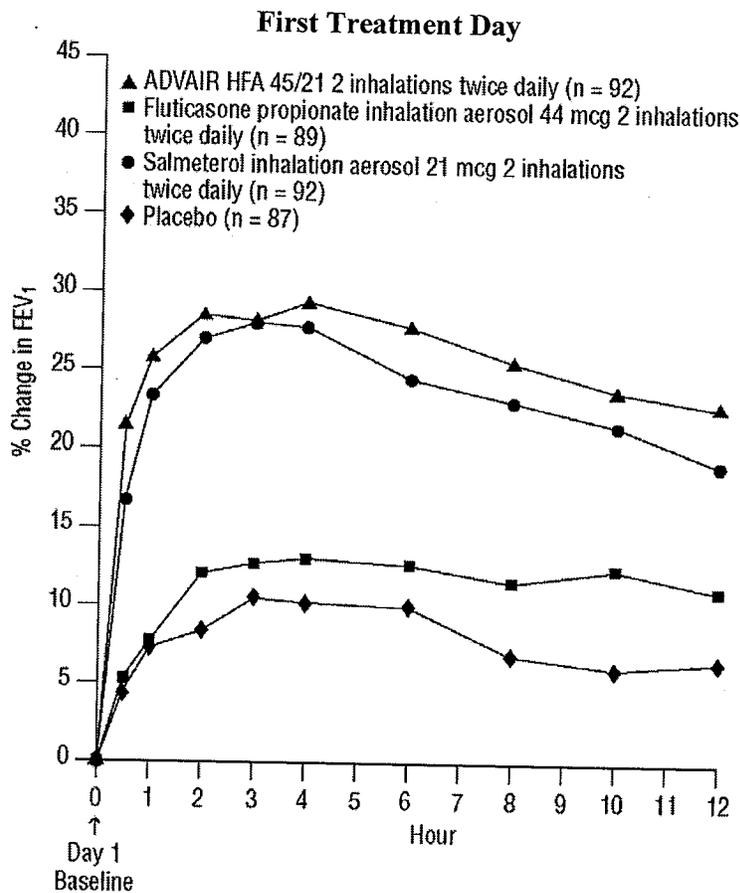
454 Improvements in FEV₁ (0.17 to 0.35 L at 4 weeks) were seen across all 3 treatments and were
 455 sustained throughout the 52-week treatment period. Few patients (3%) were withdrawn due to
 456 worsening asthma over 1 year.

457 **Onset of Action and Progression of Improvement in Asthma Control:** The onset of
 458 action and progression of improvement in asthma control were evaluated in 2 placebo-controlled
 459 US trials and 1 active-controlled US trial. Following the first dose, the median time to onset of
 460 clinically significant bronchodilatation ($\geq 15\%$ improvement in FEV₁) in most patients was seen
 461 within 30 to 60 minutes. Maximum improvement in FEV₁ occurred within 4 hours, and clinically
 462 significant improvement was maintained for 12 hours (see Figure 3).

463 Following the initial dose, predose FEV₁ relative to day 1 baseline improved markedly over
 464 the first week of treatment and continued to improve over the 12 weeks of treatment in all
 465 3 studies.

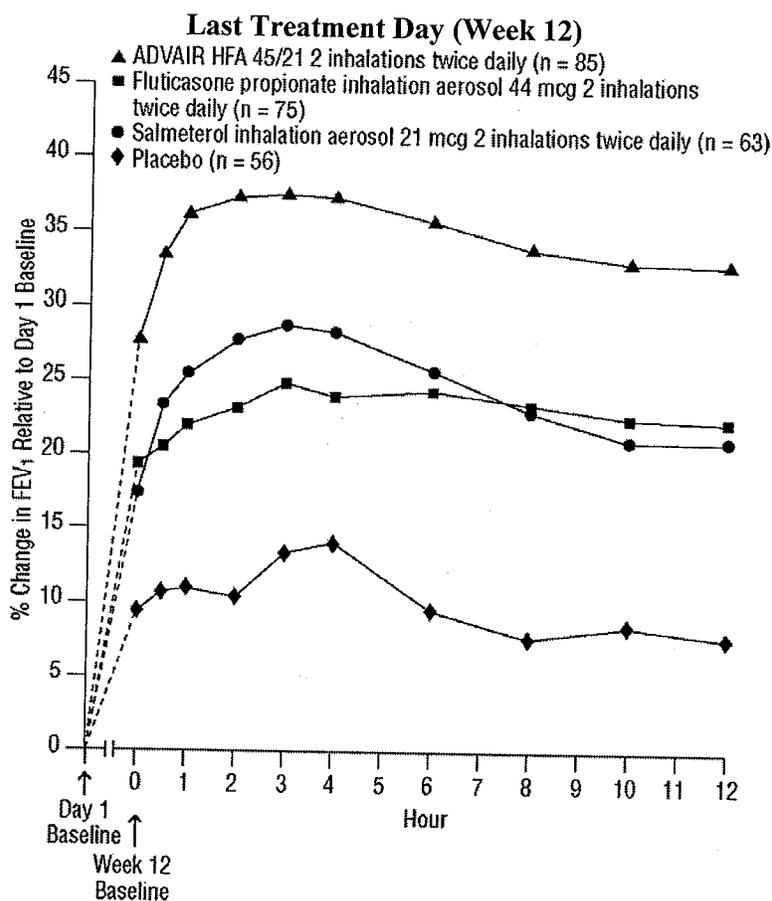
466 No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR HFA
 467 45/21 (Figures 3 and 4) or ADVAIR HFA 230/21 as assessed by FEV₁ following 12 weeks of
 468 therapy.

469
 470 **Figure 3. Percent Change in Serial 12-Hour FEV₁ in**
 471 **Patients Previously Using Either Beta₂-Agonists (Albuterol**
 472 **or Salmeterol) or Inhaled Corticosteroids (Study 1)**
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Figure 4. Percent Change in Serial 12-Hour FEV₁ in Patients Previously Using Either Beta₂-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)



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

487 **INDICATIONS AND USAGE**

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

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

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

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

499 **CONTRAINDICATIONS**

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

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

503 **WARNINGS**

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

510 A large placebo-controlled US study that compared the safety of salmeterol with placebo,
511 each added to usual asthma therapy, showed an increase in asthma-related deaths in patients
512 receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a
513 randomized, double-blind study that enrolled long-acting beta₂-agonist-naïve patients with
514 asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily
515 over 28 weeks compared to placebo when added to usual asthma therapy. A planned interim
516 analysis was conducted when approximately half of the intended number of patients had been
517 enrolled (N = 26,355), which led to premature termination of the study. The results of the interim
518 analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events
519 (see Table 3 and Figure 5). In the total population, a higher rate of asthma-related death occurred
520 in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%; relative risk
521 4.37 [95% CI 1.25, 15.34]).

522 Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death
523 occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo
524 (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also,
525 asthma-related death occurred at a higher rate in patients treated with salmeterol than those
526 treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the
527 relative risks of asthma-related death were similar in Caucasians and African Americans, the
528 estimate of excess deaths in patients treated with salmeterol was greater in African Americans
529 because there was a higher overall rate of asthma-related death in African American patients (see
530 Table 3). Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the
531 findings seen in the SMART study represent a class effect.

532 The data from the SMART study are not adequate to determine whether concurrent use of
 533 inhaled corticosteroids, such as fluticasone propionate, the other active ingredient in ADVAIR
 534 HFA, or other asthma-controller therapy modifies the risk of asthma-related death.
 535

536 **Table 3: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research**
 537 **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)

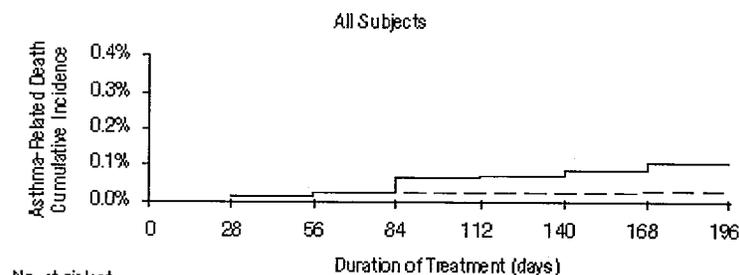
538 * Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to
 539 study treatment to account for early withdrawal of patients from the study.

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

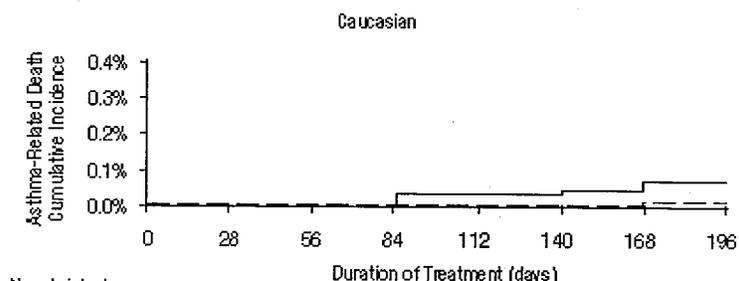
544 ‡ Estimate of the number of additional asthma-related deaths in patients treated with salmeterol
 545 in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period.
 546 Estimate calculated as the difference between the salmeterol and placebo groups in the rates of
 547 asthma-related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

548 § The Total Population includes the following ethnic origins listed on the case report form:
 549 Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population
 550 includes those patients whose ethnic origin was not reported. The results for Caucasian and
 551 African American subpopulations are shown above. No asthma-related deaths occurred in the
 552 Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149),
 553 or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death
 554 occurred in the placebo group in the subpopulation whose ethnic origin was not reported
 555 (salmeterol n = 130, placebo n = 127).
 556

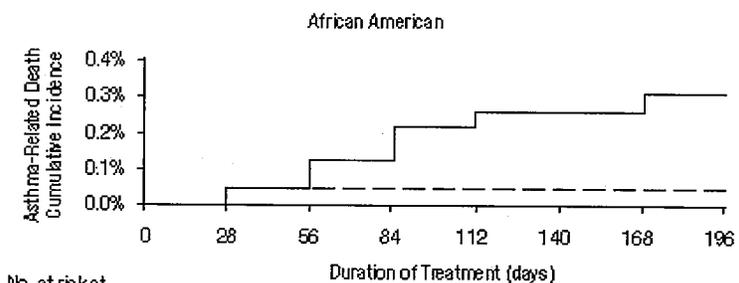
557 **Figure 5. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol**
 558 **Multi-center Asthma Research Trial (SMART), by Duration of Treatment**
 559



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



No. at risk at start of interval	0	28	56	84	112	140	168	196
— Salmeterol	9,281	9,202	9,020	8,860	8,699	8,503	8,271	
-- Placebo	9,361	9,266	9,053	8,884	8,722	8,546	8,330	



No. at risk at start of interval	0	28	56	84	112	140	168	196
— Salmeterol	2,366	2,351	2,271	2,201	2,114	2,048	1,972	
-- Placebo	2,319	2,303	2,225	2,156	2,078	2,023	1,963	

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562 A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide
 563 Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate
 564 of asthma-related death was numerically, though not statistically significantly, greater in patients
 565 with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol
 566 (180 mcg 4 times daily) added to usual asthma therapy.

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

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

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

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

591 3. Increasing use of inhaled short-acting beta₂-agonists is a marker of deteriorating asthma. The
592 physician and patient should be alert to such changes. The patient's condition may deteriorate
593 acutely over a period of hours or chronically over several days or longer. If the patient's inhaled,
594 short-acting beta₂-agonist becomes less effective, the patient needs more inhalations than usual,
595 or the patient develops a significant decrease in lung function, this may be a marker of
596 destabilization of the disease. In this setting, the patient requires immediate reevaluation with
597 reassessment of the treatment regimen, giving special consideration to the possible need for
598 replacing the current strength of ADVAIR HFA with a higher strength, adding additional inhaled
599 corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 1
600 inhalation twice daily (morning and evening) of ADVAIR HFA.

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

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

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

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

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

632 7. Paradoxical bronchospasm. As with other inhaled asthma medications, ADVAIR HFA can
633 produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm
634 occurs following dosing with ADVAIR HFA, it should be treated immediately with an inhaled,
635 short-acting bronchodilator, ADVAIR HFA should be discontinued immediately and alternative
636 therapy should be instituted.

637 8. Immediate hypersensitivity reactions. Immediate hypersensitivity reactions may occur after
638 administration of ADVAIR HFA, as demonstrated by cases of urticaria, angioedema, rash, and
639 bronchospasm.

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

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

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

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

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

666 13. Drug interaction with ritonavir. ~~[underlined] Drug interaction with ritonavir.~~ A drug
667 interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450
668 3A4 inhibitor) can significantly increase systemic fluticasone propionate exposure (AUC),
669 resulting in significantly reduced serum cortisol concentrations (see CLINICAL
670 PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug Interactions* and
671 PRECAUTIONS: Drug Interactions: *Inhibitors of Cytochrome P450*). During postmarketing use,
672 there have been reports of clinically significant drug interactions in patients receiving fluticasone
673 propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome
674 and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is
675 not recommended unless the potential benefit to the patient outweighs the risk of systemic
676 corticosteroid side effects.

677 **PRECAUTIONS**

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

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

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

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

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

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

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

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

720 It is possible that systemic corticosteroid effects such as hypercorticism and adrenal
721 suppression (including adrenal crisis) may appear in a small number of patients, particularly
722 when fluticasone propionate is administered at higher than recommended doses over prolonged
723 periods of time. If such effects occur, the dosage of ADVAIR HFA should be reduced slowly,

724 consistent with accepted procedures for reducing systemic corticosteroids and for management
725 of asthma.

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

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

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

742 Lower respiratory tract infections, including pneumonia, have been reported following the
743 inhaled administration of corticosteroids, including fluticasone propionate, a component of
744 ADVAIR HFA.

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

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

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

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

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

- 771 1. **Patients should be informed that salmeterol, one of the active ingredients in ADVAIR**
772 **HFA, may increase the risk of asthma-related death.** They should also be informed that
773 data are not adequate to determine whether the concurrent use of inhaled corticosteroids,
774 such as fluticasone propionate, the other component of ADVAIR HFA, or other
775 asthma-controller therapy modifies this risk.
- 776 2. ADVAIR HFA is not meant to relieve acute asthma symptoms and extra doses should not be
777 used for that purpose. Acute symptoms should be treated with an inhaled, short-acting
778 beta₂-agonist such as albuterol (the physician should provide the patient with such
779 medication and instruct the patient in how it should be used).
- 780 3. The physician should be notified immediately if any of the following signs of seriously
781 worsening asthma occur:
 - 782 • decreasing effectiveness of inhaled, short-acting beta₂-agonists;
 - 783 • need for more inhalations than usual of inhaled, short-acting beta₂-agonists;
 - 784 • significant decrease in lung function as outlined by the physician.
- 785 4. Patients should not stop therapy with ADVAIR HFA without physician/provider guidance
786 since symptoms may recur after discontinuation.
- 787 5. Patients should be cautioned regarding common adverse effects associated with
788 beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 789 6. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of
790 ADVAIR HFA, may increase the risk of some eye problems (cataracts or glaucoma). Regular
791 eye examinations should be considered.
- 792 7. When patients are prescribed ADVAIR HFA, other medications for asthma should be used
793 only as directed by the physician.
- 794 8. Patients who are pregnant or nursing should contact the physician about the use of ADVAIR
795 HFA.
- 796 9. Patients should use ADVAIR HFA at regular intervals as directed. Results of clinical trials
797 indicated significant improvement may occur within the first 30 minutes of taking the first
798 dose; however, the full benefit may not be achieved until treatment has been administered for
799 1 week or longer. The patient should not use more than the prescribed dosage but should
800 contact the physician if symptoms do not improve or if the condition worsens.
- 801 10. The bronchodilation from a single dose of ADVAIR HFA may last up to 12 hours or longer.
802 The recommended dosage (2 inhalations twice daily, morning and evening) should not be

803 exceeded. Patients who are receiving ADVAIR HFA twice daily should not use salmeterol or
804 other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of EIB or
805 maintenance treatment of asthma.

806 11. Patients should be warned to avoid exposure to chickenpox or measles and, if they are
807 exposed, to consult the physician without delay.

808 12. Prime the inhaler before using for the first time by releasing 4 test sprays into the air away
809 from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has
810 not been used for more than 4 weeks or when it has been dropped, prime the inhaler again by
811 shaking well before each spray and releasing 2 test sprays into the air away from the face.

812 13. After inhalation, rinse the mouth with water and spit out. Do not swallow.

813 14. Clean the inhaler at least once a week after the evening dose. Keeping the canister and plastic
814 actuator clean is important to prevent medicine build-up. (See Patient's Instructions for Use
815 leaflet accompanying the product.)

816 15. Use ADVAIR HFA only with the actuator supplied with the product. Discard the inhaler
817 after 120 sprays have been used.

818 16. Patients should never immerse the canister into water to determine the amount remaining in
819 the canister ("float test").

820 17-6.For the proper use of ADVAIR HFA and to attain maximum improvement, the patient
821 should read and carefully follow the Instructions for Using ADVAIR HFA in the Medication
822 Guide accompanying the product.

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

827 **Short-Acting Beta₂-Agonists:** In three 12-week US clinical trials, the mean daily need for
828 additional beta₂-agonist use in 277 patients receiving ADVAIR HFA was approximately
829 1.2 inhalations/day and ranged from 0 to 9 inhalations/day. Two percent (2%) of patients
830 receiving ADVAIR HFA in these trials averaged 6 or more inhalations per day over the course of
831 the 12-week trials. No increase in frequency of cardiovascular events was observed among
832 patients who averaged 6 or more inhalations per day.

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

839 **Fluticasone Propionate Nasal Spray:** In patients receiving ADVAIR HFA in three
840 12-week US clinical trials, no difference in the profile of adverse events or HPA axis effects was
841 noted between patients receiving FLONASE[®] (fluticasone propionate) Nasal Spray, 50 mcg
842 concurrently (n = 89) and those who were not (n = 192).

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

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

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

860 **Inhibitors of Cytochrome P450:** Fluticasone propionate is a substrate of cytochrome
861 P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy
862 subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can
863 significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced
864 serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics:
865 *Fluticasone Propionate: Drug Interactions*). During postmarketing use, there have been reports
866 of clinically significant drug interactions in patients receiving fluticasone propionate and
867 ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal
868 suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not
869 recommended unless the potential benefit to the patient outweighs the risk of systemic
870 corticosteroid side effects.

871 In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a
872 single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of
873 ketoconazole (200 mg) to steady state resulted in increased systemic fluticasone propionate
874 exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.
875 Caution should be exercised when ADVAIR HFA is coadministered with ketoconazole and other
876 known potent cytochrome P450 3A4 inhibitors.

877 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate:**
878 Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to
879 1,000 mcg/kg (approximately 4 times the maximum recommended human daily inhalation dose
880 on a mcg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than the
881 maximum recommended human daily inhalation dose on a mcg/m² basis) for 104 weeks.

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

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

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

896 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol
897 caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at
898 doses of 0.68 mg/kg and above (approximately 65 times the maximum recommended human
899 daily inhalation dose on a mg/m² basis). No tumors were seen at 0.21 mg/kg (approximately
900 20 times the maximum recommended human daily inhalation dose on a mg/m² basis). These
901 findings in rodents are similar to those reported previously for other beta-adrenergic agonist
902 drugs. The relevance of these findings to human use is unknown.

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

908 **Pregnancy: Teratogenic Effects: ADVAIR HFA Inhalation Aerosol:** Pregnancy
909 Category C. From the reproduction toxicity studies in mice and rats, no evidence of enhanced
910 toxicity was seen using combinations of fluticasone propionate and salmeterol compared to
911 toxicity data from the components administered separately. In mice combining 150 mcg/kg
912 subcutaneously of fluticasone propionate (less than the maximum recommended human daily
913 inhalation dose on a mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 480 times
914 the maximum recommended human daily inhalation dose on a mg/m² basis) were teratogenic.
915 Cleft palate, fetal death, increased implantation loss and delayed ossification was seen. These
916 observations are characteristic of glucocorticoids. No developmental toxicity was observed at
917 combination doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the
918 maximum recommended human daily inhalation dose on a mcg/m² basis) and up to 1.4 mg/kg
919 orally of salmeterol (approximately 70 times the maximum recommended human daily
920 inhalation dose on a mg/m² basis). In rats, no teratogenicity was observed at combination doses
921 up to 30 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended

922 human daily inhalation dose on a mcg/m² basis) and up to 1 mg/kg of salmeterol (approximately
923 95 times the maximum recommended human daily inhalation dose on a mg/m² basis).
924 Combining 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum
925 recommended human daily inhalation dose on a mcg/m² basis) with 10 mg/kg orally of
926 salmeterol (approximately 970 times the maximum recommended human daily inhalation dose
927 on a mg/m² basis) produced maternal toxicity, decreased placental weight, decreased fetal
928 weight, umbilical hernia, delayed ossification, and changes in the occipital bone.

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

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

939 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of
940 4 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m²
941 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg
942 (approximately 5 times the maximum recommended human daily inhalation dose on mcg/m²
943 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this
944 study, consistent with the established low bioavailability following oral administration (see
945 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Absorption*).

946 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose
947 of 100 mcg/kg to mice (less than the maximum recommended human daily inhalation dose on a
948 mcg/m² basis), a subcutaneous or an oral dose of 100 mcg/kg to rats (equivalent to the maximum
949 recommended human daily inhalation dose on a mcg/m² basis), and an oral dose of 300 mcg/kg
950 to rabbits (approximately 5 times the maximum recommended human daily inhalation dose on a
951 mcg/m² basis).

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

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

959 **Salmeterol:** Pregnancy Category C. No teratogenic effects occurred in the rat at oral
960 doses up to 2 mg/kg (approximately 190 times the maximum recommended human daily
961 inhalation dose on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg

962 and above (approximately 25 times the maximum recommended human daily inhalation dose
963 based on the comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically
964 resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft
965 palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial
966 bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 10 times the
967 maximum recommended human daily inhalation dose based on comparison of the AUCs).

968 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal
969 cranial bones was seen at an oral dose of 10 mg/kg (approximately 1,900 times the maximum
970 recommended human daily inhalation dose on a mg/m² basis). Extensive use of other
971 beta-agonists has provided no evidence that these class effects in animals are relevant to their use
972 in humans.

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

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

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

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

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

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

996 **Pediatric Use:** Thirty-eight (38) patients 12 to 17 years of age were treated with ADVAIR
997 HFA in US pivotal clinical trials. Patients in this age-group demonstrated efficacy results similar
998 to those observed in patients 18 years of age and older. There were no obvious differences in the
999 type or frequency of adverse events reported in this age-group compared with patients 18 years
1000 of age and older.

1001 The safety and effectiveness of ADVAIR HFA in children under 12 years have not been
1002 established.

1003 Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in
1004 growth in pediatric patients. In these studies, the mean reduction in growth velocity was
1005 approximately 1 cm/year (range, 0.3 to 1.8 cm/year) and appears to depend upon dose and
1006 duration of exposure. This effect was observed in the absence of laboratory evidence of HPA
1007 axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic
1008 corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis
1009 function. The long-term effects of this reduction in growth velocity associated with orally
1010 inhaled corticosteroids, including the impact on final adult height, are unknown. The potential
1011 for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids
1012 has not been adequately studied. The effects on growth velocity of treatment with orally inhaled
1013 corticosteroids for over 1 year, including the impact on final adult height, are unknown. The
1014 growth of children and adolescents receiving orally inhaled corticosteroids, including ADVAIR
1015 HFA, should be monitored. If a child or adolescent on any corticosteroid appears to have growth
1016 suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids
1017 should be considered. The potential growth effects of prolonged treatment should be weighed
1018 against the clinical benefits obtained and the risks associated with alternative therapies. To
1019 minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR HFA, each
1020 patient should be titrated to the lowest strength that effectively controls his/her asthma (see
1021 DOSAGE AND ADMINISTRATION).

1022 **Geriatric Use:** Of the total number of patients in clinical studies treated with ADVAIR HFA,
1023 41 were 65 years of age or older and 21 were 75 years of age or older. No overall differences in
1024 safety were observed between these patients and younger patients, and other reported clinical
1025 experience, including studies of the individual components, has not identified differences in
1026 responses between the elderly and younger patients, but greater sensitivity of some older
1027 individuals cannot be ruled out. As with other products containing beta₂-agonists, special caution
1028 should be observed when using ADVAIR HFA in geriatric patients who have concomitant
1029 cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available
1030 data for ADVAIR HFA or its active components, no adjustment of dosage of ADVAIR HFA in
1031 geriatric patients is warranted.

1032 **ADVERSE REACTIONS**

1033 Long-acting beta₂-adrenergic agonists, such as salmeterol, may increase the risk of
1034 asthma-related death. Data from a large, placebo-controlled US study that compared the
1035 safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma
1036 therapy showed an increase in asthma-related deaths in patients receiving salmeterol (see
1037 WARNINGS). Salmeterol is a component of ADVAIR HFA. However, the data from this
1038 study are not adequate to determine whether concurrent use of inhaled corticosteroids,

1039 such as fluticasone propionate, the other component of ADVAIR HFA, or other asthma
 1040 controller therapy modifies the risk of asthma-related death.

1041 The incidence of common adverse events in Table 4 is based upon 2 placebo-controlled,
 1042 12-week, US clinical studies (Studies 1 and 3) and 1 active-controlled, 12-week, US clinical
 1043 study (Study 2). A total of 1,008 adolescent and adult patients with asthma (556 females and 452
 1044 males) previously treated with albuterol alone, salmeterol, or inhaled corticosteroids were treated
 1045 twice daily with 2 inhalations of ADVAIR HFA 45/21 or ADVAIR HFA 115/21, fluticasone
 1046 propionate CFC inhalation aerosol (44- or 110-mcg doses), salmeterol CFC inhalation aerosol
 1047 21 mcg, or placebo HFA inhalation aerosol.

1048
 1049 **Table 4. Overall Adverse Events With $\geq 3\%$ Incidence in US Controlled Clinical Trials**
 1050 **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

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

1057

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

1058

Cardiovascular: Tachycardia, arrhythmias, myocardial infarction.

1059

1060

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

1061

1062

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

1063

1064

Endocrine and Metabolic: Weight gain.

1065

1066

Eye: Allergic eye disorders, eye edema and swelling.

1067

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

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

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1072

Neurology: Sleep disorders, migraines.

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1074

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

1075

1076

Reproduction: Bacterial reproductive infections.

1077 **Respiratory:** Lower respiratory signs and symptoms, lower respiratory infections, lower
1078 respiratory hemorrhage.

1079 **Skin:** Eczema, dermatitis and dermatosis.

1080 **Urology:** Urinary infections.

1081 Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare
1082 events of angioedema and bronchospasm, have been reported.

1083 The incidence of common adverse events reported in Study 4, a 12-week, non-US clinical
1084 study of 509 patients previously treated with inhaled corticosteroids who were treated twice daily
1085 with 2 inhalations of ADVAIR HFA 230/21, fluticasone propionate CFC inhalation aerosol
1086 220 mcg, or 1 inhalation of ADVAIR DISKUS 500/50 was similar to the incidences reported in
1087 Table 4.

1088 **Observed During Clinical Practice:** In addition to adverse events reported from clinical
1089 trials, the following events have been identified during worldwide use of any formulation of
1090 ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are
1091 reported voluntarily from a population of unknown size, estimates of frequency cannot be made.
1092 These events have been chosen for inclusion due to either their seriousness, frequency of
1093 reporting, or causal connection to ADVAIR, fluticasone propionate, and/or salmeterol or a
1094 combination of these factors.

1095 In extensive US and worldwide postmarketing experience with salmeterol, a component of
1096 ADVAIR HFA, serious exacerbations of asthma, including some that have been fatal, have been
1097 reported. In most cases, these have occurred in patients with severe asthma and/or in some
1098 patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also
1099 occurred in a few patients with less severe asthma. It was not possible from these reports to
1100 determine whether salmeterol contributed to these events.

1101 **Cardiovascular:** Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular
1102 tachycardia), hypertension, ventricular tachycardia.

1103 **Ear, Nose, and Throat:** Aphonia, earache, facial and oropharyngeal edema, paranasal sinus
1104 pain, rhinitis, throat soreness and irritation, tonsillitis.

1105 **Endocrine and Metabolic:** Cushing syndrome, Cushingoid features, growth velocity
1106 reduction in children/adolescents, hypercorticism, hyperglycemia, osteoporosis.

1107 **Eye:** Cataracts, glaucoma.

1108 **Gastrointestinal:** Dyspepsia, xerostomia.

1109 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1110 **Musculoskeletal:** Back pain, myositis.

1111 **Neurology:** Paresthesia, restlessness.

1112 **Non-Site Specific:** Fever, immediate and delayed hypersensitivity reaction, pallor.

1113 **Psychiatry:** Agitation, aggression, anxiety, depression. Behavioral changes, including
1114 hyperactivity and irritability, have been reported very rarely and primarily in children.

1115 **Respiratory:** Asthma; asthma exacerbation; chest congestion; chest tightness; cough;
1116 dyspnea; immediate bronchospasm; influenza; paradoxical bronchospasm; tracheitis; wheezing;

1117 pneumonia; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling;
1118 stridor; choking.

1119 **Skin:** Contact dermatitis, contusions, ecchymoses, photodermatitis, pruritus.

1120 **Urogenital:** Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal
1121 candidiasis, vaginitis, vulvovaginitis.

1122 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a
1123 component of ADVAIR HFA, may present with systemic eosinophilic conditions, with some
1124 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a
1125 condition that is often treated with systemic corticosteroid therapy. These events usually, but not
1126 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy
1127 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions
1128 have also been reported with other inhaled corticosteroids in this clinical setting. While
1129 ADVAIR HFA should not be used for transferring patients from systemic corticosteroid therapy,
1130 physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms,
1131 cardiac complications, and/or neuropathy presenting in their patients. A causal relationship
1132 between fluticasone propionate and these underlying conditions has not been established (see
1133 PRECAUTIONS: General: *Eosinophilic Conditions*).

1134 OVERDOSAGE

1135 **ADVAIR HFA Inhalation Aerosol:** No deaths occurred in rats given a single-dose
1136 combination of salmeterol 3.6 mg/kg and fluticasone propionate 1.9 mg/kg given as the
1137 inhalation powder (approximately 290 and 15 times, respectively, the maximum recommended
1138 human daily inhalation dose on a mg/m² basis).

1139 **Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in
1140 signs/symptoms of hypercorticism (see PRECAUTIONS: General: *Metabolic and Other Effects*).
1141 Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate
1142 inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate CFC
1143 inhalation aerosol were well tolerated. Fluticasone propionate given by inhalation aerosol at
1144 doses of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well
1145 tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral
1146 doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of
1147 mild or moderate severity, and incidences were similar in active and placebo treatment groups. In
1148 mice the oral median lethal dose was >1,000 mg/kg (>4,400 times the maximum recommended
1149 human daily inhalation dose on a mg/m² basis). In rats the subcutaneous median lethal dose was
1150 >1,000 mg/kg (>8,800 times the maximum recommended human daily inhalation dose on a
1151 mg/m² basis).

1152 **Salmeterol:** The expected signs and symptoms with overdosage of salmeterol are those of
1153 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and
1154 symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or
1155 hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache,

1156 tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.
1157 Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic
1158 adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or
1159 arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to
1160 clinically significant prolongation of the QTc interval, which can produce ventricular
1161 arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

1162 As with all sympathomimetic medications, cardiac arrest and even death may be associated
1163 with abuse of salmeterol.

1164 Treatment consists of discontinuation of salmeterol together with appropriate symptomatic
1165 therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing
1166 in mind that such medication can produce bronchospasm. There is insufficient evidence to
1167 determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is
1168 recommended in cases of overdosage.

1169 No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg
1170 (approximately 280 times the maximum recommended human daily inhalation dose on a mg/m²
1171 basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 230 times the maximum
1172 recommended human daily inhalation dose on a mg/m² basis). By the oral route, no deaths
1173 occurred in mice at 150 mg/kg (approximately 7,200 times the maximum recommended human
1174 daily inhalation dose on a mg/m² basis) and in rats at 1,000 mg/kg (approximately 97,000 times
1175 the maximum recommended human daily inhalation dose on a mg/m² basis).

1176 **DOSAGE AND ADMINISTRATION**

1177 ADVAIR HFA should be administered by the orally inhaled route only in patients 12 years of
1178 age and older. ADVAIR HFA should not be used for transferring patients from systemic
1179 corticosteroid therapy. ADVAIR HFA has not been studied in patients under 12 years of age or
1180 in patients with COPD.

1181 Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in
1182 ADVAIR HFA, may increase the risk of asthma-related death (see WARNINGS). Therefore,
1183 when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients
1184 not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose
1185 inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2
1186 maintenance therapies. ADVAIR HFA is not indicated in patients whose asthma can be
1187 successfully managed by inhaled corticosteroids along with occasional use of inhaled,
1188 short-acting beta₂-agonists.

1189 ADVAIR HFA is available in 3 strengths, ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR
1190 HFA 115/21 Inhalation Aerosol, and ADVAIR HFA 230/21 Inhalation Aerosol, containing 45,
1191 115, and 230 mcg of fluticasone propionate, respectively, and 21 mcg of salmeterol per
1192 inhalation.

1193 ADVAIR HFA should be administered as 2 inhalations twice daily every day. More frequent
1194 administration (more than twice daily) or a higher number of inhalations (more than 2 inhalations

1195 twice daily) of the prescribed strength of ADVAIR HFA is not recommended as some patients
 1196 are more likely to experience adverse effects with higher doses of salmeterol. The safety and
 1197 efficacy of ADVAIR HFA when administered in excess of recommended doses have not been
 1198 established.

1199 If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should
 1200 be taken for immediate relief.

1201 Patients who are receiving ADVAIR HFA twice daily should not use additional salmeterol or
 1202 other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of EIB or for any other
 1203 reason.

1204 For patients 12 years of age and older, the dosage is 2 inhalations twice daily (morning and
 1205 evening, approximately 12 hours apart).

1206 The recommended starting dosages for ADVAIR HFA are based upon patients' current
 1207 asthma therapy.

- 1208 • For patients not adequately controlled on an inhaled corticosteroid, Table 5 provides the
 1209 recommended starting dosage.
- 1210 • For patients not currently on inhaled corticosteroids, whose disease severity clearly warrants
 1211 initiation of treatment with 2 maintenance therapies, the recommended starting dosage is 2
 1212 inhalations of ADVAIR HFA 45/21 or ADVAIR HFA 115/21 twice daily (see
 1213 INDICATIONS AND USAGE).

1214 The maximum recommended dosage is 2 inhalations of ADVAIR HFA 230/21 twice daily.

1215 **For all patients it is desirable to titrate to the lowest effective strength after adequate**
 1216 **asthma stability is achieved.**

1217

1218 **Table 5. Recommended Dosages of ADVAIR HFA Inhalation Aerosol for Patients Not**
 1219 **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 320 mcg 640 mcg	45/21 115/21 230/21
Budesonide inhalation powder	≤400 mcg 800-1,200 mcg 1,600 mcg*	45/21 115/21 230/21
Flunisolide CFC inhalation aerosol	≤1,000 mcg 1,250-2,000 mcg	45/21 115/21
Flunisolide HFA inhalation aerosol	≤320 mcg 640 mcg	45/21 115/21
Fluticasone propionate HFA	≤176 mcg	45/21

inhalation aerosol	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

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

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

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

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

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

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

HOW SUPPLIED

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

1248 opened. Each canister is packaged with a Patient's Instructions for Use/Information for the
1249 Patient leaflet.

1250 *NDC 0173-0715-00 ADVAIR HFA 45/21 Inhalation Aerosol

1251 *NDC 0173-0716-00 ADVAIR HFA 115/21 Inhalation Aerosol

1252 *NDC 0173-0717-00 ADVAIR HFA 230/21 Inhalation Aerosol

1253 **The purple actuator supplied with ADVAIR HFA Inhalation Aerosol should not be used**
1254 **with any other product canisters, and actuators from other products should not be used**
1255 **with an ADVAIR HFA Inhalation Aerosol canister.**

1256 **The correct amount of medication in each inhalation cannot be assured after**
1257 **120 inhalations, even though the canister is not completely empty and will continue to**
1258 **operate. The inhaler should be discarded when 120 actuations have been used. Never**
1259 **immerse the canister into water to determine the amount remaining in the canister ("float**
1260 **test").**

1261 **Keep out of reach of children. Avoid spraying in eyes.**

1262 **Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame.**
1263 **Exposure to temperatures above 120°F may cause bursting. Never throw container into fire**
1264 **or incinerator.**

1265 **Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Store the inhaler with**
1266 **the mouthpiece down. For best results, the inhaler should be at room temperature before**
1267 **use. SHAKE WELL FOR 5 SECONDS BEFORE USING.**

1268 ADVAIR HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the
1269 propellant.

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GlaxoSmithKline

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1273 GlaxoSmithKline

1274 Research Triangle Park, NC 27709

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1278 June 2006

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MEDICATION GUIDE

1281

1282 **ADVAIR[®] HFA [ad' vair] 45/21 Inhalation Aerosol**

1283 **(fluticasone propionate 45 mcg and salmeterol 21 mcg)**

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ADVAIR[®] HFA 115/21 Inhalation Aerosol

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(fluticasone propionate 115 mcg and salmeterol 21 mcg)

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

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

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 medicine or LABA. LABA medicines are used in patients with asthma. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles 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.**
- **ADVAIR HFA should be used only if your healthcare provider decides that another asthma-controller medicine alone does not control your asthma or that you need 2 asthma-controller medicines.**

1326

1327 • **Call your healthcare provider if breathing problems worsen over time while using**
1328 **ADVAIR HFA. You may need different treatment.**

1329

1330 • **Get emergency medical care if:**

1331 • **breathing problems worsen quickly, and**

1332 • **you use your short-acting beta₂-agonist medicine, but it does not relieve your**
1333 **breathing problems.**

1334

1335 **What is ADVAIR HFA?**

1336 ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate (the same
1337 medicine found in FLOVENT) and a long-acting beta₂-agonist medicine, salmeterol (the same
1338 medicine found in SEREVENT). ADVAIR HFA is used for asthma as follows:

1339

1340 ADVAIR HFA is used long term, twice a day to control symptoms of asthma, and prevent
1341 symptoms such as wheezing in adolescents and adults 12 years of age and older.

1342

1343 **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). Because**
1344 **LABA medicines, such as salmeterol, may increase the chance of death from asthma**
1345 **problems, ADVAIR HFA is not for adults and children with asthma who:**

1346 • **are well controlled with another asthma-controller medicine, such as a low to medium**
1347 **dose of an inhaled corticosteroid medicine**

1348 • **only need short-acting beta₂-agonist medicines once in awhile**

1349

1350 **What should I tell my healthcare provider before using ADVAIR HFA?**

1351 **Tell your healthcare provider about all of your health conditions, including if you:**

1352 • **have heart problems**

1353 • **have high blood pressure**

1354 • **have seizures**

1355 • **have thyroid problems**

1356 • **have diabetes**

1357 • **have liver problems**

1358 • **have osteoporosis**

1359 • **have an immune system problem**

1360 • **are pregnant or planning to become pregnant.** It is not known if ADVAIR HFA may harm
1361 your unborn baby.

1362 • **are breastfeeding.** It is not known if ADVAIR HFA passes into your milk and if it can harm
1363 your baby.

1364 • **are allergic to ADVAIR HFA or any other medicines**

1365 • **are exposed to chickenpox or measles**

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

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

How do I use ADVAIR HFA?

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

- Use ADVAIR HFA exactly as prescribed. **Do not use ADVAIR HFA more often than prescribed.** ADVAIR HFA comes in 3 strengths. Your healthcare provider will prescribe the one that is best for your condition.
- The usual dosage of ADVAIR HFA is 2 inhalations twice a day (morning and evening). The 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR HFA.
- If you miss a dose of ADVAIR HFA, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.
- **While you are using ADVAIR HFA twice a day, do not use other medicines that contain a long-acting beta₂-agonist or LABA for any reason. Other LABA-containing medicines include ADVAIR DISKUS[®] (fluticasone propionate and salmeterol inhalation powder), SEREVENT[®] DISKUS[®] (salmeterol xinafoate inhalation powder), or FORADIL[®] AEROLIZER[™] (formoterol fumarate inhalation powder).**
- Do not change or stop any of your medicines used to control or treat your breathing problems. Your healthcare provider will adjust your medicines as needed.
- Make sure you always have a short-acting beta₂-agonist medicine with you. Use your short-acting beta₂-agonist medicine if you have breathing problems between doses of ADVAIR HFA.

- 1406 • **Call your healthcare provider or get medical care right away if:**
- 1407 • your breathing problems worsen with ADVAIR HFA
- 1408 • you need to use your short-acting beta₂-agonist medicine more often than usual
- 1409 • your short-acting beta₂-agonist medicine does not work as well for you at relieving
- 1410 symptoms
- 1411 • you need to use 4 or more inhalations of your short-acting beta₂-agonist medicine for 2 or
- 1412 more days in a row
- 1413 • you use 1 whole canister of your short-acting beta₂-agonist medicine in 8 weeks' time
- 1414 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers
- 1415 that are right for you.
- 1416 • you have asthma and your symptoms do not improve after using ADVAIR HFA regularly
- 1417 for 1 week

1418

1419 **What are the possible side effects with ADVAIR HFA?**

- 1420 • **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). In**
- 1421 **patients with asthma, LABA medicines, such as salmeterol, may increase the chance of**
- 1422 **death from asthma problems.** See “What is the most important information I should know
- 1423 about ADVAIR HFA?”

1424

1425 **Other possible side effects with ADVAIR HFA include:**

- 1426 • **serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue;**
- 1427 **and breathing problems.** Call your healthcare provider or get emergency medical care if
- 1428 you get any symptoms of a serious allergic reaction.
- 1429 • **increased blood pressure**
- 1430 • **a fast and irregular heartbeat**
- 1431 • **chest pain**
- 1432 • **headache**
- 1433 • **tremor**
- 1434 • **nervousness**
- 1435 • **immune system effects and a higher chance for infections**
- 1436 • **lower bone mineral density.** This may be a problem for people who already have a higher
- 1437 chance for low bone density (osteoporosis).
- 1438 • **eye problems including glaucoma and cataracts.** You should have regular eye exams
- 1439 while using ADVAIR HFA.
- 1440 • **slowed growth in children.** A child's growth should be checked often.
- 1441 • **throat irritation**

1442

1443 Tell your healthcare provider about any side effect that bothers you or that does not go away.

1444

1445 These are not all the side effects with ADVAIR HFA. Ask your healthcare provider or
1446 pharmacist for more information.

1447

1448 **How do I store ADVAIR HFA?**

- 1449 • **Store ADVAIR HFA at room temperature with the mouthpiece down.**
- 1450 • **Do not puncture the canister. Do not use or store ADVAIR HFA near heat or an open**
1451 **flame. Never throw it into a fire or incinerator.**
- 1452 • **Keep ADVAIR HFA and all medicines out of the reach of children.**

1453

1454 **General Information about ADVAIR HFA**

1455 Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not
1456 use ADVAIR HFA for a condition for which it was not prescribed. Do not give your ADVAIR
1457 HFA to other people, even if they have the same condition. It may harm them.

1458 This Medication Guide summarizes the most important information about ADVAIR HFA. If you
1459 would like more information, talk with your healthcare provider or pharmacist. You can ask your
1460 healthcare provider or pharmacist for information about ADVAIR HFA that was written for
1461 healthcare professionals. You can also contact the company that makes ADVAIR HFA (toll free)
1462 at 1-888-825-5249 or at www.advair.com.

1463

1464

Instructions for Using Your ADVAIR HFA

1465 Follow the instructions below for using your ADVAIR HFA.

1466 Take your ADVAIR HFA inhaler out of the moisture-protective foil pouch just before you use it
1467 for the first time. Safely throw away the foil pouch and the drying packet that comes inside the
1468 pouch.

1469 The inhaler should be at room temperature before you use it.

1470 **The purple actuator that comes with ADVAIR HFA should not be used with any other**
1471 **product canisters. Actuators that come with other products should not be used with an**
1472 **ADVAIR HFA canister.**

1473 **Prime the inhaler** before using it for the first time. To prime the inhaler, shake it well for
1474 5 seconds. Then spray it 1 time into the air away from your face. Shake and spray the inhaler like
1475 this 3 more times to finish priming it. **Avoid spraying in eyes.**

1476 If you have not used your inhaler in more than 4 weeks or if you have dropped it, shake it well
1477 for 5 seconds and spray it 2 times into the air away from your face.

1478 **Shake the inhaler well** for 5 seconds just before each use. The inhaler should be at room
1479 temperature before you use it.

1480 1. Take the cap off the mouthpiece (see Figure 1). The strap on the cap will stay attached to the
1481 actuator.

1482 Look for foreign objects inside the inhaler before each use, especially if the strap is no longer
1483 attached to the actuator or if the cap is not being used to cover the mouthpiece.

1484 Make sure the canister is fully and firmly inserted into the actuator.

1485 **Shake the inhaler well** for 5 seconds right before each use.

1486

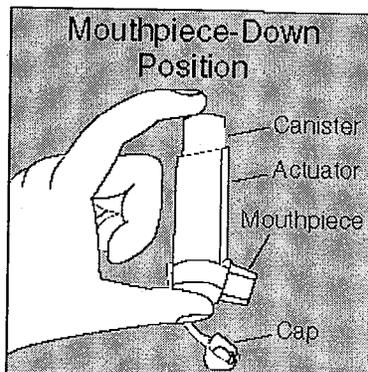


Figure 1

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1490 **2. Breathe out fully through your mouth**, pushing as much air out of your lungs as you can.

1491 Put the mouthpiece all the way into your mouth. Hold the inhaler with the mouthpiece down
1492 (see Figure 1). Close your lips around it.

1493 **3. It is important to get the medicine in the spray into your lungs where it works. To do this, you**
1494 **need to inhale the spray at the same time you take in a slow, deep breath.**

1495 So, just after starting to take in a slow, deep breath through your mouth, press down firmly on
1496 the top of the metal canister (see Figure 2) and keep breathing in through your mouth.

1497 Take your finger off the canister after the spray comes out of the canister. Take the
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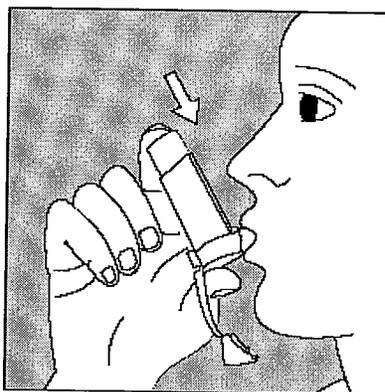


Figure 2

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1501 4. **Hold your breath as long as you can**, up to 10 seconds. Then breathe normally.
1502 5. **Wait about 30 seconds and shake** the inhaler again. Repeat steps 2 through 4.
1503 6. **Put the cap back on the mouthpiece after each time you use the inhaler.**
1504 7. After you finish taking this medicine, rinse your mouth with water. Spit out the water. Do not
1505 swallow it.

1506 8. Never put the canister in water to find out how much medicine is left in the canister (“float
1507 test”).

1508 9. You should keep track of the number of inhalations used from your inhaler. **Then throw away**
1509 **the inhaler after you have used 120 inhalations.** Even though the canister might not be empty
1510 and will keep spraying, you might not get the right amount of medicine in each inhalation.
1511 Before you get to 120 inhalations, ask your doctor if you need to refill your prescription.

1512 **Do not** use after the expiration date, which is shown as “EXP” on the product label and box.

1513 **Cleaning your ADVAIR HFA Inhalation Aerosol:**

1514 Clean the inhaler at least once a week after your evening dose. Keeping the canister and plastic
1515 actuator clean is important to prevent medicine build-up.

1516 Step 1. Take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator.
1517 cap. Do not take the canister out of the plastic actuator.

1518 Step 2. Use a dry cotton swab to clean the small circular opening where the medicine sprays out
1519 of the canister. Carefully twist the swab in a circular motion to take off any medicine (see Figure
1520 3). Then wipe the inside of the mouthpiece with a clean tissue dampened with water. Let the
1521 actuator air-dry overnight.

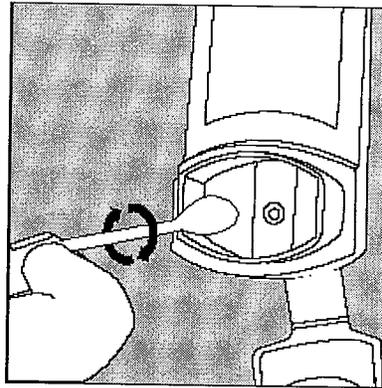


Figure 3

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1524 Step 3. Put the mouthpiece cover back on after the actuator has dried.

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1526 **Rx only**
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GlaxoSmithKline
Research Triangle Park, NC 27709

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Corporation.

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June 2006

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PHARMACIST—DETACH HERE AND GIVE MEDICATION GUIDE TO PATIENT

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1546
1547

MEDICATION GUIDE

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ADVAIR[®] HFA [ad' vair] 45/21 Inhalation Aerosol
(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 the Medication Guide that comes with ADVAIR HFA before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

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 medicine or LABA. LABA medicines are used in patients with asthma. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles 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.**

- 1589 • **ADVAIR HFA should be used only if your healthcare provider decides that another**
1590 **asthma-controller medicine alone does not control your asthma or that you need 2**
1591 **asthma-controller medicines.**
- 1592
- 1593 • **Call your healthcare provider if breathing problems worsen over time while using**
1594 **ADVAIR HFA. You may need different treatment.**
- 1595
- 1596 • **Get emergency medical care if:**
- 1597 • **breathing problems worsen quickly, and**
- 1598 • **you use your short-acting beta₂-agonist medicine, but it does not relieve your**
1599 **breathing problems.**

1600

1601 **What is ADVAIR HFA?**

1602 ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate (the same
1603 medicine found in FLOVENT) and a long-acting beta₂-agonist medicine, salmeterol (the same
1604 medicine found in SEREVENT). ADVAIR HFA is used for asthma as follows:

1605

1606 ADVAIR HFA is used long term, twice a day to control symptoms of asthma, and prevent
1607 symptoms such as wheezing in adolescents and adults 12 years of age and older.

1608

1609 **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). Because**
1610 **LABA medicines, such as salmeterol, may increase the chance of death from asthma**
1611 **problems, ADVAIR HFA is not for adults and children with asthma who:**

- 1612 • **are well controlled with another asthma-controller medicine, such as a low to medium**
1613 **dose of an inhaled corticosteroid medicine**
- 1614 • **only need short-acting beta₂-agonist medicines once in awhile**

1615

1616 **What should I tell my healthcare provider before using ADVAIR HFA?**

1617 **Tell your healthcare provider about all of your health conditions, including if you:**

1618 • **have heart problems**

1619 • **have high blood pressure**

1620 • **have seizures**

1621 • **have thyroid problems**

1622 • **have diabetes**

1623 • **have liver problems**

1624 • **have osteoporosis**

1625 • **have an immune system problem**

1626 • **are pregnant or planning to become pregnant. It is not known if ADVAIR HFA may harm**
1627 **your unborn baby.**

- 1628 • **are breastfeeding.** It is not known if ADVAIR HFA passes into your milk and if it can harm
1629 your baby.
1630 • **are allergic to ADVAIR HFA any other medicines**
1631 • **are exposed to chickenpox or measles**
1632

1633 Tell your healthcare provider about all the medicines you take including prescription and
1634 non-prescription medicines, vitamins, and herbal supplements. ADVAIR HFA and certain other
1635 medicines may interact with each other. This may cause serious side effects. Especially, tell your
1636 healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR[®] (ritonavir capsules)
1637 Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA[®] (lopinavir/ritonavir) Tablets
1638 contain ritonavir.
1639

1640 Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist
1641 each time you get a new medicine.
1642

1643 **How do I use ADVAIR HFA?**

1644 **See the step-by-step instructions for using ADVAIR HFA at the end of this Medication**
1645 **Guide.** Do not use the ADVAIR HFA unless your healthcare provider has taught you and you
1646 understand everything. Ask your healthcare provider or pharmacist if you have any questions.
1647

- 1648 • Use ADVAIR HFA exactly as prescribed. **Do not use ADVAIR HFA more often than**
1649 **prescribed.** ADVAIR HFA comes in 3 strengths. Your healthcare provider will prescribe the
1650 one that is best for your condition.
1651
- 1652 • The usual dosage of ADVAIR HFA is 2 inhalations twice a day (morning and evening). The
1653 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR
1654 HFA.
1655
- 1656 • If you miss a dose of ADVAIR HFA, just skip that dose. Take your next dose at your usual
1657 time. Do not take 2 doses at one time.
1658
- 1659 • **While you are using ADVAIR HFA twice a day, do not use other medicines that contain**
1660 **a long-acting beta₂-agonist or LABA for any reason. Other LABA-containing medicines**
1661 **include ADVAIR DISKUS[®] (fluticasone propionate and salmeterol inhalation powder),**
1662 **SEREVENT[®] DISKUS[®] (salmeterol xinafoate inhalation powder), or FORADIL[®]**
1663 **AEROLIZER[™] (formoterol fumarate inhalation powder).**
1664
- 1665 • Do not change or stop any of your medicines used to control or treat your breathing
1666 problems. Your healthcare provider will adjust your medicines as needed.
1667

- 1668 • Make sure you always have a short-acting beta₂-agonist medicine with you. Use your
1669 short-acting beta₂-agonist medicine if you have breathing problems between doses of
1670 ADVAIR HFA.
1671
- 1672 • **Call your healthcare provider or get medical care right away if:**
- 1673 • your breathing problems worsen with ADVAIR HFA
 - 1674 • you need to use your short-acting beta₂-agonist medicine more often than usual
 - 1675 • your short-acting beta₂-agonist medicine does not work as well for you at relieving
1676 symptoms
 - 1677 • you need to use 4 or more inhalations of your short-acting beta₂-agonist medicine for 2 or
1678 more days in a row
 - 1679 • you use 1 whole canister of your short-acting beta₂-agonist medicine in 8 weeks' time
 - 1680 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers
1681 that are right for you.
 - 1682 • you have asthma and your symptoms do not improve after using ADVAIR HFA regularly
1683 for 1 week
1684

1685 **What are the possible side effects with ADVAIR HFA?**

- 1686 • **ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). In**
1687 **patients with asthma, LABA medicines, such as salmeterol, may increase the chance of**
1688 **death from asthma problems.** See “What is the most important information I should know
1689 about ADVAIR HFA?”
1690

1691 **Other possible side effects with ADVAIR HFA include:**

- 1692 • **serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue;**
1693 **and breathing problems.** Call your healthcare provider or get emergency medical care if
1694 you get any symptoms of a serious allergic reaction.
- 1695 • **increased blood pressure**
- 1696 • **a fast and irregular heartbeat**
- 1697 • **chest pain**
- 1698 • **headache**
- 1699 • **tremor**
- 1700 • **nervousness**
- 1701 • **immune system effects and a higher chance for infections**
- 1702 • **lower bone mineral density.** This may be a problem for people who already have a higher
1703 chance for low bone density (osteoporosis).
- 1704 • **eye problems including glaucoma and cataracts.** You should have regular eye exams
1705 while using ADVAIR HFA.
- 1706 • **slowed growth in children.** A child's growth should be checked often.
- 1707 • **throat irritation**

1708
1709 Tell your healthcare provider about any side effect that bothers you or that does not go away.
1710
1711 These are not all the side effects with ADVAIR HFA. Ask your healthcare provider or
1712 pharmacist for more information.

1713
1714 **How do I store ADVAIR HFA?**

- 1715 • **Store ADVAIR HFA at room temperature with the mouthpiece down.**
- 1716 • **Do not puncture the canister. Do not use or store ADVAIR HFA near heat or an open**
1717 **flame. Never throw it into a fire or incinerator.**
- 1718 • **Keep ADVAIR HFA and all medicines out of the reach of children.**

1719
1720 **General Information about ADVAIR HFA**

1721 Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not
1722 use ADVAIR HFA for a condition for which it was not prescribed. Do not give your ADVAIR
1723 HFA to other people, even if they have the same condition. It may harm them.

1724 This Medication Guide summarizes the most important information about ADVAIR HFA. If you
1725 would like more information, talk with your healthcare provider or pharmacist. You can ask your
1726 healthcare provider or pharmacist for information about ADVAIR HFA that was written for
1727 healthcare professionals. You can also contact the company that makes ADVAIR HFA (toll free)
1728 at 1-888-825-5249 or at www.advail.com.

1729

1730 **Instructions for Using Your ADVAIR HFA**

1731 Follow the instructions below for using your ADVAIR HFA.

1732 Take your ADVAIR HFA inhaler out of the moisture-protective foil pouch before you use it for
1733 the first time. Safely throw away the foil pouch and the drying packet that comes inside the
1734 pouch.

1735 The inhaler should be at room temperature before you use it.

1736 **The purple actuator that comes with ADVAIR HFA should not be used with any other**
1737 **product canisters. Actuators that come with other products should not be used with an**
1738 **ADVAIR HFA canister.**

1739 **Prime the inhaler** before using it for the first time. To prime the inhaler, shake it well for
1740 5 seconds. Then spray it 1 time into the air away from your face. Shake and spray the inhaler like
1741 this 3 more times to finish priming it. **Avoid spraying in eyes.**

1742 If you have not used your inhaler in more than 4 weeks or if you have dropped it, shake it well
1743 for 5 seconds and spray it 1 time into the air away from your face.

1744 **Shake the inhaler well** for 5 seconds just before before each use. The inhaler should be at room
1745 temperature before you use it.

1746 **1. Take the cap off the mouthpiece** (see Figure 1). The strap on the cap will stay attached to the
1747 actuator.

1748 Look for foreign objects inside the inhaler before each use, especially if the strap is no longer
1749 attached to the actuator or if the cap is not being used to cover the mouthpiece.

1750 Make sure the canister is fully and firmly inserted into the actuator.

1751 **Shake the inhaler well** for 5 seconds right before each use.

1752

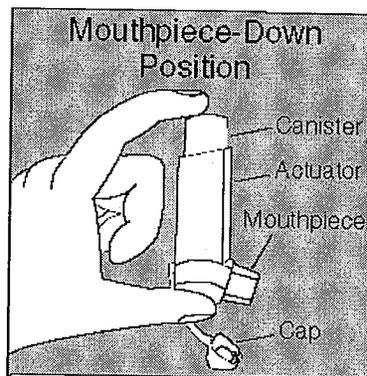


Figure 1

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1756 **2. Breathe out fully through your mouth**, pushing as much air out of your lungs as you can.

1757 Put the mouthpiece all the way into your mouth. Hold the inhaler with the mouthpiece down
1758 (see Figure 1). Close your lips around it.

1759 **3. It is important to get the medicine in the spray into your lungs where it works. To do this, you**
1760 **need to inhale the spray at the same time you take in a slow, deep breath.**

1761 So, just after starting to take in a slow, deep breath through your mouth, press down firmly on
1762 the top of the metal canister (see Figure 2) and keep breathing in through your mouth.

1763 Take your finger off the canister right after the spray comes out of the canister. Take the
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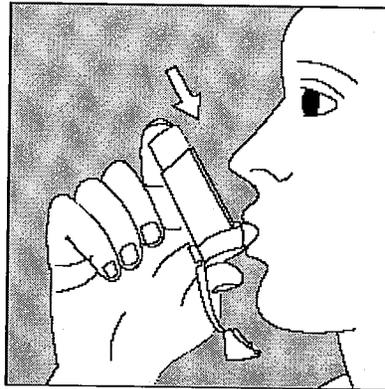


Figure 2

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- 1767 4. **Hold your breath as long as you can**, up to 10 seconds. Then breathe normally.
- 1768 5. **Wait about 30 seconds and shake** the inhaler again. Repeat steps 2 through 4.
- 1769 6. **Put the cap back on the mouthpiece after each time you use the inhaler.**
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1786 3). Then wipe the inside of the mouthpiece with a clean tissue dampened with water. Let the
1787 actuator air-dry overnight.

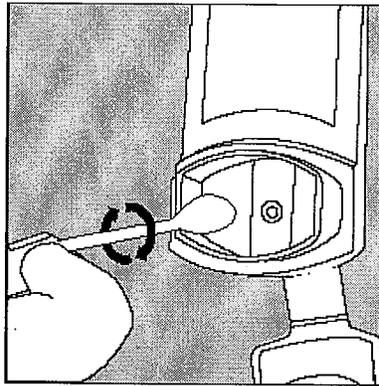


Figure 3

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1790 Step 3. Put the mouthpiece cover back on after the actuator has dried.

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