

1 PRESCRIBING INFORMATION

2 **ADVAIR DISKUS[®] 100/50**

3 (fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)

4

5 **ADVAIR DISKUS[®] 250/50**

6 (fluticasone propionate 250 mcg and salmeterol* 50 mcg inhalation powder)

7

8 **ADVAIR DISKUS[®] 500/50**

9 (fluticasone propionate 500 mcg and salmeterol* 50 mcg inhalation powder)

10

11 *As salmeterol xinafoate salt 72.5 mcg, equivalent to salmeterol base 50 mcg

12

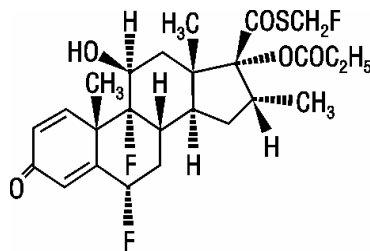
13 **For Oral Inhalation Only**

14 **WARNING:** Data from a large placebo-controlled US study that compared the safety of
15 salmeterol (SEREVENT[®] Inhalation Aerosol) or placebo added to usual asthma therapy showed
16 a small but significant increase in asthma-related deaths in patients receiving salmeterol (13
17 deaths out of 13,174 patients treated for 28 weeks) versus those on placebo (4 of 13,179).
18 Subgroup analyses suggest the risk may be greater in African American patients compared to
19 Caucasians (see WARNINGS).

20 **DESCRIPTION**

21 ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are
22 combinations of fluticasone propionate and salmeterol xinafoate.

23 One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having
24 the chemical name *S*-(fluoromethyl) 6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-
25 oxoandrosta-1,4-diene-17 β -carbothioate, 17-propionate and the following chemical structure:



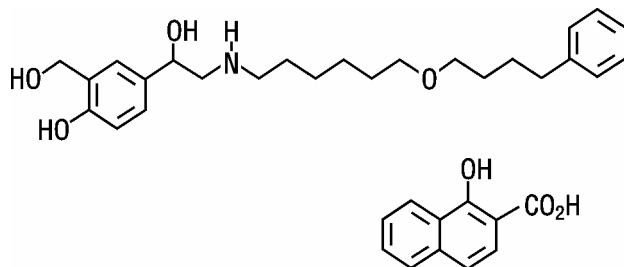
27

28

29 Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and
30 the empirical formula is C₂₅H₃₁F₃O₅S. It is practically insoluble in water, freely soluble in
31 dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

32 The other active component of ADVAIR DISKUS is salmeterol xinafoate, a beta₂-adrenergic
33 bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt

34 of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy- α^1 -[[[6-(4-
35 phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-
36 naphthalenecarboxylate, and it has the following chemical structure:



38
39
40 Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8, and the
41 empirical formula is $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in
42 ethanol, chloroform, and isopropanol; and sparingly soluble in water.

43 ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are
44 specially designed plastic devices containing a double-foil blister strip of a powder formulation
45 of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister
46 on the double-foil strip within the device contains 100, 250, or 500 mcg of microfine fluticasone
47 propionate and 72.5 mcg of microfine salmeterol xinafoate salt, equivalent to 50 mcg of
48 salmeterol base, in 12.5 mg of formulation containing lactose (which contains milk proteins).
49 Each blister contains 1 complete dose of both medications. After a blister containing medication
50 is opened by activating the device, the medication is dispersed into the airstream created by the
51 patient inhaling through the mouthpiece.

52 Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg
53 of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS
54 100/50, 250/50, and 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds.
55 In adult patients with obstructive lung disease and severely compromised lung function (mean
56 forced expiratory volume in 1 second [FEV₁] 20% to 30% of predicted), mean peak inspiratory
57 flow (PIF) through a DISKUS[®] inhalation device was 82.4 L/min (range, 46.1 to 115.3 L/min).

58 Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to
59 50 years) patients with asthma inhaling maximally through the DISKUS device show mean PIF
60 of 122.2 L/min (range, 81.6 to 152.1 L/min).

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

63 **CLINICAL PHARMACOLOGY**

64 **Mechanism of Action: ADVAIR DISKUS:** Since ADVAIR DISKUS contains both
65 fluticasone propionate and salmeterol, the mechanisms of action described below for the
66 individual components apply to ADVAIR DISKUS. These drugs represent 2 classes of

67 medications (a synthetic corticosteroid and a selective, long-acting beta-adrenergic receptor
68 agonist) that have different effects on clinical and physiological indices.

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

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

81 Inflammation is also a component in the pathogenesis of COPD. In contrast to asthma,
82 however, the predominant inflammatory cells in COPD include neutrophils, CD8+
83 T-lymphocytes, and macrophages. The effects of corticosteroids in the treatment of COPD are
84 not well defined and inhaled corticosteroids and fluticasone propionate when used apart from
85 ADVAIR DISKUS are not indicated for the treatment of COPD.

86 **Salmeterol Xinafoate:** Salmeterol is a long-acting beta₂-adrenergic agonist. In vitro studies
87 and in vivo pharmacologic studies demonstrate that salmeterol is selective for
88 beta₂-adrenoceptors compared with isoproterenol, which has approximately equal agonist
89 activity on beta₁- and beta₂-adrenoceptors. In vitro studies show salmeterol to be at least 50 times
90 more selective for beta₂-adrenoceptors than albuterol. Although beta₂-adrenoceptors are the
91 predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenoceptors are the
92 predominant receptors in the heart, there are also beta₂-adrenoceptors in the human heart
93 comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors
94 has not been established, but they raise the possibility that even highly selective beta₂-agonists
95 may have cardiac effects.

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

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

107 **Pharmacokinetics: ADVAIR DISKUS:** Following administration of ADVAIR DISKUS to
108 healthy subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to
109 2 hours and those of salmeterol were achieved in about 5 minutes.

110 In a single-dose crossover study, a higher than recommended dose of ADVAIR DISKUS was
111 administered to 14 healthy subjects. Two (2) inhalations of the following treatments were
112 administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol
113 powder 50 mcg given concurrently, and fluticasone propionate powder 500 mcg alone. Mean
114 peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL,
115 respectively, and of salmeterol averaged 200 and 150 pg/mL, respectively, indicating no
116 significant changes in systemic exposures of fluticasone propionate and salmeterol.

117 In a repeat-dose study, the highest recommended dose of ADVAIR DISKUS was
118 administered to 45 patients with asthma. One (1) inhalation twice daily of the following
119 treatments was administered: ADVAIR DISKUS 500/50, fluticasone propionate powder
120 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder
121 500 mcg alone. Mean peak steady-state plasma concentrations of fluticasone propionate
122 averaged 57, 73, and 70 pg/mL, respectively, indicating no significant changes in systemic
123 exposure of fluticasone propionate. No plasma concentrations of salmeterol were measured in
124 this repeat-dose study.

125 No significant changes in excretion of fluticasone propionate or salmeterol were observed.
126 The terminal half-life of fluticasone propionate averaged 5.33 to 7.65 hours when ADVAIR
127 DISKUS was administered, which is similar to that reported when fluticasone propionate was
128 given concurrently with salmeterol or when fluticasone propionate was given alone (average,
129 5.30 to 6.91 hours). No terminal half-life of salmeterol was reported upon administration of
130 ADVAIR DISKUS or salmeterol given concurrently with fluticasone propionate.

131 **Special Populations:** Formal pharmacokinetic studies using ADVAIR DISKUS have
132 not been conducted to examine gender differences or in special populations, such as elderly
133 patients or patients with hepatic or renal impairment.

134 **Drug Interactions:** In the repeat- and single-dose studies, there was no evidence of
135 significant drug interaction in systemic exposure between fluticasone propionate and salmeterol
136 when given as ADVAIR DISKUS.

137 **Fluticasone Propionate: Absorption:** Fluticasone propionate acts locally in the lung;
138 therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled
139 and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone
140 propionate is negligible (<1%), primarily due to incomplete absorption and presystemic
141 metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered
142 to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate from
143 the DISKUS device in healthy volunteers averages 18%.

144 Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma
145 (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone

146 propionate inhalation powder using the DISKUS device. The mean fluticasone propionate
147 plasma concentration was 110 pg/mL.

148 Peak steady-state fluticasone propionate plasma concentrations in subjects with COPD
149 averaged 53 pg/mL (range, 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily
150 (N = 30) via the DISKUS device.

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

154 The percentage of fluticasone propionate bound to human plasma proteins averages 91%.
155 Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly
156 bound to human transcortin.

157 **Metabolism:** The total clearance of fluticasone propionate is high (average,
158 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only
159 circulating metabolite detected in man is the 17 β -carboxylic acid derivative of fluticasone
160 propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had
161 less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of
162 human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other
163 metabolites detected in vitro using cultured human hepatoma cells have not been detected in
164 man.

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

169 **Special Populations: Hepatic Impairment:** Since fluticasone propionate is
170 predominantly cleared by hepatic metabolism, impairment of liver function may lead to
171 accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease
172 should be closely monitored.

173 **Gender:** Full pharmacokinetic profiles were obtained from 9 female and 16 male
174 patients with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using
175 the DISKUS device and from 14 female and 43 male patients with COPD given 250 or 500 mcg
176 twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

177 **Age:** No relationship between fluticasone propionate systemic exposure and age was
178 observed in 57 patients with COPD (aged 40 to 82 years) given 250 or 500 mcg twice daily.

179 **Other:** Formal pharmacokinetic studies using fluticasone propionate have not been
180 conducted in other special populations.

181 **Drug Interactions:** Fluticasone propionate is a substrate of cytochrome P450 3A4.
182 Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor
183 ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18
184 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was
185 coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate

186 concentrations following fluticasone propionate aqueous nasal spray alone were undetectable
187 (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{\max}
188 averaged 11.9 pg/mL [range, 10.8 to 14.1 pg/mL] and $AUC_{(0-\tau)}$ averaged 8.43 pg•hr/mL [range,
189 4.2 to 18.8 pg•hr/mL]). Fluticasone propionate C_{\max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range,
190 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively,
191 after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This
192 significant increase in plasma fluticasone propionate exposure resulted in a significant decrease
193 (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

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

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

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

206 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low
207 or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder
208 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol
209 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7
210 patients with asthma; plasma concentrations were very low, with mean peak concentrations of
211 167 pg/mL at 20 minutes and no accumulation with repeated doses.

212 **Distribution:** The percentage of salmeterol bound to human plasma proteins averages
213 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much
214 higher concentrations than those achieved following therapeutic doses of salmeterol.

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

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

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

224 **Special Populations: Hepatic Impairment:** Since salmeterol is predominantly
225 cleared by hepatic metabolism, impairment of liver function may lead to accumulation of
226 salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

227 **Other:** Formal pharmacokinetic studies using salmeterol base have not been conducted
228 in other special populations.

229 **Pharmacodynamics: ADVAIR DISKUS:** Since systemic pharmacodynamic effects of
230 salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce
231 measurable effects. Four studies were conducted in healthy subjects: (1) a single-dose crossover
232 study using 2 inhalations of ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg
233 and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg
234 given alone, (2) a cumulative dose study using 50 to 400 mcg of salmeterol powder given alone
235 or as ADVAIR DISKUS 500/50, (3) a repeat-dose study for 11 days using 2 inhalations twice
236 daily of ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, or salmeterol
237 powder 50 mcg, and (4) a single-dose study using 5 inhalations of ADVAIR DISKUS 100/50,
238 fluticasone propionate powder 100 mcg alone, or placebo. In these studies no significant
239 differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood
240 pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as ADVAIR
241 DISKUS, concurrently with fluticasone propionate from separate inhalers, or as salmeterol alone.
242 The systemic pharmacodynamic effects of salmeterol were not altered by the presence of
243 fluticasone propionate in ADVAIR DISKUS. The potential effect of salmeterol on the effects of
244 fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis was also evaluated in
245 these studies. No significant differences across treatments were observed in 24-hour urinary
246 cortisol excretion and, where measured, 24-hour plasma cortisol AUC. The systemic
247 pharmacodynamic effects of fluticasone propionate were not altered by the presence of
248 salmeterol in ADVAIR DISKUS in healthy subjects.

249 **Asthma:** In clinical studies with ADVAIR DISKUS in patients with asthma, no
250 significant differences were observed in the systemic pharmacodynamic effects of salmeterol
251 (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was
252 given alone or as ADVAIR DISKUS. In 72 adolescent and adult patients with asthma given
253 either ADVAIR DISKUS 100/50 or ADVAIR DISKUS 250/50, continuous 24-hour
254 electrocardiographic monitoring was performed after the first dose and after 12 weeks of
255 therapy, and no clinically significant dysrhythmias were noted.

256 In a 28-week study in patients with asthma, ADVAIR DISKUS 500/50 twice daily was
257 compared with the concurrent use of salmeterol powder 50 mcg plus fluticasone propionate
258 powder 500 mcg from separate inhalers or fluticasone propionate powder 500 mcg alone. No
259 significant differences across treatments were observed in plasma cortisol AUC after 12 weeks
260 of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

261 In a 12-week study in patients with asthma, ADVAIR DISKUS 250/50 twice daily was
262 compared with fluticasone propionate powder 250 mcg alone, salmeterol powder 50 mcg alone,
263 and placebo. For most patients, the ability to increase cortisol production in response to stress, as

264 assessed by 30-minute cosyntropin stimulation, remained intact with ADVAIR DISKUS. One
265 patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal response (peak serum
266 cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who received placebo,
267 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients who received
268 salmeterol.

269 **Chronic Obstructive Pulmonary Disease:** In clinical studies with ADVAIR
270 DISKUS in patients with COPD associated with chronic bronchitis, no significant differences
271 were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR DISKUS, the
272 individual components of ADVAIR DISKUS, and placebo. In a study of ADVAIR DISKUS
273 250/50, 8 subjects (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in the
274 fluticasone propionate 250 mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the
275 placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5)
276 of these 8 subjects had a prolonged QTc interval at baseline.

277 In a 24-week study, 130 patients with COPD associated with chronic bronchitis received
278 continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of
279 twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate powder
280 500 mcg, salmeterol powder 50 mcg, or placebo. No significant differences in ventricular or
281 supraventricular arrhythmias and heart rate were observed among the groups treated with
282 ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the
283 fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the
284 group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of
285 nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone 500 mcg
286 treatment groups).

287 Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in
288 101 patients with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate
289 powder 250 mcg, salmeterol powder 50 mcg, or placebo. For most patients, the ability to
290 increase cortisol production in response to stress, as assessed by short cosyntropin stimulation,
291 remained intact with ADVAIR DISKUS 250/50. One (1) patient (3%) who received ADVAIR
292 DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL
293 assessed by high-performance liquid chromatography) after dosing, compared with 2 patients
294 (9%) who received fluticasone propionate 250 mcg, 2 patients (7%) who received salmeterol
295 50 mcg, and 1 patient (4%) who received placebo following 24 weeks of treatment or early
296 discontinuation from study.

297 **Fluticasone Propionate: Asthma:** In clinical trials with fluticasone propionate inhalation
298 powder using doses up to and including 250 mcg twice daily, occasional abnormal short
299 cosyntropin tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted
300 both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence
301 of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out
302 with the DISKHALER[®] inhalation device in 64 patients with mild, persistent asthma (mean
303 FEV₁ 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo,

304 no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin
305 infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1
306 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing
307 at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had
308 an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or
309 2 years.

310 **Chronic Obstructive Pulmonary Disease:** In a 24-week study, the steady-state
311 fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of
312 patients with COPD associated with chronic bronchitis (N = 86) randomized to twice-daily
313 fluticasone propionate inhalation powder via the DISKUS 500 mcg, fluticasone propionate
314 inhalation powder 250 mcg, or placebo. Serial serum cortisol concentrations were measured
315 across a 12-hour dosing interval following at least 4 weeks of dosing. Serum cortisol
316 concentrations following 250 and 500 mcg twice-daily dosing were 10% and 21% lower than
317 placebo, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

318 **Salmeterol Xinafoate:** Inhaled salmeterol, like other beta-adrenergic agonist drugs, can
319 produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium
320 (see PRECAUTIONS: General). The cardiovascular effects (heart rate, blood pressure)
321 associated with salmeterol occur with similar frequency, and are of similar type and severity, as
322 those noted following albuterol administration.

323 **Asthma:** The effects of rising doses of salmeterol and standard inhaled doses of albuterol
324 were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg
325 administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the
326 same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and
327 adult patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent
328 continuous electrocardiographic monitoring during two 12-hour periods after the first dose and
329 after 1 month of therapy, and no clinically significant dysrhythmias were noted.

330 **Chronic Obstructive Pulmonary Disease:** In 24-week clinical studies in patients
331 with COPD associated with chronic bronchitis, the incidence of clinically significant
332 electrocardiogram (ECG) abnormalities (myocardial ischemia, ventricular hypertrophy, clinically
333 significant conduction abnormalities, clinically significant arrhythmias) was lower for patients
334 who received salmeterol (1%, 9 of 688 patients who received either salmeterol 50 mcg or
335 ADVAIR DISKUS) compared with placebo (3%, 10 of 370 subjects).

336 No significant differences with salmeterol 50 mcg alone or in combination with fluticasone
337 propionate as ADVAIR DISKUS 500/50 was observed on pulse rate and systolic and diastolic
338 blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign
339 measurements after the first dose (N = 183) and after 12 weeks of therapy (N = 149). Median
340 changes from baseline in pulse rate and systolic and diastolic blood pressure were similar to
341 those seen with placebo (see ADVERSE REACTIONS: Chronic Obstructive Pulmonary Disease
342 Associated With Chronic Bronchitis).

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

347 **CLINICAL TRIALS**

348 **Asthma:** In clinical trials comparing ADVAIR DISKUS with the individual components,
349 improvements in most efficacy endpoints were greater with ADVAIR DISKUS than with the use
350 of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar
351 results between ADVAIR DISKUS and the concurrent use of fluticasone propionate plus
352 salmeterol at corresponding doses from separate inhalers.

353 **Studies Comparing ADVAIR DISKUS to Fluticasone Propionate Alone or**
354 **Salmeterol Alone:** Three (3) double-blind, parallel-group clinical trials were conducted with
355 ADVAIR DISKUS in 1,208 adolescent and adult patients (≥ 12 years, baseline FEV₁ 63% to 72%
356 of predicted normal) with asthma that was not optimally controlled on their current therapy. All
357 treatments were inhalation powders, given as 1 inhalation from the DISKUS device twice daily,
358 and other maintenance therapies were discontinued.

359 **Study 1: Clinical Trial With ADVAIR DISKUS 100/50:** This placebo-controlled,
360 12-week, US study compared ADVAIR DISKUS 100/50 with its individual components,
361 fluticasone propionate 100 mcg and salmeterol 50 mcg. The study was stratified according to
362 baseline asthma maintenance therapy; patients were using either inhaled corticosteroids
363 (N = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg;
364 fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg)
365 or salmeterol (N = 106). Baseline FEV₁ measurements were similar across treatments: ADVAIR
366 DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and
367 placebo, 2.15 L.

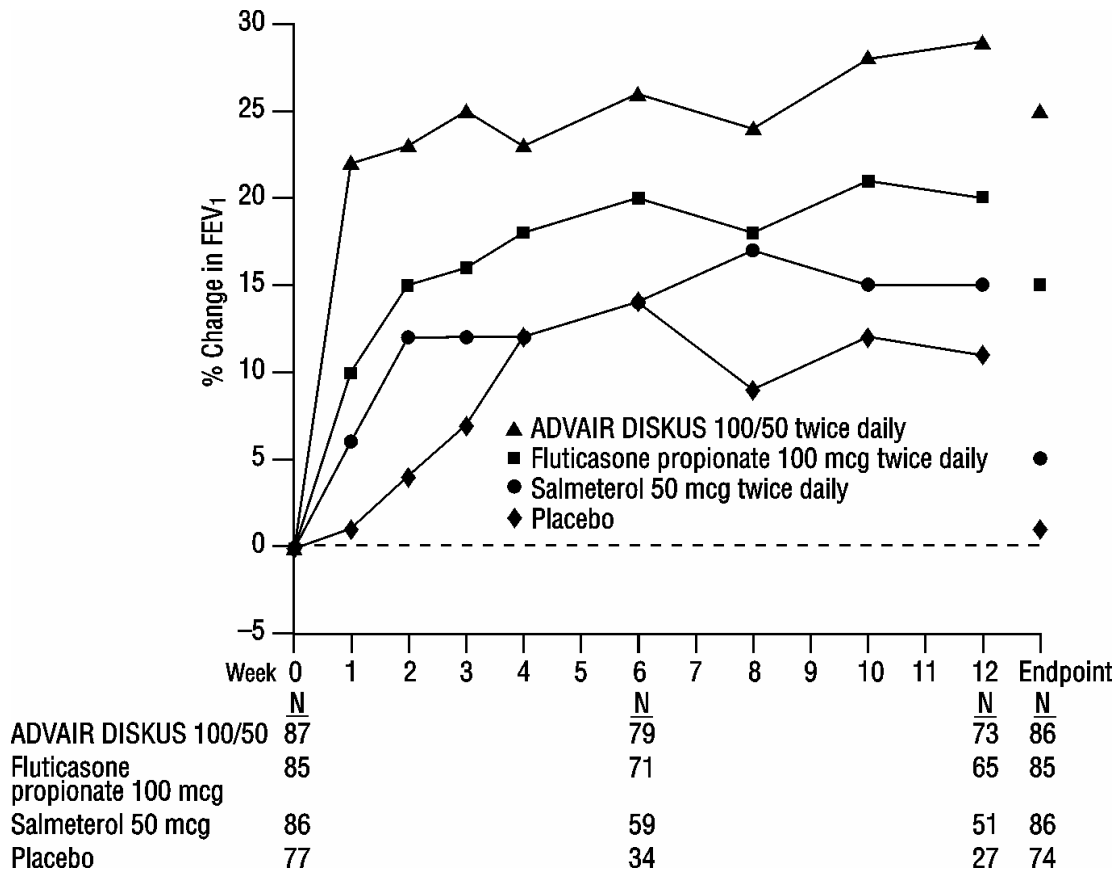
368 Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were
369 utilized for this placebo-controlled study. Worsening asthma was defined as a clinically
370 important decrease in FEV₁ or peak expiratory flow (PEF), increase in use of VENTOLIN[®]
371 (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency
372 intervention or hospitalization due to asthma, or requirement for asthma medication not allowed
373 by the protocol. As shown in Table 1, statistically significantly fewer patients receiving
374 ADVAIR DISKUS 100/50 were withdrawn due to worsening asthma compared with fluticasone
375 propionate, salmeterol, and placebo.
376

377 **Table 1. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously**
 378 **Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**

ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
3%	11%	35%	49%

379
 380 The FEV₁ results are displayed in Figure 1. Because this trial used predetermined criteria for
 381 worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV₁
 382 results at Endpoint (last available FEV₁ result) are also provided. Patients receiving ADVAIR
 383 DISKUS 100/50 had significantly greater improvements in FEV₁ (0.51 L, 25%) compared with
 384 fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L,
 385 1%). These improvements in FEV₁ with ADVAIR DISKUS were achieved regardless of baseline
 386 asthma maintenance therapy (inhaled corticosteroids or salmeterol).

387
 388 **Figure 1. Mean Percent Change From Baseline in FEV₁ in Patients With Asthma**
 389 **Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**



393 The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in
 394 Table 2.

395

396 **Table 2. Peak Expiratory Flow Results for Patients With Asthma Previously Treated**
 397 **With Either Inhaled Corticosteroids or Salmeterol (Study 1)**

Efficacy Variable*	ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
AM PEF (L/min)				
Baseline	393	374	369	382
Change from baseline	53	17	-2	-24
PM PEF (L/min)				
Baseline	418	390	396	398
Change from baseline	35	18	-7	-13

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

398

399 The subjective impact of asthma on patients' perception of health was evaluated through use
 400 of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point
 401 scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR DISKUS
 402 100/50 had clinically meaningful improvements in overall asthma-specific quality of life as
 403 defined by a difference between groups of ≥ 0.5 points in change from baseline AQLQ scores
 404 (difference in AQLQ score of 1.25 compared to placebo).

405 **Study 2: Clinical Trial With ADVAIR DISKUS 250/50:** This placebo-controlled,
 406 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components,
 407 fluticasone propionate 250 mcg and salmeterol 50 mcg in 349 patients with asthma using inhaled
 408 corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to
 409 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100
 410 to 1,600 mcg). Baseline FEV₁ measurements were similar across treatments: ADVAIR DISKUS
 411 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

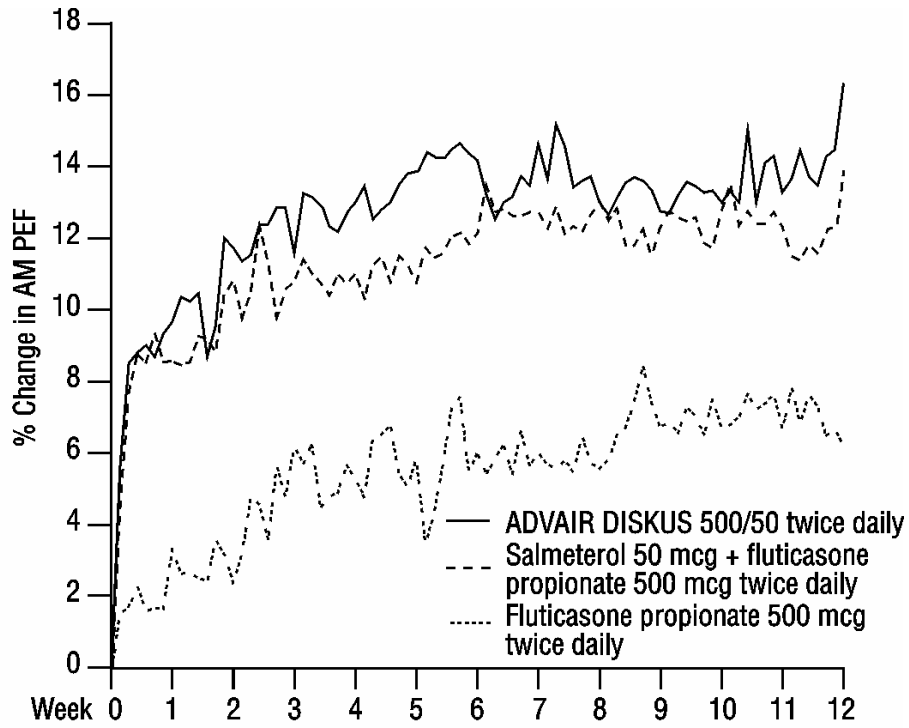
412 Efficacy results in this study were similar to those observed in Study 1. Patients receiving
 413 ADVAIR DISKUS 250/50 had significantly greater improvements in FEV₁ (0.48 L, 23%)
 414 compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and
 415 placebo (decrease of 0.11 L, decrease of 5%). Statistically significantly fewer patients receiving
 416 ADVAIR DISKUS 250/50 were withdrawn from this study for worsening asthma (4%)
 417 compared with fluticasone propionate (22%), salmeterol (38%), and placebo (62%). In addition,
 418 ADVAIR DISKUS 250/50 was superior to fluticasone propionate, salmeterol, and placebo for
 419 improvements in morning and evening PEF. Patients receiving ADVAIR DISKUS 250/50 also
 420 had clinically meaningful improvements in overall asthma-specific quality of life as described in
 421 Study 1 (difference in AQLQ score of 1.29 compared to placebo).

422 **Study 3: Clinical Trial With ADVAIR DISKUS 500/50:** This 28-week, non-US study
423 compared ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and concurrent
424 therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from separate
425 inhalers) twice daily in 503 patients with asthma using inhaled corticosteroids (daily doses of
426 beclomethasone dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg; flunisolide
427 1,500 to 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750 to
428 1,000 mcg inhalation powder]). The primary efficacy parameter, morning PEF, was collected
429 daily for the first 12 weeks of the study. The primary purpose of weeks 13 to 28 was to collect
430 safety data.

431 Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50,
432 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. As
433 shown in Figure 2, morning PEF improved significantly with ADVAIR DISKUS 500/50
434 compared with fluticasone propionate 500 mcg over the 12-week treatment period.
435 Improvements in morning PEF observed with ADVAIR DISKUS 500/50 were similar to
436 improvements observed with concurrent therapy.

437

438 **Figure 2. Mean Percent Change From Baseline in Morning Peak Expiratory**
 439 **Flow in Patients With Asthma Previously Treated With Inhaled Corticosteroids**
 440 **(Study 3)**
 441



	Week 0	Week 6	Week 12
	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 500/50	167	159	149
Salmeterol 50 mcg + fluticasone propionate 500 mcg	170	160	147
Fluticasone propionate 500 mcg	164	148	136

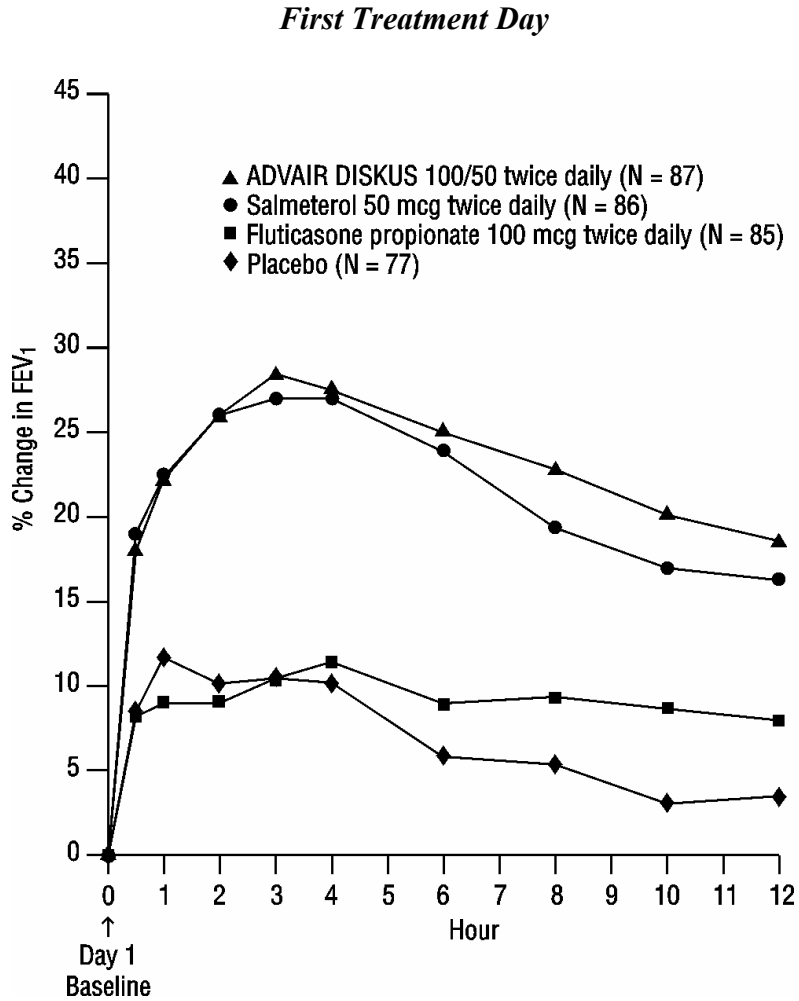
442
 443
 444 **Onset of Action and Progression of Improvement in Asthma Control:** The onset
 445 of action and progression of improvement in asthma control were evaluated in the 2
 446 placebo-controlled US trials. Following the first dose, the median time to onset of clinically
 447 significant bronchodilatation ($\geq 15\%$ improvement in FEV₁) in most patients was seen within 30
 448 to 60 minutes. Maximum improvement in FEV₁ generally occurred within 3 hours, and clinically
 449 significant improvement was maintained for 12 hours (see Figure 3).

450 Following the initial dose, predose FEV₁ relative to Day 1 baseline improved markedly over
 451 the first week of treatment and continued to improve over the 12 weeks of treatment in both
 452 studies.

453 No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR
 454 DISKUS 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV₁ following
 455 12 weeks of therapy.
 456

457 **Figure 3. Percent Change in Serial 12-hour FEV₁**
458 **in Patients With Asthma Previously Using Either Inhaled**
459 **Corticosteroids or Salmeterol (Study 1)**

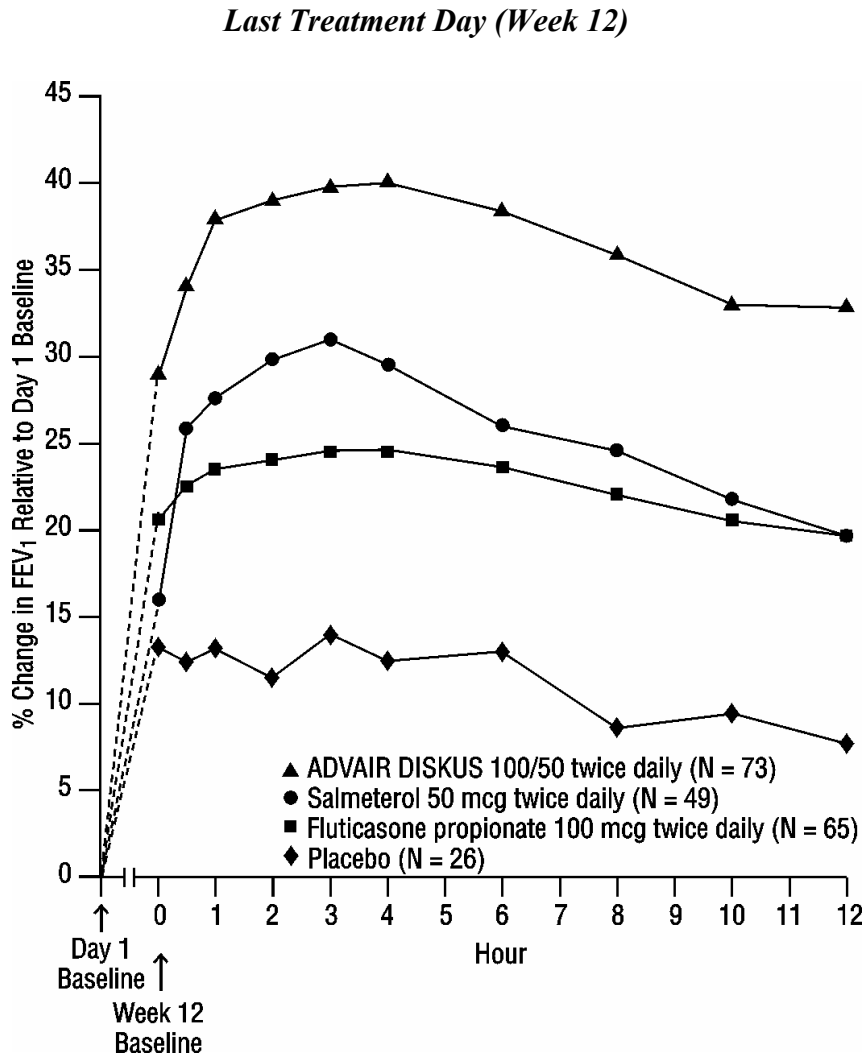
460
461
462



463
464

465 **Figure 4. Percent Change in Serial 12-hour FEV₁**
 466 **in Patients Previously With Asthma Using Either Inhaled**
 467 **Corticosteroids or Salmeterol (Study 1)**

468
 469
 470



471
 472

473 Reduction in asthma symptoms, use of rescue VENTOLIN Inhalation Aerosol, and
 474 improvement in morning and evening PEF also occurred within the first day of treatment with
 475 ADVAIR DISKUS, and continued to improve over the 12 weeks of therapy in both studies.

476 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** In a
 477 clinical trial evaluating twice-daily treatment with ADVAIR DISKUS 250/50 in patients with
 478 COPD associated with chronic bronchitis, improvements in lung function (as defined by predose
 479 and postdose FEV₁) were significantly greater with ADVAIR DISKUS than with fluticasone
 480 propionate 250 mcg, salmeterol 50 mcg, or placebo. The study was a randomized, double-blind,
 481 parallel-group, 24-week trial. All patients had a history of cough productive of sputum that was
 482 not attributable to another disease process on most days for at least 3 months of the year for at

483 least 2 years. Study treatments were inhalation powders given as 1 inhalation from the DISKUS
 484 device twice daily. Maintenance COPD therapies were discontinued, with the exception of
 485 theophylline.

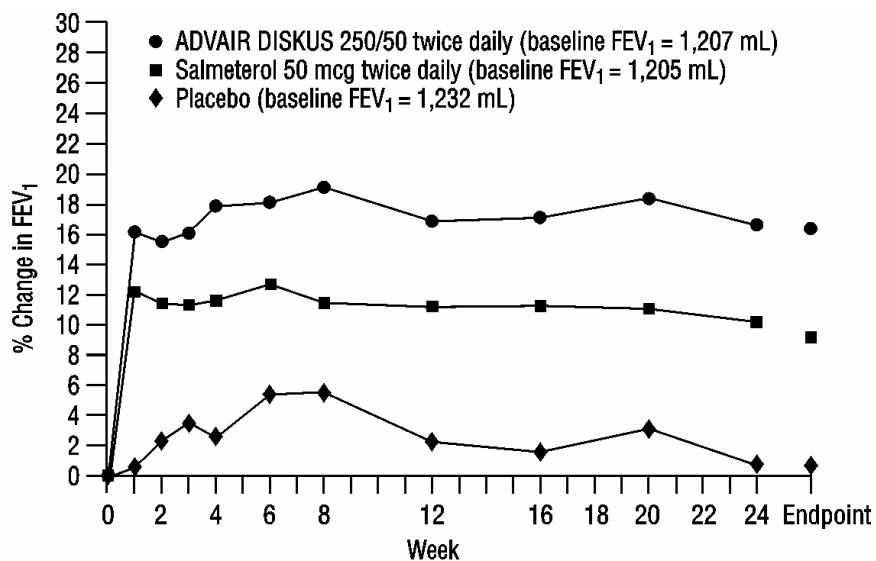
486 Figures 5 and 6 display predose and 2-hour postdose FEV₁ results. To account for patient
 487 withdrawals during the study, FEV₁ at Endpoint (last evaluable FEV₁) was evaluated. Patients
 488 receiving ADVAIR DISKUS 250/50 had significantly greater improvements in predose FEV₁ at
 489 Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL,
 490 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung
 491 function with ADVAIR DISKUS (Figure 5). Patients receiving ADVAIR DISKUS 250/50 had
 492 significantly greater improvements in postdose FEV₁ at Endpoint (281 mL, 27%) compared with
 493 fluticasone propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the
 494 contribution of salmeterol to the improvement in lung function with ADVAIR DISKUS
 495 (Figure 6).

496 A similar degree of improvement in lung function was also observed with ADVAIR DISKUS
 497 500/50 twice daily.

498

499 **Figure 5. Predose FEV₁: Mean Percent Change From Baseline in Patients**
 500 **With COPD Associated With Chronic Bronchitis**

501

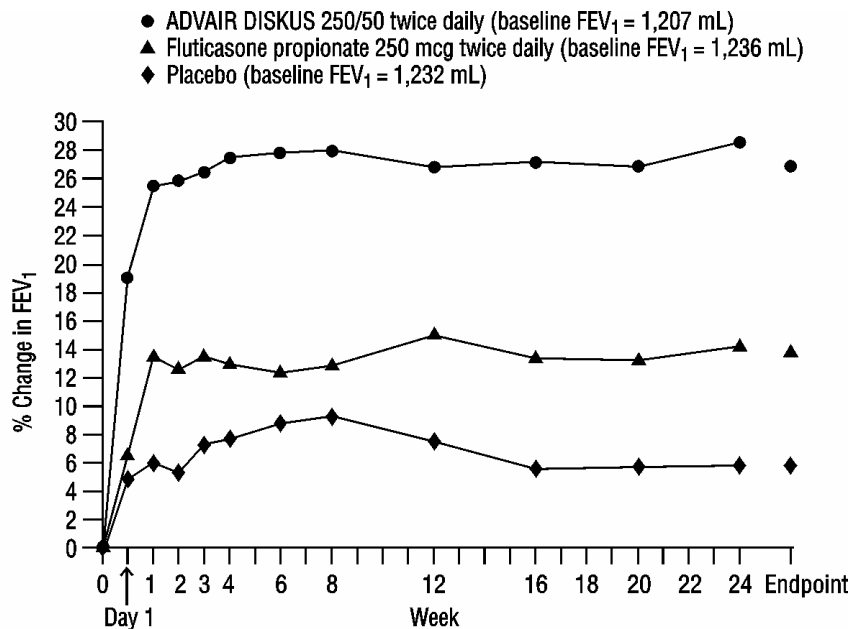


	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 250/50	178	144	124	171
Salmeterol 50 mcg	177	135	119	168
Placebo	185	139	125	172

502

503

504 **Figure 6. Two-Hour Postdose FEV₁: Mean Percent Changes From Baseline**
 505 **Over Time in Patients With COPD Associated With Chronic Bronchitis**
 506



	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 250/50	178	144	117	171
Fluticasone propionate 250 mcg	183	147	130	175
Placebo	185	139	119	172

507
 508
 509 Patients treated with ADVAIR DISKUS 250/50 or ADVAIR DISKUS 500/50 did not have a
 510 significant reduction in chronic bronchitis symptoms (as measured by the Chronic Bronchitis
 511 Symptom Questionnaire) or in COPD exacerbations compared to patients treated with placebo
 512 over the 24 weeks of therapy. The improvement in lung function with ADVAIR DISKUS 500/50
 513 was similar to the improvement seen with ADVAIR DISKUS 250/50. Since there is evidence of
 514 more systemic exposure to fluticasone from this higher dose and no documented advantage for
 515 efficacy, ADVAIR DISKUS 500/50 is not recommended for use in COPD.

516 The benefit of treatment of patients with COPD associated with chronic bronchitis with
 517 ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated.

518 **INDICATIONS AND USAGE**

519 **Asthma:** ADVAIR DISKUS is indicated for the long-term, twice-daily, maintenance treatment
 520 of asthma in patients 12 years of age and older.

521 ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

522 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:**

523 ADVAIR DISKUS 250/50 is indicated for the twice-daily maintenance treatment of airflow
 524 obstruction in patients with COPD associated with chronic bronchitis.

525 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of
 526 COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50,

527 are not recommended (see DOSAGE AND ADMINISTRATION: Chronic Obstructive
528 Pulmonary Disease Associated With Chronic Bronchitis).

529 The benefit of treating patients with COPD associated with chronic bronchitis with ADVAIR
530 DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients who are
531 treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis for periods
532 longer than 6 months should be reevaluated periodically to assess the continuing benefits and
533 potential risks of treatment.

534 ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

535 **CONTRAINDICATIONS**

536 ADVAIR DISKUS is contraindicated in the primary treatment of status asthmaticus or other
537 acute episodes of asthma or COPD where intensive measures are required.

538 Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see
539 DESCRIPTION and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site*
540 *Specific*).

541 **WARNINGS**

542 DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS
543 STOPPED EARLY SUGGEST THAT SALMETEROL, A COMPONENT OF ADVAIR
544 DISKUS, MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR
545 ASTHMA-RELATED DEATHS. The Salmeterol Multi-center Asthma Research Trial
546 (SMART) enrolled long-acting beta₂-agonist-naïve patients with asthma to assess the safety of
547 salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared to
548 placebo, when added to usual asthma therapy. The primary endpoint was the combined number
549 of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and
550 mechanical ventilation). Other endpoints included combined asthma-related deaths or
551 life-threatening experiences and asthma-related deaths.

552 A planned interim analysis was conducted when approximately half of the intended number of
553 patients had been enrolled (N = 26,353). The analysis showed no significant difference for the
554 primary endpoint for the total population. However, a higher number of asthma-related deaths or
555 life-threatening experiences (36 vs. 23) and a higher number of asthma-related deaths (13 vs. 4)
556 occurred in the patients treated with SEREVENT Inhalation Aerosol. Post hoc subgroup analyses
557 revealed no significant increase in respiratory- or asthma-related episodes, including deaths, in
558 Caucasian patients. In African Americans, the study showed a small, though statistically
559 significantly greater, number of primary events (20 vs. 7), asthma-related deaths or
560 life-threatening experiences (19 vs. 4), and asthma-related deaths (8 vs. 1) in patients taking
561 SEREVENT Inhalation Aerosol compared to those taking placebo. Even though SMART did not
562 reach predetermined stopping criteria for the total population, the study was stopped due to the
563 findings in African American patients and difficulties in enrollment. The data from the SMART
564 study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as
565 fluticasone propionate, a component of ADVAIR DISKUS, provides protection from this risk.

566 Therefore, it is not known whether the findings seen with SEREVENT Inhalation Aerosol would
567 apply to ADVAIR DISKUS.

568 Findings similar to the SMART study findings were reported in a prior 16-week clinical study
569 performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the
570 SNS study, the incidence of asthma-related death was numerically, though not statistically,
571 greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol
572 (180 mcg 4 times daily) added to usual asthma therapy.

573 Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the findings
574 seen in the SMART study may be consistent with a class effect.

575 **1. ADVAIR DISKUS SHOULD NOT BE USED FOR TRANSFERRING PATIENTS**
576 **FROM SYSTEMIC CORTICOSTEROID THERAPY.** Particular care is needed for patients
577 who have been transferred from systemically active corticosteroids to inhaled corticosteroids
578 because deaths due to adrenal insufficiency have occurred in patients with asthma during and
579 after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids.
580 After withdrawal from systemic corticosteroids, a number of months are required for recovery of
581 HPA function.

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

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

596 **2. ADVAIR DISKUS SHOULD NOT BE INITIATED IN PATIENTS DURING RAPIDLY**
597 **DETERIORATING OR POTENTIALLY LIFE-THREATENING EPISODES OF**
598 **ASTHMA. Serious acute respiratory events, including fatalities, have been reported both in**
599 **the United States and worldwide when salmeterol, a component of ADVAIR DISKUS, has**
600 **been initiated in patients with significantly worsening or acutely deteriorating asthma.** In
601 most cases, these have occurred in patients with severe asthma (e.g., patients with a history of
602 corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent
603 hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients
604 in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications;
605 increasing need for inhaled, short-acting beta₂-agonists; increasing need for systemic

606 corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or
607 progressive deterioration in pulmonary function). However, they have occurred in a few patients
608 with less severe asthma as well. It was not possible from these reports to determine whether
609 salmeterol contributed to these events or simply failed to relieve the deteriorating asthma.

610 **3. Drug Interaction With Ritonavir:** A drug interaction study in healthy subjects has shown
611 that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma
612 fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations
613 (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug*
614 *Interactions* and PRECAUTIONS: Drug Interactions: *Inhibitors of Cytochrome P450*). During
615 postmarketing use, there have been reports of clinically significant drug interactions in patients
616 receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects
617 including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone
618 propionate and ritonavir is not recommended unless the potential benefit to the patient
619 outweighs the risk of systemic corticosteroid side effects.

620 **4. Do Not Use ADVAIR DISKUS to Treat Acute Symptoms:** An inhaled, short-acting
621 beta₂-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms of shortness of
622 breath. When prescribing ADVAIR DISKUS, the physician must also provide the patient with an
623 inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of shortness of breath that
624 occurs acutely, despite regular twice-daily (morning and evening) use of ADVAIR DISKUS.

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

630 **5. Watch for Increasing Use of Inhaled, Short-Acting Beta₂-Agonists, Which Is a Marker of**
631 **Deteriorating Asthma:** Asthma may deteriorate acutely over a period of hours or chronically over
632 several days or longer. If the patient's inhaled, short-acting beta₂-agonist becomes less effective,
633 the patient needs more inhalations than usual, or the patient develops a significant decrease in
634 lung function, this may be a marker of destabilization of the disease. In this setting, the patient
635 requires immediate reevaluation with reassessment of the treatment regimen, giving special
636 consideration to the possible need for replacing the current strength of ADVAIR DISKUS with a
637 higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids.
638 Patients should not use more than 1 inhalation twice daily (morning and evening) of ADVAIR
639 DISKUS.

640 **6. Do Not Use an Inhaled, Long-Acting Beta₂-Agonist in Conjunction With ADVAIR DISKUS:**
641 Patients who are receiving ADVAIR DISKUS twice daily should not use additional salmeterol
642 or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of exercise-induced
643 bronchospasm (EIB) or the maintenance treatment of asthma or the maintenance treatment of
644 bronchospasm associated with COPD. Additional benefit would not be gained from using

645 supplemental salmeterol or formoterol for prevention of EIB since ADVAIR DISKUS already
646 contains an inhaled, long-acting beta₂-agonist.

647 7. Do Not Exceed Recommended Dosage: ADVAIR DISKUS should not be used more often or
648 at higher doses than recommended. Fatalities have been reported in association with excessive
649 use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times
650 the recommended dose) have been associated with clinically significant prolongation of the QTc
651 interval, which has the potential for producing ventricular arrhythmias.

652 8. Paradoxical Bronchospasm: As with other inhaled asthma and COPD medications, ADVAIR
653 DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical
654 bronchospasm occurs following dosing with ADVAIR DISKUS, it should be treated
655 immediately with an inhaled, short-acting bronchodilator, ADVAIR DISKUS should be
656 discontinued immediately, and alternative therapy should be instituted.

657 9. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after
658 administration of ADVAIR DISKUS, as demonstrated by cases of urticaria, angioedema, rash,
659 and bronchospasm.

660 10. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as
661 stridor and choking, have been reported in patients receiving fluticasone propionate and
662 salmeterol, components of ADVAIR DISKUS.

663 11. Cardiovascular Disorders: ADVAIR DISKUS, like all products containing sympathomimetic
664 amines, should be used with caution in patients with cardiovascular disorders, especially
665 coronary insufficiency, cardiac arrhythmias, and hypertension. Salmeterol, a component of
666 ADVAIR DISKUS, can produce a clinically significant cardiovascular effect in some patients as
667 measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon
668 after administration of salmeterol at recommended doses, if they occur, the drug may need to be
669 discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as
670 flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The
671 clinical significance of these findings is unknown.

672 12. Discontinuation of Systemic Corticosteroids: Transfer of patients from systemic
673 corticosteroid therapy to ADVAIR DISKUS may unmask conditions previously suppressed by
674 the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and
675 eosinophilic conditions.

676 13. Immunosuppression: Persons who are using drugs that suppress the immune system are more
677 susceptible to infections than healthy individuals. Chickenpox and measles, for example, can
678 have a more serious or even fatal course in susceptible children or adults using corticosteroids.
679 In such children or adults who have not had these diseases or been properly immunized,
680 particular care should be taken to avoid exposure. How the dose, route, and duration of
681 corticosteroid administration affect the risk of developing a disseminated infection is not known.
682 The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also
683 not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG)
684 may be indicated. If exposed to measles, prophylaxis with pooled intramuscular

685 immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG
686 and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be
687 considered.

688 **PRECAUTIONS**

689 **General: Cardiovascular Effects:** Cardiovascular and central nervous system effects seen
690 with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can
691 occur after use of salmeterol, a component of ADVAIR DISKUS, and may require
692 discontinuation of ADVAIR DISKUS. ADVAIR DISKUS, like all medications containing
693 sympathomimetic amines, should be used with caution in patients with cardiovascular disorders,
694 especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with
695 convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to
696 sympathomimetic amines.

697 As has been described with other beta-adrenergic agonist bronchodilators, clinically
698 significant changes in ECGs have been seen infrequently in individual patients in controlled
699 clinical studies with ADVAIR DISKUS and salmeterol. Clinically significant changes in systolic
700 and/or diastolic blood pressure and pulse rate have been seen infrequently in individual patients
701 in controlled clinical studies with salmeterol, a component of ADVAIR DISKUS.

702 **Metabolic and Other Effects:** Long-term use of orally inhaled corticosteroids may affect
703 normal bone metabolism, resulting in a loss of bone mineral density (BMD). A 2-year study of
704 160 patients (females 18 to 40 and males 18 to 50 years of age) with asthma receiving
705 chlorofluorocarbon-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice
706 daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and
707 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar
708 region L1 through L4. Long-term treatment effects of fluticasone propionate on BMD in the
709 COPD population have not been studied.

710 In patients with major risk factors for decreased bone mineral content, such as tobacco use,
711 advanced age, sedentary lifestyle, poor nutrition, family history of osteoporosis, or chronic use of
712 drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), ADVAIR DISKUS
713 may pose an additional risk. Since patients with COPD often have multiple risk factors for
714 reduced BMD, assessment of BMD is recommended, including prior to instituting ADVAIR
715 DISKUS 250/50 and periodically thereafter. If significant reductions in BMD are seen and
716 ADVAIR DISKUS 250/50 is still considered medically important for that patient's COPD
717 therapy, use of medication to treat or prevent osteoporosis should be strongly considered.
718 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of
719 COPD associated with chronic bronchitis, and higher doses, including ADVAIR DISKUS
720 500/50, are not recommended.

721 Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with
722 asthma and COPD following the long-term administration of inhaled corticosteroids, including

723 fluticasone propionate, a component of ADVAIR DISKUS; therefore, regular eye examinations
724 should be considered.

725 Lower respiratory tract infections, including pneumonia, have been reported following the
726 inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR
727 DISKUS.

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

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

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

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

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

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

758 Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to
759 pediatric patients (see PRECAUTIONS: Pediatric Use). Patients should be maintained on the
760 lowest strength of ADVAIR DISKUS that effectively controls their asthma.

761 The long-term effects of ADVAIR DISKUS in human subjects are not fully known. In
762 particular, the effects resulting from chronic use of fluticasone propionate on developmental or

763 immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients
764 have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or
765 longer. In clinical studies in patients with asthma treated for 2 years with inhaled fluticasone
766 propionate, no apparent differences in the type or severity of adverse reactions were observed
767 after long- versus short-term treatment.

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

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

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

787 **Chronic Obstructive Pulmonary Disease:** ADVAIR DISKUS 250/50 twice daily is the
788 only dosage recommended for the treatment of airflow obstruction in patients with COPD
789 associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not
790 recommended, as no additional improvement in lung function (defined by predose and postdose
791 FEV₁) was observed in clinical trials and higher doses of corticosteroids increase the risk of
792 systemic effects.

793 The benefit of treatment of patients with COPD associated with chronic bronchitis with
794 ADVAIR DISKUS 250/50 for periods longer than 6 months has not been evaluated. Patients
795 who are treated with ADVAIR DISKUS 250/50 for COPD associated with chronic bronchitis
796 for periods longer than 6 months should be reevaluated periodically to assess the continuing
797 benefits and potential risks of treatment.

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

801 It is important that patients understand how to use the DISKUS inhalation device
802 appropriately and how it should be used in relation to other asthma or COPD medications they
803 are taking. Patients should be given the following information:

- 804 1. Patients should use ADVAIR DISKUS at regular intervals as directed. Results of clinical
805 trials indicate significant improvement may occur within the first 30 minutes of taking the
806 first dose; however, the full benefit may not be achieved until treatment has been
807 administered for 1 week or longer. The patient should not use more than the prescribed
808 dosage but should contact the physician if symptoms do not improve or if the condition
809 worsens.
- 810 2. Most patients are able to taste or feel a dose delivered from ADVAIR DISKUS. However,
811 whether or not patients are able to sense delivery of a dose, you should instruct them not to
812 exceed the recommended dose of 1 inhalation each morning and evening, approximately 12
813 hours apart. You should instruct them to contact you or the pharmacist if they have questions.
- 814 3. The bronchodilation from a single dose of ADVAIR DISKUS may last up to 12 hours or
815 longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not
816 be exceeded. Patients who are receiving ADVAIR DISKUS twice daily should not use
817 salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of
818 EIB or maintenance treatment of asthma or the maintenance treatment of bronchospasm in
819 COPD.
- 820 4. ADVAIR DISKUS is not meant to relieve acute asthma symptoms and extra doses should
821 not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting
822 beta₂-agonist such as albuterol (the physician should provide the patient with such
823 medication and instruct the patient in how it should be used). ADVAIR DISKUS is not
824 meant to relieve acute asthma symptoms or exacerbations of COPD.
- 825 5. Patients should not stop therapy with ADVAIR DISKUS without physician/provider
826 guidance since symptoms may recur after discontinuation.
- 827 6. The physician should be notified immediately if any of the following situations occur, which
828 may be a sign of seriously worsening asthma:
 - 829 • decreasing effectiveness of inhaled, short-acting beta₂-agonists;
 - 830 • need for more inhalations than usual of inhaled, short-acting beta₂-agonists;
 - 831 • significant decrease in lung function as outlined by the physician.
- 832 7. Patients should be cautioned regarding common adverse effects associated with
833 beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 834 8. Patients who are at an increased risk for decreased BMD should be advised that the use of
835 corticosteroids may pose an additional risk and should be told to monitor and, where
836 appropriate, seek treatment for this condition.
- 837 9. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of
838 ADVAIR DISKUS, may increase the risk of some eye problems (cataracts or glaucoma).
839 Regular eye examinations should be considered.

- 840 10. When patients are prescribed ADVAIR DISKUS, other medications for asthma and COPD
841 should be used only as directed by their physicians.
- 842 11. ADVAIR DISKUS should not be used with a spacer device.
- 843 12. Patients who are pregnant or nursing should contact their physicians about the use of
844 ADVAIR DISKUS.
- 845 13. Effective and safe use of ADVAIR DISKUS includes an understanding of the way that it
846 should be used:
- 847 • Never exhale into the DISKUS.
 - 848 • Never attempt to take the DISKUS apart.
 - 849 • Always activate and use the DISKUS in a level, horizontal position.
 - 850 • After inhalation, rinse the mouth with water without swallowing.
 - 851 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
 - 852 • Always keep the DISKUS in a dry place.
 - 853 • Discard **1 month** after removal from the moisture-protective foil overwrap pouch or after
854 all blisters have been used (when the dose indicator reads “0”), whichever comes first.
- 855 14. Patients should be warned to avoid exposure to chickenpox or measles and, if they are
856 exposed, to consult their physicians without delay.
- 857 15. For the proper use of ADVAIR DISKUS and to attain maximum improvement, the patient
858 should read and carefully follow the Patient’s Instructions for Use accompanying the
859 product.

860 **Drug Interactions:** ADVAIR DISKUS has been used concomitantly with other drugs,
861 including short-acting beta₂-agonists, methylxanthines, and intranasal corticosteroids, commonly
862 used in patients with asthma or COPD, without adverse drug reactions. No formal drug
863 interaction studies have been performed with ADVAIR DISKUS.

864 **Short-Acting Beta₂-Agonists:** In clinical trials with patients with asthma, the mean daily
865 need for albuterol by 166 patients using ADVAIR DISKUS was approximately
866 1.3 inhalations/day, and ranged from 0 to 9 inhalations/day. Five percent (5%) of patients using
867 ADVAIR DISKUS in these trials averaged 6 or more inhalations per day over the course of the
868 12-week trials. No increase in frequency of cardiovascular adverse reactions was observed
869 among patients who averaged 6 or more inhalations per day.

870 In a COPD clinical trial, the mean daily need for albuterol for patients using ADVAIR
871 DISKUS 250/50 was 4.1 inhalations/day. Twenty-six percent (26%) of patients using ADVAIR
872 DISKUS 250/50 averaged 6 or more inhalations per day over the course of the 24-week trial. No
873 increase in frequency of cardiovascular adverse reactions was observed among patients who
874 averaged 6 or more inhalations of albuterol per day.

875 **Methylxanthines:** The concurrent use of intravenously or orally administered
876 methylxanthines (e.g., aminophylline, theophylline) by patients receiving ADVAIR DISKUS has
877 not been completely evaluated. In clinical trials with patients with asthma, 39 patients receiving
878 ADVAIR DISKUS 100/50, 250/50, or 500/50 twice daily concurrently with a theophylline
879 product had adverse event rates similar to those in 304 patients receiving ADVAIR DISKUS

880 without theophylline. Similar results were observed in patients receiving salmeterol 50 mcg plus
881 fluticasone propionate 500 mcg twice daily concurrently with a theophylline product (N = 39) or
882 without theophylline (N = 132).

883 In a COPD clinical trial, 17 patients receiving ADVAIR DISKUS 250/50 twice daily
884 concurrently with a theophylline product had adverse event rates similar to those in 161 patients
885 receiving ADVAIR DISKUS without theophylline. Based on the available data, the concomitant
886 administration of methylxanthines with ADVAIR DISKUS did not alter the observed adverse
887 event profile.

888 **Fluticasone Propionate Nasal Spray:** In patients taking ADVAIR DISKUS in clinical
889 trials, no difference in the profile of adverse events or HPA axis effects was noted between
890 patients taking FLONASE[®] (fluticasone propionate) Nasal Spray, 50 mcg concurrently (N = 46)
891 and those who were not (N = 130).

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

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

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

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

920 In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single
921 dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole
922 (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a
923 reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should
924 be exercised when ADVAIR DISKUS is coadministered with ketoconazole and other known
925 potent cytochrome P450 3A4 inhibitors.

926 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate:**

927 Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to
928 1,000 mcg/kg (approximately 4 times the maximum recommended daily inhalation dose in adults
929 on a mcg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than the
930 maximum recommended daily inhalation dose in adults on a mcg/m² basis) for 104 weeks.

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

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

938 **Salmeterol:** In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of
939 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose
940 in adults based on comparison of the plasma area under the curves [AUCs]) caused a
941 dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular
942 hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of
943 leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg
944 (approximately 3 times the maximum recommended daily inhalation doses in adults based on
945 comparison of the AUCs).

946 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol
947 caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at
948 doses of 0.68 mg/kg and above (approximately 60 times the maximum recommended daily
949 inhalation dose in adults on a mg/m² basis). No tumors were seen at 0.21 mg/kg (approximately
950 20 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). These
951 findings in rodents are similar to those reported previously for other beta-adrenergic agonist
952 drugs. The relevance of these findings to human use is unknown.

953 Salmeterol produced no detectable or reproducible increases in microbial and mammalian
954 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo
955 in a rat micronucleus test. No effects on fertility were identified in male and female rats treated
956 with salmeterol at oral doses up to 2 mg/kg (approximately 180 times the maximum
957 recommended daily inhalation dose in adults on a mg/m² basis).

958 **Pregnancy: Teratogenic Effects: ADVAIR DISKUS:** Pregnancy Category C. From the
959 reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using

960 combinations of fluticasone propionate and salmeterol compared to toxicity data from the
961 components administered separately. In mice combining 150 mcg/kg subcutaneously of
962 fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a
963 mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 450 times the maximum
964 recommended daily inhalation dose in adults on a mg/m² basis) was teratogenic. Cleft palate,
965 fetal death, increased implantation loss and delayed ossification were seen. These observations
966 are characteristic of glucocorticoids. No developmental toxicity was observed at combination
967 doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum
968 recommended daily inhalation dose in adults on a mcg/m² basis) and up to 1.4 mg/kg orally of
969 salmeterol (approximately 65 times the maximum recommended daily inhalation dose in adults
970 on a mg/m² basis). In rats, no teratogenicity was observed at combination doses up to 30 mcg/kg
971 subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation
972 dose in adults on a mcg/m² basis) and up to 1 mg/kg of salmeterol (approximately 90 times the
973 maximum recommended daily inhalation dose in adults on a mg/m² basis). Combining
974 100 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended
975 daily inhalation dose in adults on a mcg/m² basis) with 10 mg/kg orally of salmeterol
976 (approximately 900 times the maximum recommended daily inhalation dose in adults on a
977 mg/m² basis) produced maternal toxicity, decreased placental weight, decreased fetal weight,
978 umbilical hernia, delayed ossification, and changes in the occipital bone. There are no adequate
979 and well-controlled studies with ADVAIR DISKUS in pregnant women. ADVAIR DISKUS
980 should be used during pregnancy only if the potential benefit justifies the potential risk to the
981 fetus.

982 **Fluticasone Propionate:** Pregnancy Category C. Subcutaneous studies in the mouse
983 and rat at 45 and 100 mcg/kg (less than or equivalent to the maximum recommended daily
984 inhalation dose in adults on a mcg/m² basis), respectively, revealed fetal toxicity characteristic of
985 potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft
986 palate, and retarded cranial ossification.

987 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of
988 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m²
989 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg
990 (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m²
991 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this
992 study, consistent with the established low bioavailability following oral administration (see
993 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Absorption*).

994 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose
995 of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a
996 mcg/m² basis) administration of a subcutaneous or an oral dose of 100 mcg/kg to rats
997 (approximately equivalent to the maximum recommended daily inhalation dose in adults on a
998 mcg/m² basis) and an oral dose of 300 mcg/kg administered to rabbits (approximately 5 times the
999 maximum recommended daily inhalation dose in adults on a mcg/m² basis).

1000 There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate
1001 should be used during pregnancy only if the potential benefit justifies the potential risk to the
1002 fetus.

1003 Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to
1004 physiologic, doses suggests that rodents are more prone to teratogenic effects from
1005 corticosteroids than humans. In addition, because there is a natural increase in corticosteroid
1006 production during pregnancy, most women will require a lower exogenous corticosteroid dose
1007 and many will not need corticosteroid treatment during pregnancy.

1008 **Salmeterol:** Pregnancy Category C. No teratogenic effects occurred in rats at oral doses
1009 up to 2 mg/kg (approximately 180 times the maximum recommended daily inhalation dose in
1010 adults on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and
1011 above (approximately 50 times the maximum recommended daily inhalation dose in adults based
1012 on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting
1013 from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate,
1014 sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones.
1015 No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the
1016 maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

1017 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal
1018 bones was seen at an oral dose of 10 mg/kg (approximately 1,800 times the maximum
1019 recommended daily inhalation dose in adults on a mg/m² basis). Extensive use of other
1020 beta-agonists has provided no evidence that these class effects in animals are relevant to their use
1021 in humans. There are no adequate and well-controlled studies with salmeterol in pregnant
1022 women. Salmeterol should be used during pregnancy only if the potential benefit justifies the
1023 potential risk to the fetus.

1024 Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice
1025 and rats (approximately 450 and 900 times, respectively, the maximum recommended daily
1026 inhalation dose in adults on a mg/m² basis).

1027 **Use in Labor and Delivery:** There are no well-controlled human studies that have
1028 investigated effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the
1029 potential for beta-agonist interference with uterine contractility, use of ADVAIR DISKUS during
1030 labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

1031 **Nursing Mothers:** Plasma levels of salmeterol, a component of ADVAIR DISKUS, after
1032 inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There
1033 are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known
1034 whether fluticasone propionate, a component of ADVAIR DISKUS, is excreted in human breast
1035 milk. However, other corticosteroids have been detected in human milk. Subcutaneous
1036 administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the
1037 maximum recommended daily inhalation dose in adults on a mcg/m² basis) resulted in
1038 measurable radioactivity in milk.

1039 Since there are no data from controlled trials on the use of ADVAIR DISKUS by nursing
1040 mothers, a decision should be made whether to discontinue nursing or to discontinue ADVAIR
1041 DISKUS, taking into account the importance of ADVAIR DISKUS to the mother.

1042 Caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.

1043 **Pediatric Use:** The safety and effectiveness of ADVAIR DISKUS in children with asthma
1044 under 12 years of age have not been established. In one 12-week study, 257 patients 4 to
1045 11 years inadequately controlled using inhaled corticosteroids were randomized to ADVAIR
1046 DISKUS 100/50 or concurrent therapy with fluticasone propionate inhalation powder 100 mcg
1047 plus salmeterol inhalation powder 50 mcg twice daily. The pattern of adverse events reported in
1048 patients 4 to 11 years of age was similar to that seen in patients 12 years of age and older treated
1049 with ADVAIR DISKUS.

1050 Controlled clinical studies have shown that orally inhaled corticosteroids may cause a
1051 reduction in growth velocity in pediatric patients. This effect has been observed in the absence of
1052 laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive
1053 indicator of systemic corticosteroid exposure in pediatric patients than some commonly used
1054 tests of HPA axis function. The long-term effects of this reduction in growth velocity associated
1055 with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The
1056 potential for “catch-up” growth following discontinuation of treatment with orally inhaled
1057 corticosteroids has not been adequately studied.

1058 Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS,
1059 may cause a reduction in growth velocity in children and adolescents (see PRECAUTIONS:
1060 General: *Metabolic and Other Effects*). The growth of pediatric patients receiving orally inhaled
1061 corticosteroids, including ADVAIR DISKUS, should be monitored. If a child or adolescent on
1062 any corticosteroid appears to have growth suppression, the possibility that he/she is particularly
1063 sensitive to this effect of corticosteroids should be considered. The potential growth effects of
1064 prolonged treatment should be weighed against the clinical benefits obtained. To minimize the
1065 systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, each patient
1066 should be titrated to the lowest strength that effectively controls his/her asthma (see DOSAGE
1067 AND ADMINISTRATION: Asthma).

1068 **Geriatric Use:** Of the total number of patients in clinical studies of ADVAIR DISKUS for
1069 asthma, 44 were 65 years of age or older and 3 were 75 years of age or older. Of the total
1070 number of patients in a clinical study of ADVAIR DISKUS 250/50 for COPD, 85 were 65 years
1071 of age or older and 31 were 75 years of age or older. For both diseases, no overall differences in
1072 safety were observed between these patients and younger patients, and other reported clinical
1073 experience, including studies of the individual components, has not identified differences in
1074 responses between the elderly and younger patients, but greater sensitivity of some older
1075 individuals cannot be ruled out. As with other products containing beta₂-agonists, special caution
1076 should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant
1077 cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available

1078 data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR
1079 DISKUS in geriatric patients is warranted.

1080 **ADVERSE REACTIONS**

1081 **Asthma:** The incidence of common adverse events in Table 3 is based upon 2
1082 placebo-controlled, 12-week, US clinical studies (Studies 1 and 2). A total of 705 adolescent and
1083 adult patients (349 females and 356 males) previously treated with salmeterol or inhaled
1084 corticosteroids were treated twice daily with ADVAIR DISKUS (100/50- or 250/50-mcg doses),
1085 fluticasone propionate inhalation powder (100- or 250-mcg doses), salmeterol inhalation powder
1086 50 mcg, or placebo.
1087

1088 **Table 3. Overall Adverse Events With $\geq 3\%$ Incidence in US Controlled Clinical Trials**
 1089 **With ADVAIR DISKUS in Patients With Asthma**

Adverse Event	ADVAIR DISKUS 100/50 (N = 92) %	ADVAIR DISKUS 250/50 (N = 84) %	Fluticasone Propionate 100 mcg (N = 90) %	Fluticasone Propionate 250 mcg (N = 84) %	Salmeterol 50 mcg (N = 180) %	Placebo (N = 175) %
Ear, nose, and throat						
Upper respiratory tract infection	27	21	29	25	19	14
Pharyngitis	13	10	7	12	8	6
Upper respiratory inflammation	7	6	7	8	8	5
Sinusitis	4	5	6	1	3	4
Hoarseness/dysphonia	5	2	2	4	<1	<1
Oral candidiasis	1	4	2	2	0	0
Lower respiratory						
Viral respiratory infections	4	4	4	10	6	3
Bronchitis	2	8	1	2	2	2
Cough	3	6	0	0	3	2
Neurology						
Headaches	12	13	14	8	10	7
Gastrointestinal						
Nausea & vomiting	4	6	3	4	1	1
Gastrointestinal discomfort & pain	4	1	0	2	1	1
Diarrhea	4	2	2	2	1	1
Viral gastrointestinal infections	3	0	3	1	2	2
Non-site specific						
Candidiasis unspecified site	3	0	1	4	0	1
Musculoskeletal						
Musculoskeletal pain	4	2	1	5	3	3
Average duration of exposure (days)	77.3	78.7	72.4	70.1	60.1	42.3

1090
 1091 Table 3 includes all events (whether considered drug-related or nondrug-related by the
 1092 investigator) that occurred at a rate of 3% or greater in either of the groups receiving ADVAIR
 1093 DISKUS and were more common than in the placebo group. In considering these data,

1094 differences in average duration of exposure should be taken into account. Rare cases of
1095 immediate and delayed hypersensitivity reactions, including rash and other rare events of
1096 angioedema and bronchospasm, have been reported.

1097 These adverse reactions were mostly mild to moderate in severity.

1098 Other adverse events that occurred in the groups receiving ADVAIR DISKUS in these studies
1099 with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1100 **Blood and Lymphatic:** Lymphatic signs and symptoms.

1101 **Cardiovascular:** Palpitations.

1102 **Drug Interaction, Overdose, and Trauma:** Muscle injuries, fractures, wounds and
1103 lacerations, contusions and hematomas, burns.

1104 **Ear, Nose, and Throat:** Rhinorrhea/postnasal drip; ear, nose and throat infections; ear
1105 signs and symptoms; nasal signs and symptoms; nasal sinus disorders; rhinitis; sneezing; nasal
1106 irritation; blood in nasal mucosa.

1107 **Eye:** Keratitis and conjunctivitis, viral eye infections, eye redness.

1108 **Gastrointestinal:** Dental discomfort and pain, gastrointestinal signs and symptoms,
1109 gastrointestinal infections, gastroenteritis, gastrointestinal disorders, oral ulcerations, oral
1110 erythema and rashes, constipation, appendicitis, oral discomfort and pain.

1111 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1112 **Lower Respiratory:** Lower respiratory signs and symptoms, pneumonia, lower respiratory
1113 infections.

1114 **Musculoskeletal:** Arthralgia and articular rheumatism; muscle stiffness, tightness, and
1115 rigidity; bone and cartilage disorders.

1116 **Neurology:** Sleep disorders, tremors, hypnagogic effects, compressed nerve syndromes.

1117 **Non-Site Specific:** Allergies and allergic reactions, congestion, viral infections, pain, chest
1118 symptoms, fluid retention, bacterial infections, wheeze and hives, unusual taste.

1119 **Skin:** Viral skin infections, urticaria, skin flakiness and acquired ichthyosis, disorders of
1120 sweat and sebum, sweating.

1121 The incidence of common adverse events reported in Study 3, a 28-week, non-US clinical
1122 study of 503 patients previously treated with inhaled corticosteroids who were treated twice daily
1123 with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and
1124 salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation
1125 powder 500 mcg was similar to the incidences reported in Table 3.

1126 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The
1127 incidence of common adverse events in Table 4 is based upon 1 placebo-controlled, 24-week, US
1128 clinical trial in patients with COPD associated with chronic bronchitis. A total of 723 adult
1129 patients (266 females and 457 males) were treated twice daily with ADVAIR DISKUS 250/50,
1130 fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder 50 mcg, or
1131 placebo.

1132

1133 **Table 4. Overall Adverse Events With ≥3% Incidence With ADVAIR DISKUS 250/50**
 1134 **in Patients With Chronic Obstructive Pulmonary Disease Associated With Chronic**
 1135 **Bronchitis**

Adverse Event	ADVAIR DISKUS 250/50 (N = 178) %	Fluticasone Propionate 250 mcg (N = 183) %	Salmeterol 50 mcg (N = 177) %	Placebo (N = 185) %
Ear, nose, and throat				
Candidiasis mouth/throat	10	6	3	1
Throat irritation	8	5	4	7
Hoarseness/dysphonia	5	3	<1	0
Sinusitis	3	8	5	3
Lower respiratory				
Viral respiratory infections	6	4	3	3
Neurology				
Headaches	16	11	10	12
Dizziness	4	<1	3	2
Non-site specific				
Fever	4	3	0	3
Malaise & fatigue	3	2	2	3
Musculoskeletal				
Musculoskeletal pain	9	8	12	9
Muscle cramps & spasms	3	3	1	1
Average duration of exposure (days)	141.3	138.5	136.1	131.6

1136
 1137 Table 4 includes all events (whether considered drug-related or nondrug-related by the
 1138 investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS
 1139 250/50 and were more common than in the placebo group.

1140 These adverse reactions were mostly mild to moderate in severity.

1141 Other adverse events that occurred in the groups receiving ADVAIR DISKUS 250/50 with an
 1142 incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1143 **Cardiovascular:** Syncope.

1144 **Drug Interaction, Overdose, and Trauma:** Postoperative complications.

1145 **Ear, Nose, and Throat:** Ear, nose, and throat infections; ear signs and symptoms;
 1146 laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection.

1147 **Endocrine and Metabolic:** Hypothyroidism.

1148 **Eye:** Dry eyes, eye infections.

1149 **Gastrointestinal:** Constipation, gastrointestinal signs and symptoms, oral lesions.

1150 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1151 **Lower Respiratory:** Breathing disorders, lower respiratory signs and symptoms.
1152 **Non-Site Specific:** Bacterial infections, candidiasis unspecified site, edema and swelling,
1153 nonspecific conditions, viral infections.
1154 **Psychiatry:** Situational disorders.
1155 **Observed During Clinical Practice:** In addition to adverse events reported from clinical
1156 trials, the following events have been identified during worldwide use of any formulation of
1157 ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are
1158 reported voluntarily from a population of unknown size, estimates of frequency cannot be made.
1159 These events have been chosen for inclusion due to either their seriousness, frequency of
1160 reporting, or causal connection to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol
1161 or a combination of these factors.
1162 In extensive US and worldwide postmarketing experience with salmeterol, a component of
1163 ADVAIR DISKUS, serious exacerbations of asthma, including some that have been fatal, have
1164 been reported. In most cases, these have occurred in patients with severe asthma and/or in some
1165 patients in whom asthma has been acutely deteriorating (see WARNINGS no. 2), but they have
1166 also occurred in a few patients with less severe asthma. It was not possible from these reports to
1167 determine whether salmeterol contributed to these events or simply failed to relieve the
1168 deteriorating asthma.
1169 **Cardiovascular:** Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular
1170 tachycardia), ventricular tachycardia.
1171 **Ear, Nose, and Throat:** Aphonia, earache, facial and oropharyngeal edema, paranasal sinus
1172 pain, throat soreness.
1173 **Endocrine and Metabolic:** Cushing syndrome, Cushingoid features, growth velocity
1174 reduction in children/adolescents, hypercorticism, hyperglycemia, weight gain, osteoporosis.
1175 **Eye:** Cataracts, glaucoma.
1176 **Gastrointestinal:** Abdominal pain, dyspepsia, xerostomia.
1177 **Musculoskeletal:** Back pain, cramps, muscle spasm, myositis.
1178 **Neurology:** Paresthesia, restlessness.
1179 **Non-Site Specific:** Immediate and delayed hypersensitivity reaction (including very rare
1180 anaphylactic reaction), pallor. Very rare anaphylactic reaction in patients with severe milk
1181 protein allergy.
1182 **Psychiatry:** Agitation, aggression, depression.
1183 **Respiratory:** Chest congestion; chest tightness; dyspnea; immediate bronchospasm;
1184 influenza; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory
1185 symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.
1186 **Skin:** Contact dermatitis, contusions, ecchymoses, photodermatitis.
1187 **Urogenital:** Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal
1188 candidiasis, vaginitis, vulvovaginitis.
1189 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a
1190 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some

1191 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a
1192 condition that is often treated with systemic corticosteroid therapy. These events usually, but not
1193 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy
1194 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions
1195 have also been reported with other inhaled corticosteroids in this clinical setting. While
1196 ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid
1197 therapy, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary
1198 symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal
1199 relationship between fluticasone propionate and these underlying conditions has not been
1200 established (see PRECAUTIONS: General: *Eosinophilic Conditions*).

1201 **OVERDOSAGE**

1202 **ADVAIR DISKUS:** No deaths occurred in rats given combinations of salmeterol and
1203 fluticasone propionate at acute inhalation doses of 3.6 and 1.9 mg/kg, respectively
1204 (approximately 320 and 15 times the maximum recommended daily inhalation dose in adults on
1205 a mg/m² basis).

1206 **Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in
1207 signs/symptoms of hypercorticism (see PRECAUTIONS: General: *Metabolic and Other*
1208 *Effects*). Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate
1209 inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate inhalation
1210 aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of
1211 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated.
1212 Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to
1213 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or
1214 moderate severity, and incidences were similar in active and placebo treatment groups. The oral
1215 and subcutaneous median lethal doses in mice and rats were >1,000 mg/kg (>4,300 and >8,700
1216 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m²
1217 basis).

1218 **Salmeterol:** The expected signs and symptoms with overdosage of salmeterol are those of
1219 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and
1220 symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or
1221 hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache,
1222 tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and
1223 insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the
1224 pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia
1225 and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead
1226 to clinically significant prolongation of the QTc interval, which can produce ventricular
1227 arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

1228 As with all sympathomimetic medications, cardiac arrest and even death may be associated
1229 with abuse of salmeterol.

1230 Treatment consists of discontinuation of salmeterol together with appropriate symptomatic
1231 therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing
1232 in mind that such medication can produce bronchospasm. There is insufficient evidence to
1233 determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is
1234 recommended in cases of overdosage.

1235 No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg
1236 (approximately 250 times the maximum recommended daily inhalation dose in adults on a
1237 mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 times the
1238 maximum recommended daily inhalation dose in adults on a mg/m² basis). By the oral route, no
1239 deaths occurred in mice at 150 mg/kg (approximately 6,500 times the maximum recommended
1240 daily inhalation dose in adults on a mg/m² basis) and in rats at 1,000 mg/kg (approximately
1241 86,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis).

1242 **DOSAGE AND ADMINISTRATION**

1243 ADVAIR DISKUS should be administered by the orally inhaled route only (see PATIENT'S
1244 INSTRUCTIONS FOR USE). After inhalation, the patient should rinse the mouth with water
1245 without swallowing. ADVAIR DISKUS should not be used for transferring patients from
1246 systemic corticosteroid therapy.

1247 **Asthma:** ADVAIR DISKUS is available in 3 strengths, ADVAIR DISKUS 100/50, ADVAIR
1248 DISKUS 250/50, and ADVAIR DISKUS 500/50, containing 100, 250, and 500 mcg of
1249 fluticasone propionate, respectively, and 50 mcg of salmeterol per inhalation.

1250 For patients 12 years of age and older, the dosage is 1 inhalation twice daily (morning and
1251 evening, approximately 12 hours apart).

1252 The recommended starting dosages for ADVAIR DISKUS are based upon patients' current
1253 asthma therapy.

1254 • For patients who are not currently on an inhaled corticosteroid, whose disease severity
1255 warrants treatment with 2 maintenance therapies, including patients on non-corticosteroid
1256 maintenance therapy, the recommended starting dosage is ADVAIR DISKUS 100/50 twice
1257 daily.

1258 • For patients on an inhaled corticosteroid, Table 5 provides the recommended starting dosage.

1259 The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

1260 **For all patients it is desirable to titrate to the lowest effective strength after adequate**
1261 **asthma stability is achieved.**

1262

1263
1264

Table 5. Recommended Dosages of ADVAIR DISKUS for Patients With Asthma Taking Inhaled Corticosteroids

Current Daily Dose of Inhaled Corticosteroid		Recommended Strength and Dosing Schedule of ADVAIR DISKUS
Beclomethasone dipropionate	≤420 mcg	100/50 twice daily
	462-840 mcg	250/50 twice daily
Budesonide	≤400 mcg	100/50 twice daily
	800-1,200 mcg	250/50 twice daily
	1,600 mcg*	500/50 twice daily
Flunisolide	≤1,000 mcg	100/50 twice daily
	1,250-2,000 mcg	250/50 twice daily
Fluticasone propionate inhalation aerosol	≤176 mcg	100/50 twice daily
	440 mcg	250/50 twice daily
	660-880 mcg*	500/50 twice daily
Fluticasone propionate inhalation powder	≤200 mcg	100/50 twice daily
	500 mcg	250/50 twice daily
	1,000 mcg*	500/50 twice daily
Triamcinolone acetonide	≤1,000 mcg	100/50 twice daily
	1,100-1,600 mcg	250/50 twice daily

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

1265

1266 ADVAIR DISKUS should be administered twice daily every day. More frequent
1267 administration (more than twice daily) or a higher number of inhalations (more than 1 inhalation
1268 twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some
1269 patients are more likely to experience adverse effects with higher doses of salmeterol. The safety
1270 and efficacy of ADVAIR DISKUS when administered in excess of recommended doses have not
1271 been established.

1272 If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should
1273 be taken for immediate relief.

1274 Patients who are receiving ADVAIR DISKUS twice daily should not use additional
1275 salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of EIB,
1276 or for any other reason.

1277 Improvement in asthma control following inhaled administration of ADVAIR DISKUS can
1278 occur within 30 minutes of beginning treatment, although maximum benefit may not be
1279 achieved for 1 week or longer after starting treatment. Individual patients will experience a
1280 variable time to onset and degree of symptom relief.

1281 For patients who do not respond adequately to the starting dosage after 2 weeks of therapy,
1282 replacing the current strength of ADVAIR DISKUS with a higher strength may provide
1283 additional improvement in asthma control.

1284 If a previously effective dosage regimen of ADVAIR DISKUS fails to provide adequate
1285 improvement in asthma control, the therapeutic regimen should be reevaluated and additional
1286 therapeutic options, e.g., replacing the current strength of ADVAIR DISKUS with a higher
1287 strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be
1288 considered.

1289 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The
1290 dosage for adults is 1 inhalation (250/50 mcg) twice daily (morning and evening, approximately
1291 12 hours apart).

1292 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of
1293 COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50,
1294 are not recommended, as no additional improvement in lung function was observed in clinical
1295 trials and higher doses of corticosteroids increase the risk of systemic effects.

1296 If shortness of breath occurs in the period between doses, an inhaled, short-acting
1297 beta₂-agonist should be taken for immediate relief.

1298 Patients who are receiving ADVAIR DISKUS twice daily should not use additional
1299 salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for the maintenance
1300 treatment of COPD or for any other reason.

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

1305 **Directions for Use:** Illustrated Patient's Instructions for Use accompany each package of
1306 ADVAIR DISKUS.

1307 **HOW SUPPLIED**

1308 ADVAIR DISKUS 100/50 is supplied as a disposable, purple device containing 60 blisters.
1309 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective
1310 foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional
1311 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS
1312 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch
1313 (NDC 0173-0695-02).

1314 ADVAIR DISKUS 250/50 is supplied as a disposable, purple device containing 60 blisters.
1315 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective
1316 foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional
1317 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS
1318 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch
1319 (NDC 0173-0696-02).

1320 ADVAIR DISKUS 500/50 is supplied as a disposable, purple device containing 60 blisters.
1321 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective
1322 foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional
1323 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS
1324 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch
1325 (NDC 0173-0697-02).

1326 **Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place**
1327 **away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation**
1328 **device is not reusable. The device should be discarded 1 month after removal from the**
1329 **moisture-protective foil overwrap pouch or after all blisters have been used (when the dose**
1330 **indicator reads “0”), whichever comes first. Do not attempt to take the device apart.**

1331
1332



1333
1334 GlaxoSmithKline
1335 Research Triangle Park, NC 27709

1336
1337 ©Year, GlaxoSmithKline. All rights reserved.

1338
1339 Month Year RL-

1 **Patient's Instructions for Use**

2
3 Product logo
4

5
6 **ADVAIR DISKUS[®] 100/50**
7 **(fluticasone propionate 100 mcg and salmeterol* 50 mcg inhalation powder)**

8
9 **ADVAIR DISKUS[®] 250/50**
10 **(fluticasone propionate 250 mcg and salmeterol* 50 mcg inhalation powder)**

11
12 **ADVAIR DISKUS[®] 500/50**
13 **(fluticasone propionate 500 mcg and salmeterol* 50 mcg inhalation powder)**

14
15 * As salmeterol xinafoate salt 72.5 mcg, equivalent to salmeterol base 50 mcg
16

17 **FOR ORAL INHALATION ONLY**

18
19 (illustration of device with parts labeled:

- 20 Outer Case
- 21 Mouthpiece
- 22 Lever
- 23 Thumbgrip
- 24 Dose Indicator)
- 25
- 26

27 Read this leaflet carefully before you start to take your medicine. It provides a summary of
28 information about your medicine. Keep it for future use. Read the leaflet every time you refill
29 your prescription because there may be new information.
30

31 *For more information ask your doctor or pharmacist.*

32
33 **What Is ADVAIR DISKUS[®]?**

34 Your doctor has prescribed ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR
35 DISKUS 500/50. The medicine is available in 3 different strengths, and your doctor has chosen
36 the one most suitable for you.

37 Asthma is a long-term condition affecting the lungs. Symptoms of asthma include shortness of
38 breath, wheezing, chest tightness, and cough. Two main causes of asthma symptoms are

39 bronchoconstriction (tightening of the muscles surrounding the airways) and inflammation
40 (swelling and irritation of the airways).

41 Chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis is a
42 long-term, progressively worsening condition that restricts airflow into and out of the lungs. The
43 main cause of COPD is exposure to lung irritants, including tobacco smoke and airborne
44 pollutants, which may lead to bronchoconstriction, inflammation, and lung tissue damage.

45 ADVAIR DISKUS contains 2 medicines, fluticasone propionate (a synthetic corticosteroid) and
46 salmeterol xinafoate (a long-acting bronchodilator), which work in different ways in the lungs to
47 improve lung function and symptoms in patients with asthma. Fluticasone propionate is used to
48 reduce the airway inflammation and salmeterol a long-acting bronchodilator helps prevent and
49 relieve bronchospasm, making it easier to breathe.

50 Fluticasone propionate and salmeterol in ADVAIR DISKUS work together to improve lung
51 function in patients with COPD associated with chronic bronchitis.

Important Points to Remember About Using ADVAIR DISKUS

52
53 **1. TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE if you**
54 **are:**

- 55 • pregnant (or intending to become pregnant);
- 56 • breastfeeding a baby;
- 57 • allergic to ADVAIR DISKUS, any other medicines, or food products;
- 58 • taking a medicine containing ritonavir (commonly used to treat HIV infection or AIDS); or
- 59 • taking other medicines, especially any other orally inhaled bronchodilator or
60 corticosteroids, over-the-counter medicines, and herbal products.

61 In some circumstances, this medicine may not be suitable for you, and your doctor may wish
62 to give you a different medicine.

63 **2. It is important that you inhale each dose as your doctor has advised. The label provided by**
64 **your pharmacist will usually tell you what dose to take and how often. If it doesn't, or if you**
65 **are not sure, ask your doctor or pharmacist. Do not use ADVAIR DISKUS more**
66 **frequently than 2 times daily, morning and evening, approximately 12 hours apart, at**
67 **the recommended dose of 1 inhalation each time.**

68 **3. ADVAIR DISKUS delivers your dose of medicine as a very fine powder that most, but not**
69 **all, patients can taste or feel.** Whether or not you are able to taste or feel your dose of
70 medicine, you should not exceed the recommended dose of 1 inhalation each morning and
71 evening, approximately 12 hours apart. If you are not sure you are receiving your dose of
72 ADVAIR DISKUS, contact your doctor or pharmacist.

73 **4. You may breathe more easily after the first dose of ADVAIR DISKUS; however, it may take**
74 **1 week or longer to achieve maximum benefit. It is IMPORTANT THAT YOU USE**

75 **ADVAIR DISKUS REGULARLY. DO NOT STOP TREATMENT EVEN IF YOU**
76 **ARE FEELING BETTER** unless told to do so by your doctor.

77 5. If you miss a dose, just take your next scheduled dose when it is due. **DO NOT DOUBLE**
78 the dose.

79 6. **DO NOT USE ADVAIR DISKUS TO RELIEVE SUDDEN SYMPTOMS OF**
80 **SHORTNESS OF BREATH** (e.g., sudden severe onset or worsening of wheezing, cough,
81 chest tightness). **An inhaled, short-acting bronchodilator such as albuterol should be**
82 **used to relieve sudden symptoms of shortness of breath.** If you do not have an inhaled,
83 short-acting bronchodilator, contact your doctor to have one prescribed for you. **You should**
84 **continue to take ADVAIR DISKUS as instructed by your doctor.**

85 7. **Tell your doctor immediately if your condition is getting worse, as indicated by any of**
86 **the following situations.**

- 87 • Your inhaled, short-acting bronchodilator becomes less effective.
- 88 • You need more inhalations than usual of your inhaled, short-acting bronchodilator.
- 89 • You have asthma and you have a significant decrease in your peak flow measurement as
90 previously defined by your doctor.

91 8. If you have asthma and your symptoms do not improve after using ADVAIR DISKUS
92 regularly for 2 weeks, tell your doctor.

93 9. **While you are taking ADVAIR DISKUS twice daily, you should not use SEREVENT[®]**
94 **DISKUS[®] (salmeterol xinafoate inhalation powder) or FORADIL[®] AEROLIZER[™]**
95 **(formoterol fumarate inhalation powder) for any reason, including prevention of**
96 **exercise-induced asthma or the maintenance treatment of asthma or COPD.**

97 10. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of
98 ADVAIR DISKUS, may increase the risk of some eye problems (cataracts or glaucoma).
99 Regular eye examinations should be considered.

100 11. If you have COPD, you may be at greater risk of developing bone loss (osteoporosis) and the
101 use of corticosteroids, including ADVAIR DISKUS, may increase your risk. Talk to your
102 doctor about ways to reduce your risk.

103 12. Use other asthma or COPD medicines only as directed by your doctor.

104 13. Do not use ADVAIR DISKUS with a spacer device.

How to Use Your ADVAIR[™] DISKUS[®]

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

108 When you take the ADVAIR DISKUS out of the box and foil overwrap pouch, write the **“Pouch**
109 **opened”** and **“Use by”** dates on the label in the space provided on the device. **The “Use by”**
110 **date is 1 month from date of opening.**

111 The DISKUS[®] inhalation device will be in the closed position when the pouch is opened.
112 The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose
113 indicator number will decrease each time you use the DISKUS. After the DISKUS has delivered
114 55 doses (23 doses for the institutional or sample pack), numbers 5 to 0 will appear in **red** to
115 warn you that there are only a few doses left (*see Figure 1*).

116

117 *Figure 1*

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

119 **1 OPEN:** Hold the DISKUS in one hand and put the thumb of your other hand on the
120 **thumbgrip**. Push your thumb away from you as far as it will go until the mouthpiece appears
121 and snaps into position (*see Figure 2*).

122

123 *Figure 2*

124 **2 CLICK:** Hold the DISKUS in a level, horizontal position with the mouthpiece towards you.
125 Slide the **lever** away from you as far as it will go until it **clicks** (*see Figure 3*). The DISKUS
126 is now ready to use.

127

128 *Figure 3*

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

- 131 • **Do not close the DISKUS.**
- 132 • **Do not tilt the DISKUS.**
- 133 • **Do not play with the lever.**
- 134 • **Do not advance the lever more than once.**

135 **3 INHALE:** Before inhaling your dose of ADVAIR DISKUS, breathe out as far as is
136 comfortable, holding the DISKUS level and away from your mouth (*see Figure 4*).
137 **Remember, never breathe out into the DISKUS mouthpiece.**

138

139 *Figure 4*

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

142

143 *Figure 5*

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

146 **CLOSE the DISKUS when you are finished taking a dose so that the DISKUS will be ready**
147 **for you to take your next dose.** Put your thumb on the thumbgrip and slide the thumbgrip back
148 towards you as far as it will go (*see Figure 6*). The DISKUS will click shut. The lever will
149 automatically return to its original position. The DISKUS is now ready for you to take your next
150 scheduled dose, due in approximately 12 hours. (Repeat steps 1 through 3.)

151

152

Figure 6

153 REMEMBER:

- 154 • Never exhale into the DISKUS.
- 155 • Never attempt to take the DISKUS apart.
- 156 • Always activate and use the DISKUS in a level, horizontal position.
- 157 • After inhalation, rinse the mouth with water without swallowing.
- 158 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
- 159 • Always keep the DISKUS in a dry place.
- 160 • Never take an extra dose, even if you feel you did not receive a dose.

161

Storing Your ADVAIR DISKUS

162 **Store at controlled room temperature, 20° to 25°C (68° to 77°F) in a dry place away from**
163 **direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation device is not**
164 **reusable. The device should be discarded 1 month after removal from the**
165 **moisture-protective foil overwrap pouch or after all blisters have been used (when the dose**
166 **indicator reads “0”) , whichever comes first. Do not attempt to take the device apart.**

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

169

Further Information

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

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

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

177 ADVAIR DISKUS and SEREVENT DISKUS are registered trademarks of GlaxoSmithKline.
178 FORADIL AEROLIZER is a trademark of Novartis Pharmaceuticals Corporaion.

179



180

GlaxoSmithKline

181

Research Triangle Park, NC 27709

182

183

©Year, GlaxoSmithKline. All rights reserved.

184

185

186

Month Year

RL-