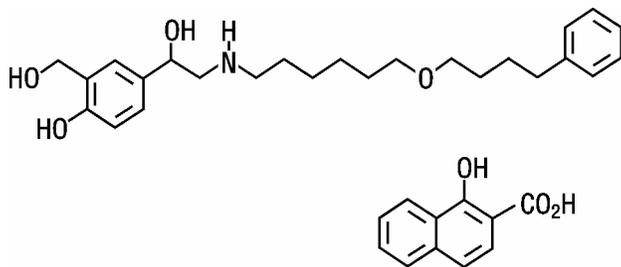


34 Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and
35 the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in
36 dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

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

42



43

44

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

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

57 Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg
58 of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS
59 100/50, 250/50, and 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds.
60 In adult patients with obstructive lung disease and severely compromised lung function (mean
61 forced expiratory volume in 1 second [FEV₁] 20% to 30% of predicted), mean peak inspiratory
62 flow (PIF) through a DISKUS[®] inhalation device was 82.4 L/min (range, 46.1 to 115.3 L/min).

63 Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to
64 50 years) patients with asthma inhaling maximally through the DISKUS device show mean PIF
65 of 122.2 L/min (range, 81.6 to 152.1 L/min). Inhalation profiles for pediatric patients with
66 asthma inhaling maximally through the DISKUS device show a mean PIF of 75.5 L/min (range,
67 49.0 to 104.8 L/min) for the 4-year-old patient set (N = 20) and 107.3 L/min (range, 82.8 to
68 125.6 L/min) for the 8-year-old patient set (N = 20).

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

71 **CLINICAL PHARMACOLOGY**

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

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

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

89 Inflammation is also a component in the pathogenesis of chronic obstructive pulmonary
90 disease (COPD). In contrast to asthma, however, the predominant inflammatory cells in COPD
91 include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of corticosteroids in
92 the treatment of COPD are not well defined and inhaled corticosteroids and fluticasone
93 propionate when used apart from *ADVAIR DISKUS* are not indicated for the treatment of
94 COPD.

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

105 The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are at
106 least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes
107 the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic

108 AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition
109 of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

110 In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast
111 cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung.

112 Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits
113 platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when
114 administered by the inhaled route. In humans, single doses of salmeterol administered via
115 inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

116 **Pharmacokinetics: ADVAIR DISKUS: Adult and Adolescent Patients 12 Years of**
117 **Age and Older:** Following administration of ADVAIR DISKUS to healthy adult subjects, peak
118 plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours and those of
119 salmeterol were achieved in about 5 minutes.

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

127 In a repeat-dose study, the highest recommended dose of ADVAIR DISKUS was
128 administered to 45 adolescent and adult patients with asthma. One (1) inhalation twice daily of
129 the following treatments was administered: ADVAIR DISKUS 500/50, fluticasone propionate
130 powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate
131 powder 500 mcg alone. Mean peak steady-state plasma concentrations of fluticasone propionate
132 averaged 57, 73, and 70 pg/mL, respectively, indicating no significant changes in systemic
133 exposure of fluticasone propionate. No plasma concentrations of salmeterol were measured in
134 this repeat-dose study.

135 No significant changes in excretion of fluticasone propionate or salmeterol were observed.
136 The terminal half-life of fluticasone propionate averaged 5.33 to 7.65 hours when ADVAIR
137 DISKUS was administered, which is similar to that reported when fluticasone propionate was
138 given concurrently with salmeterol or when fluticasone propionate was given alone (average,
139 5.30 to 6.91 hours). No terminal half-life of salmeterol was reported upon administration of
140 ADVAIR DISKUS or salmeterol given concurrently with fluticasone propionate.

141 **Pediatric Patients:** In a clinical study conducted in patients with asthma aged 4 to
142 11 years, fluticasone propionate concentrations were obtained in 61 patients at 20 and 40 minutes
143 after dosing with 50 and 100 mcg of fluticasone propionate inhalation powder twice daily using
144 the DISKUS. Plasma concentrations were low and ranged from undetectable (about 80% of the
145 plasma samples) to 88 pg/mL. Mean peak fluticasone propionate plasma concentrations at the
146 50- and 100-mcg dose levels were 5 and 8 pg/mL, respectively.

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

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

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

160 Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma
161 (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone
162 propionate inhalation powder using the DISKUS device. The mean fluticasone propionate
163 plasma concentration was 110 pg/mL.

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

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

170 The percentage of fluticasone propionate bound to human plasma proteins averages 91%.
171 Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly
172 bound to human transcortin.

173 **Metabolism:** The total clearance of fluticasone propionate is high (average,
174 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only
175 circulating metabolite detected in man is the 17 β -carboxylic acid derivative of fluticasone
176 propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had
177 less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of
178 human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other
179 metabolites detected in vitro using cultured human hepatoma cells have not been detected in
180 man.

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

185 **Special Populations: Hepatic Impairment:** Since fluticasone propionate is
186 predominantly cleared by hepatic metabolism, impairment of liver function may lead to

187 accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease
188 should be closely monitored.

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

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

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

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

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

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

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

222 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low
223 or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder
224 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol
225 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7

226 patients with asthma; plasma concentrations were very low, with mean peak concentrations of
227 167 pg/mL at 20 minutes and no accumulation with repeated doses.

228 **Distribution:** The percentage of salmeterol bound to human plasma proteins averages
229 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much
230 higher concentrations than those achieved following therapeutic doses of salmeterol.

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

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

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

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

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

245 **Pharmacodynamics: ADVAIR DISKUS: Adult and Adolescent Patients:** Since
246 systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose,
247 higher doses were used to produce measurable effects. Four (4) studies were conducted in
248 healthy adult subjects: (1) a single-dose crossover study using 2 inhalations of ADVAIR
249 DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given
250 concurrently, or fluticasone propionate powder 500 mcg given alone, (2) a cumulative dose study
251 using 50 to 400 mcg of salmeterol powder given alone or as ADVAIR DISKUS 500/50, (3) a
252 repeat-dose study for 11 days using 2 inhalations twice daily of ADVAIR DISKUS 250/50,
253 fluticasone propionate powder 250 mcg, or salmeterol powder 50 mcg, and (4) a single-dose
254 study using 5 inhalations of ADVAIR DISKUS 100/50, fluticasone propionate powder 100 mcg
255 alone, or placebo. In these studies no significant differences were observed in the
256 pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and
257 glucose) whether the salmeterol was given as ADVAIR DISKUS, concurrently with fluticasone
258 propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic
259 effects of salmeterol were not altered by the presence of fluticasone propionate in ADVAIR
260 DISKUS. The potential effect of salmeterol on the effects of fluticasone propionate on the
261 hypothalamic-pituitary-adrenal (HPA) axis was also evaluated in these studies. No significant
262 differences across treatments were observed in 24-hour urinary cortisol excretion and, where
263 measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone
264 propionate were not altered by the presence of salmeterol in ADVAIR DISKUS in healthy
265 subjects.

266 **Asthma:** In clinical studies with ADVAIR DISKUS in adult and adolescent patients 12
267 years of age and older with asthma, no significant differences were observed in the systemic
268 pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and
269 glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adolescent and
270 adult patients with asthma given either ADVAIR DISKUS 100/50 or ADVAIR DISKUS
271 250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose
272 and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

273 In a 28-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 500/50
274 twice daily was compared with the concurrent use of salmeterol powder 50 mcg plus fluticasone
275 propionate powder 500 mcg from separate inhalers or fluticasone propionate powder 500 mcg
276 alone. No significant differences across treatments were observed in plasma cortisol AUC after
277 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

278 In a 12-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 250/50
279 twice daily was compared with fluticasone propionate powder 250 mcg alone, salmeterol powder
280 50 mcg alone, and placebo. For most patients, the ability to increase cortisol production in
281 response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with
282 ADVAIR DISKUS. One patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal
283 response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who
284 received placebo, 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients
285 who received salmeterol.

286 **Chronic Obstructive Pulmonary Disease:** In clinical studies with ADVAIR
287 DISKUS in patients with COPD associated with chronic bronchitis, no significant differences
288 were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR DISKUS, the
289 individual components of ADVAIR DISKUS, and placebo. In a study of ADVAIR DISKUS
290 250/50, 8 subjects (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in the
291 fluticasone propionate 250 mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the
292 placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5)
293 of these 8 subjects had a prolonged QTc interval at baseline.

294 In a 24-week study, 130 patients with COPD associated with chronic bronchitis received
295 continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of
296 twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate powder
297 500 mcg, salmeterol powder 50 mcg, or placebo. No significant differences in ventricular or
298 supraventricular arrhythmias and heart rate were observed among the groups treated with
299 ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the
300 fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the
301 group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of
302 nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone
303 propionate 500 mcg treatment groups).

304 Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in
305 101 patients with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate

306 powder 250 mcg, salmeterol powder 50 mcg, or placebo. For most patients, the ability to
307 increase cortisol production in response to stress, as assessed by short cosyntropin stimulation,
308 remained intact with ADVAIR DISKUS 250/50. One (1) patient (3%) who received ADVAIR
309 DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL
310 assessed by high-performance liquid chromatography) after dosing, compared with 2 patients
311 (9%) who received fluticasone propionate 250 mcg, 2 patients (7%) who received salmeterol
312 50 mcg, and 1 patient (4%) who received placebo following 24 weeks of treatment or early
313 discontinuation from study.

314 **Pediatric Patients:** In a 12-week study in patients with asthma aged 4 to 11 years who
315 were receiving inhaled corticosteroids at study entry, ADVAIR DISKUS 100/50 twice daily was
316 compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via
317 the DISKUS. The values for 24-hour urinary cortisol excretion at study entry and after 12 weeks
318 of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol
319 excretion was also similar between the 2 groups.

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

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

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

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

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

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

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

370 **CLINICAL TRIALS**

371 **Asthma: Adult and Adolescent Patients 12 Years of Age and Older:** In clinical trials
372 comparing ADVAIR DISKUS with the individual components, improvements in most efficacy
373 endpoints were greater with ADVAIR DISKUS than with the use of either fluticasone propionate
374 or salmeterol alone. In addition, clinical trials showed similar results between ADVAIR DISKUS
375 and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from
376 separate inhalers.

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

383 **Study 1: Clinical Trial With ADVAIR DISKUS 100/50:** This placebo-controlled,
384 12-week, US study compared ADVAIR DISKUS 100/50 with its individual components,

385 fluticasone propionate 100 mcg and salmeterol 50 mcg. The study was stratified according to
 386 baseline asthma maintenance therapy; patients were using either inhaled corticosteroids
 387 (N = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg;
 388 fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg)
 389 or salmeterol (N = 106). Baseline FEV₁ measurements were similar across treatments: ADVAIR
 390 DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and
 391 placebo, 2.15 L.

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

400

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

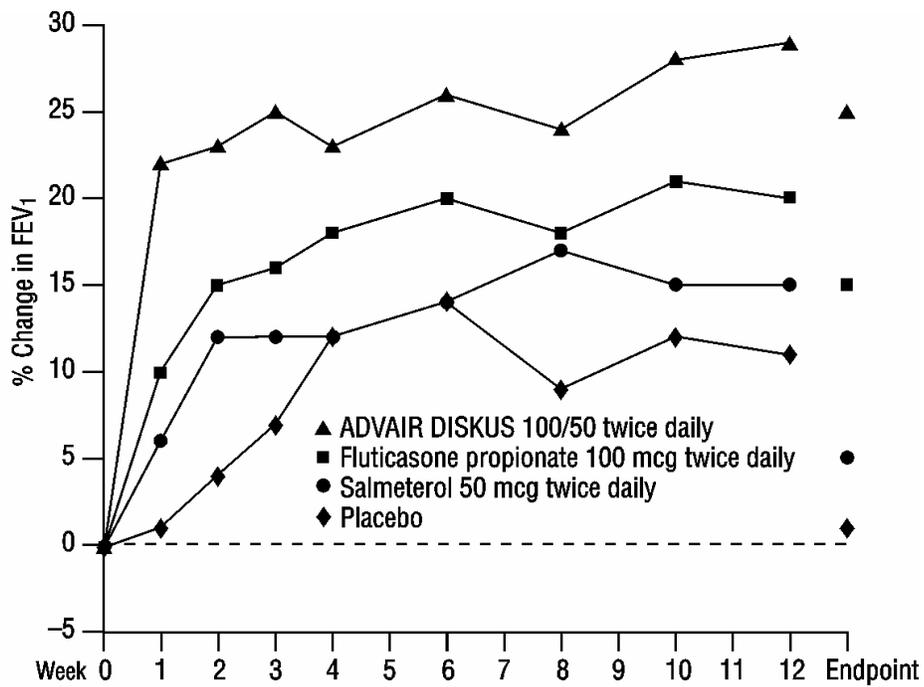
ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
3%	11%	35%	49%

403

404 The FEV₁ results are displayed in Figure 1. Because this trial used predetermined criteria for
 405 worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV₁
 406 results at Endpoint (last available FEV₁ result) are also provided. Patients receiving ADVAIR
 407 DISKUS 100/50 had significantly greater improvements in FEV₁ (0.51 L, 25%) compared with
 408 fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L,
 409 1%). These improvements in FEV₁ with ADVAIR DISKUS were achieved regardless of baseline
 410 asthma maintenance therapy (inhaled corticosteroids or salmeterol).

411

412 **Figure 1. Mean Percent Change From Baseline in FEV₁ in Patients With Asthma**
 413 **Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**
 414



	Week 0	Week 6	Week 12	Endpoint
	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 100/50	87	79	73	86
Fluticasone propionate 100 mcg	85	71	65	85
Salmeterol 50 mcg	86	59	51	86
Placebo	77	34	27	74

415
 416
 417 The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in
 418 Table 2.
 419

420 **Table 2. Peak Expiratory Flow Results for Patients With Asthma Previously Treated With**
 421 **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

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

423

424 The subjective impact of asthma on patients' perception of health was evaluated through use
425 of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point
426 scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR DISKUS
427 100/50 had clinically meaningful improvements in overall asthma-specific quality of life as
428 defined by a difference between groups of ≥ 0.5 points in change from baseline AQLQ scores
429 (difference in AQLQ score of 1.25 compared to placebo).

430 **Study 2: Clinical Trial With ADVAIR DISKUS 250/50:** This placebo-controlled,
431 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components,
432 fluticasone propionate 250 mcg and salmeterol 50 mcg in 349 patients with asthma using inhaled
433 corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to
434 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100
435 to 1,600 mcg). Baseline FEV₁ measurements were similar across treatments: ADVAIR DISKUS
436 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

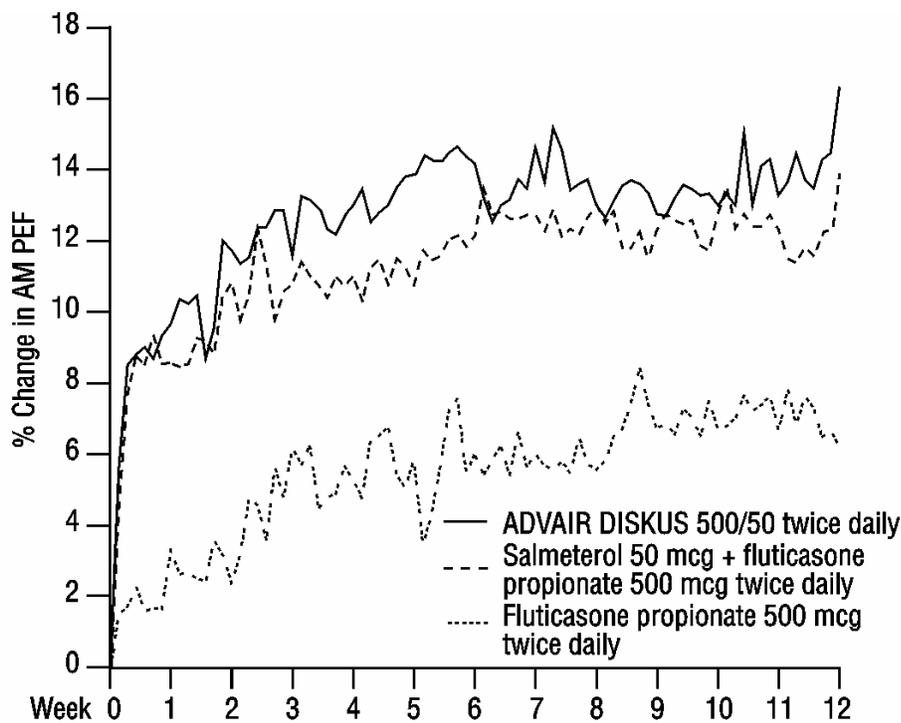
437 Efficacy results in this study were similar to those observed in Study 1. Patients receiving
438 ADVAIR DISKUS 250/50 had significantly greater improvements in FEV₁ (0.48 L, 23%)
439 compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and
440 placebo (decrease of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

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

456 Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50,
457 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. As
458 shown in Figure 2, morning PEF improved significantly with ADVAIR DISKUS 500/50
459 compared with fluticasone propionate 500 mcg over the 12-week treatment period.
460 Improvements in morning PEF observed with ADVAIR DISKUS 500/50 were similar to
461 improvements observed with concurrent therapy.

462

463 **Figure 2. Mean Percent Change From Baseline in Morning Peak Expiratory Flow in**
 464 **Patients With Asthma Previously Treated With Inhaled Corticosteroids (Study 3)**
 465



	<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

466
 467
 468 **Onset of Action and Progression of Improvement in Asthma Control:** The
 469 onset of action and progression of improvement in asthma control were evaluated in the 2
 470 placebo-controlled US trials. Following the first dose, the median time to onset of clinically
 471 significant bronchodilatation ($\geq 15\%$ improvement in FEV₁) in most patients was seen within 30
 472 to 60 minutes. Maximum improvement in FEV₁ generally occurred within 3 hours, and clinically
 473 significant improvement was maintained for 12 hours (see Figure 3).

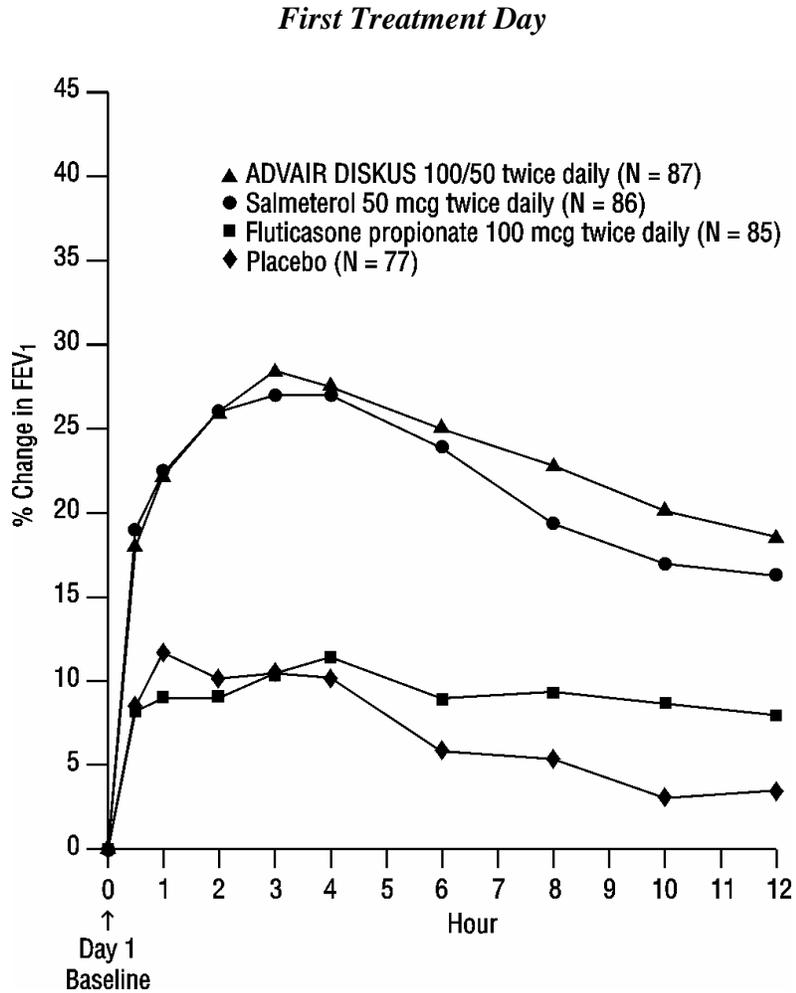
474 Following the initial dose, predose FEV₁ relative to Day 1 baseline improved markedly over
 475 the first week of treatment and continued to improve over the 12 weeks of treatment in both
 476 studies.

477 No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR
 478 DISKUS 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV₁ following
 479 12 weeks of therapy.

480

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

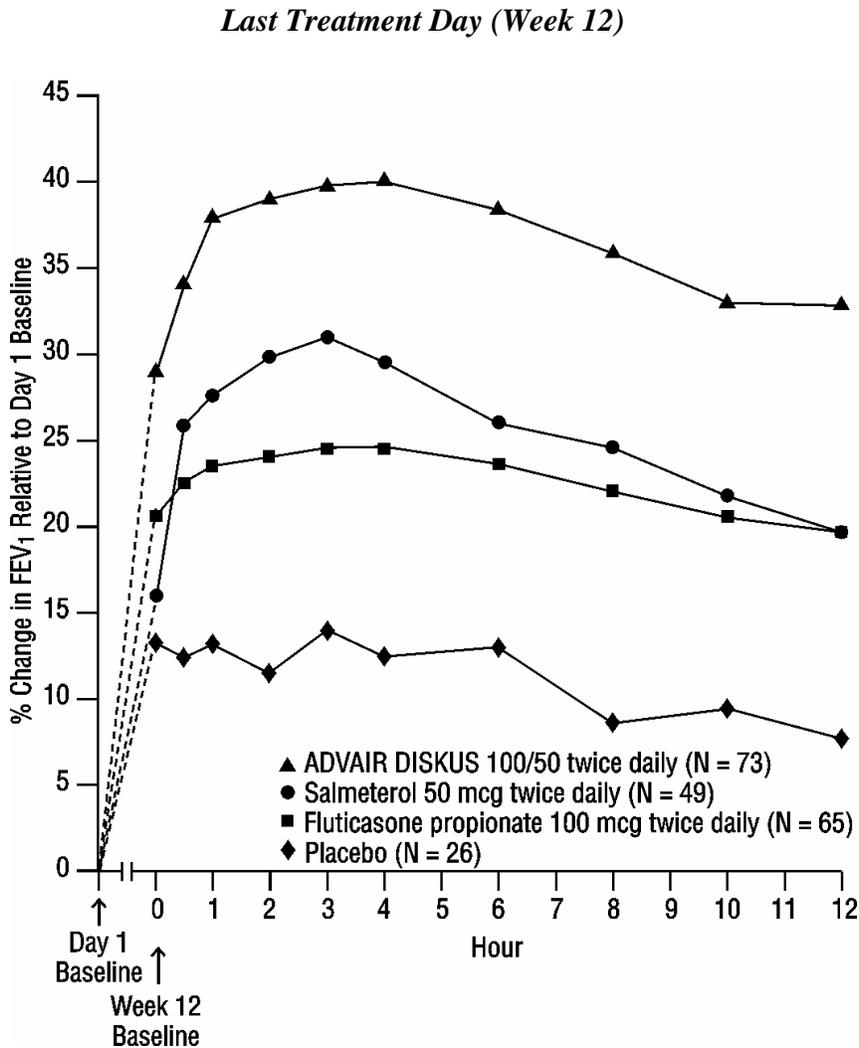
484
485
486



487
488

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

492
 493
 494



495
 496

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

500 **Pediatric Patients:** In a 12-week US study, ADVAIR DISKUS 100/50 twice daily was
 501 compared with fluticasone propionate inhalation powder 100 mcg twice daily in 203 children
 502 with asthma aged 4 to 11 years. At study entry, the children were symptomatic on low doses of
 503 inhaled corticosteroids (beclomethasone dipropionate 252 to 336 mcg/day; budesonide 200 to
 504 400 mcg/day; flunisolide 1,000 mcg/day; triamcinolone acetonide 600 to 1,000 mcg/day; or
 505 fluticasone propionate 88 to 250 mcg/day). The primary objective of this study was to determine
 506 the safety of ADVAIR DISKUS 100/50 compared with fluticasone propionate inhalation powder

507 100 mcg in this age-group; however, the study also included secondary efficacy measures of
508 pulmonary function. Morning predose FEV₁ was obtained at baseline and Endpoint (last
509 available FEV₁ result) in children aged 6 to 11 years. In patients receiving ADVAIR DISKUS
510 100/50, FEV₁ increased from 1.70 L at baseline (N = 79) to 1.88 L at Endpoint (N = 69)
511 compared with an increase from 1.65 L at baseline (N = 83) to 1.77 L at Endpoint (N = 75) in
512 patients receiving fluticasone propionate 100 mcg.

513 The findings of this study, along with extrapolation of efficacy data from patients 12 years of
514 age and older, support the overall conclusion that ADVAIR DISKUS 100/50 is efficacious in the
515 maintenance treatment of asthma in patients aged 4 to 11 years.

516 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** In a
517 clinical trial evaluating twice-daily treatment with ADVAIR DISKUS 250/50 in patients with
518 COPD associated with chronic bronchitis, improvements in lung function (as defined by predose
519 and postdose FEV₁) were significantly greater with ADVAIR DISKUS than with fluticasone
520 propionate 250 mcg, salmeterol 50 mcg, or placebo. The study was a randomized, double-blind,
521 parallel-group, 24-week trial. All patients had a history of cough productive of sputum that was
522 not attributable to another disease process on most days for at least 3 months of the year for at
523 least 2 years. Study treatments were inhalation powders given as 1 inhalation from the DISKUS
524 device twice daily. Maintenance COPD therapies were discontinued, with the exception of
525 theophylline.

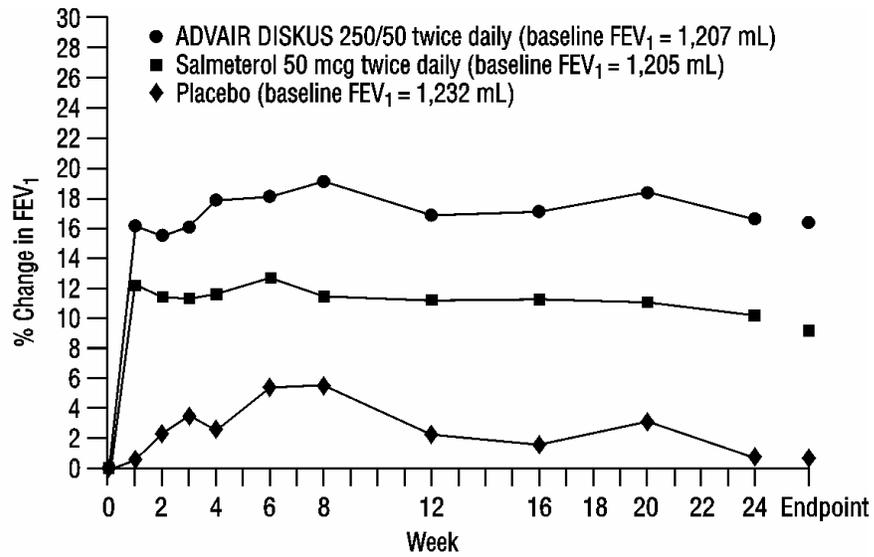
526 Figures 5 and 6 display predose and 2-hour postdose FEV₁ results. To account for patient
527 withdrawals during the study, FEV₁ at Endpoint (last evaluable FEV₁) was evaluated. Patients
528 receiving ADVAIR DISKUS 250/50 had significantly greater improvements in predose FEV₁ at
529 Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL,
530 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung
531 function with ADVAIR DISKUS (Figure 5). Patients receiving ADVAIR DISKUS 250/50 had
532 significantly greater improvements in postdose FEV₁ at Endpoint (281 mL, 27%) compared with
533 fluticasone propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the
534 contribution of salmeterol to the improvement in lung function with ADVAIR DISKUS
535 (Figure 6).

536 A similar degree of improvement in lung function was also observed with ADVAIR DISKUS
537 500/50 twice daily.

538

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

541

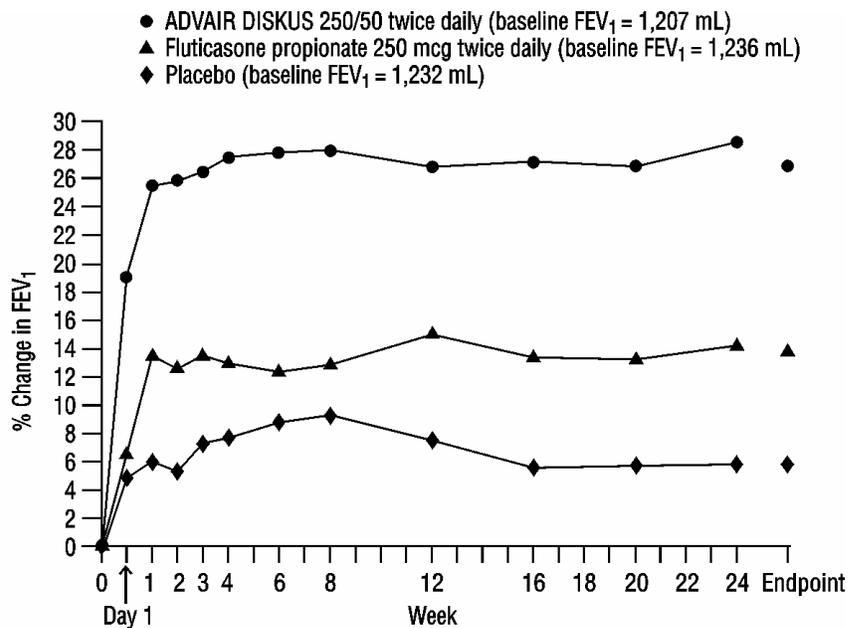


	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 250/50	178	144	124	171
Salmeterol 50 mcg	177	135	119	168
Placebo	185	139	125	172

542

543

544 **Figure 6. Two-Hour Postdose FEV₁: Mean Percent Changes From Baseline Over**
 545 **Time in Patients With COPD Associated With Chronic Bronchitis**
 546



	<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

547
548

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

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

558 **INDICATIONS AND USAGE**

559 **Asthma:** ADVAIR DISKUS is indicated for the long-term, twice-daily, maintenance treatment
 560 of asthma in patients 4 years of age and older.

561 Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in
 562 ADVAIR DISKUS, may increase the risk of asthma-related death (see WARNINGS).
 563 Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR
 564 DISKUS for patients not adequately controlled on other asthma-controller medications (e.g.,
 565 low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants
 566 initiation of treatment with 2 maintenance therapies. ADVAIR DISKUS is not indicated in

567 patients whose asthma can be successfully managed by inhaled corticosteroids along with
568 occasional use of inhaled, short-acting beta₂-agonists.

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

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

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

573 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of
574 COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50,
575 are not recommended (see DOSAGE AND ADMINISTRATION: Chronic Obstructive
576 Pulmonary Disease Associated With Chronic Bronchitis).

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

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

583 **CONTRAINDICATIONS**

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

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

589 **WARNINGS**

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

596 A large placebo-controlled US study that compared the safety of salmeterol with placebo,
597 each added to usual asthma therapy, showed an increase in asthma-related deaths in patients
598 receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a
599 randomized, double-blind study that enrolled long-acting beta₂-agonist-naïve patients with
600 asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily
601 over 28 weeks compared to placebo when added to usual asthma therapy. A planned interim
602 analysis was conducted when approximately half of the intended number of patients had been
603 enrolled (N = 26,355), which led to premature termination of the study. The results of the interim
604 analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events
605 (see Table 3 and Figure 7). In the total population, a higher rate of asthma-related death occurred

606 in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%; relative risk
 607 4.37 [95% CI 1.25, 15.34]).

608 Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death
 609 occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo
 610 (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also,
 611 asthma-related death occurred at a higher rate in patients treated with salmeterol than those
 612 treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the
 613 relative risks of asthma-related death were similar in Caucasians and African Americans, the
 614 estimate of excess deaths in patients treated with salmeterol was greater in African Americans
 615 because there was a higher overall rate of asthma-related death in African American patients (see
 616 Table 3). Given the similar basic mechanisms of action of beta₂-agonists, it is possible that the
 617 findings seen in the SMART study represent a class effect.

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

621
 622 **Table 3: Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research**
 623 **Trial (SMART)**

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

624 ^{*} Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to
 625 study treatment to account for early withdrawal of patients from the study.

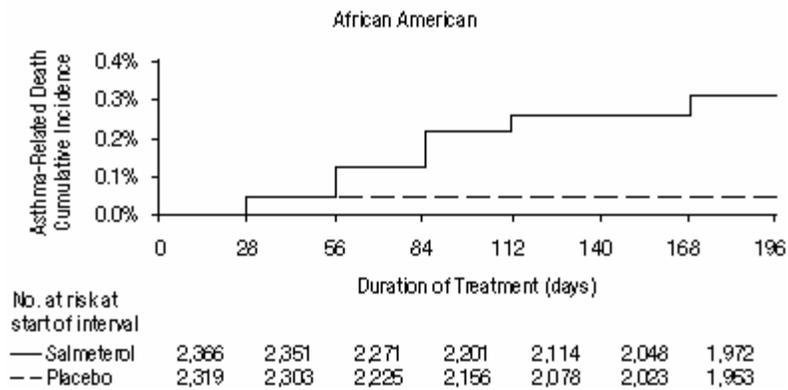
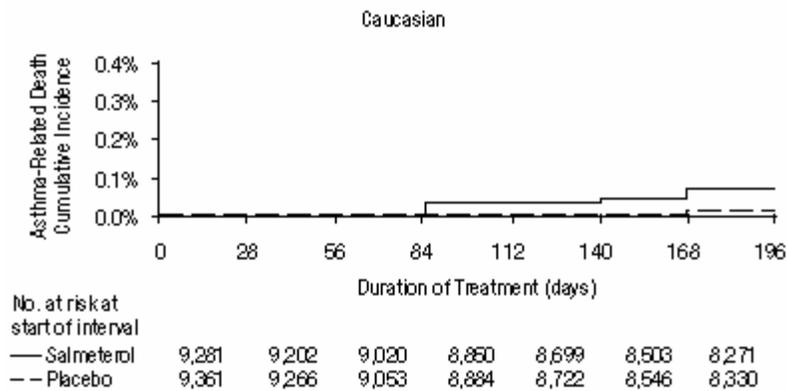
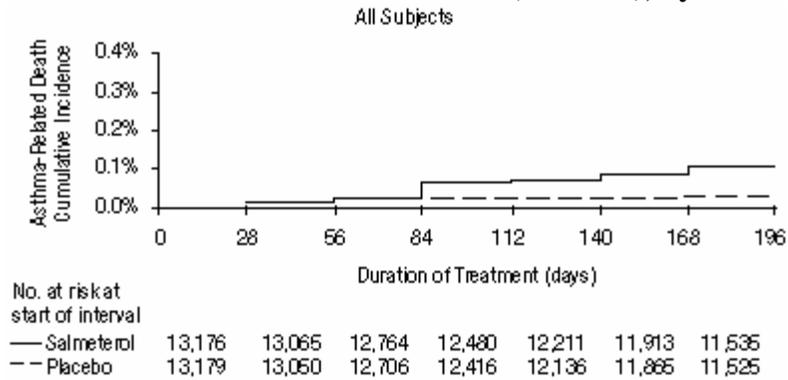
626 [†] Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the
 627 rate in the placebo group. The relative risk indicates how many more times likely an
 628 asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week
 629 treatment period.

630 [‡] Estimate of the number of additional asthma-related deaths in patients treated with salmeterol
 631 in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period.

632 Estimate calculated as the difference between the salmeterol and placebo groups in the rates of
633 asthma-related death multiplied by 10,000.

634 § The Total Population includes the following ethnic origins listed on the case report form:
635 Caucasian, African American, Hispanic, Asian, and “Other.” In addition, the Total Population
636 includes those subjects whose ethnic origin was not reported. The results for Caucasian and
637 African American subpopulations are shown above. No asthma-related deaths occurred in the
638 Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149),
639 or “Other” (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death
640 occurred in the placebo group in the subpopulation whose ethnic origin was not reported
641 (salmeterol n = 130, placebo n = 127).
642

643 **Figure 7. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol**
 644 **Multi-center Asthma Research Trial (SMART), by Duration of Treatment**



645
 646
 647 A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide
 648 Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate
 649 of asthma-related death was numerically, though not statistically significantly, greater in patients
 650 with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol
 651 (180 mcg 4 times daily) added to usual asthma therapy.

652 **The SNS and SMART studies enrolled patients with asthma. No studies have been**
653 **conducted that were adequate to determine whether the rate of death in patients with**
654 **COPD is increased by long-acting beta₂ adrenergic agonists.**

655 **The following additional WARNINGS about ADVAIR DISKUS should be noted.**

656 1. ADVAIR DISKUS should not be initiated in patients during rapidly deteriorating or
657 potentially life-threatening episodes of asthma. Serious acute respiratory events, including
658 fatalities, have been reported both in the United States and worldwide when salmeterol, a
659 component of ADVAIR DISKUS, has been initiated in patients with significantly worsening or
660 acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma
661 (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation,
662 mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma
663 exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (e.g.,
664 unresponsive to usual medications; increasing need for inhaled, short-acting beta₂-agonists;
665 increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency
666 room visits; sudden or progressive deterioration in pulmonary function). However, they have
667 occurred in a few patients with less severe asthma as well. It was not possible from these reports
668 to determine whether salmeterol contributed to these events.

669 2. ADVAIR DISKUS Should Not Be Used to Treat Acute Symptoms. An inhaled, short-acting
670 beta₂-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms of shortness of
671 breath. When prescribing ADVAIR DISKUS, the physician must also provide the patient with an
672 inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of shortness of breath that
673 occurs acutely, despite regular twice-daily (morning and evening) use of ADVAIR DISKUS.

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

679 3. Increasing Use of Inhaled Short-Acting Beta₂-Agonists Is a Marker of Deteriorating Asthma.
680 The physician and patient should be alert to such changes. The patient's condition may
681 deteriorate acutely over a period of hours or chronically over several days or longer. If the
682 patient's inhaled, short-acting beta₂-agonist becomes less effective, the patient needs more
683 inhalations than usual, or the patient develops a significant decrease in lung function, this may be
684 a marker of destabilization of the disease. In this setting, the patient requires immediate
685 reevaluation with reassessment of the treatment regimen, giving special consideration to the
686 possible need for replacing the current strength of ADVAIR DISKUS with a higher strength,
687 adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should
688 not use more than 1 inhalation twice daily (morning and evening) of ADVAIR DISKUS.

689 4. ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid
690 therapy. Particular care is needed for patients who have been transferred from systemically active
691 corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have

692 occurred in patients with asthma during and after transfer from systemic corticosteroids to less
693 systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a
694 number of months are required for recovery of HPA function.

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

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

709 5. ADVAIR DISKUS Should Not Be Used in Conjunction With an Inhaled, Long-Acting Beta₂-
710 Agonist. Patients who are receiving ADVAIR DISKUS twice daily should not use additional
711 salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of
712 exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma or the
713 maintenance treatment of bronchospasm associated with COPD. Additional benefit would not be
714 gained from using supplemental salmeterol or formoterol for prevention of EIB since ADVAIR
715 DISKUS already contains an inhaled, long-acting beta₂-agonist.

716 6. The Recommended Dosage Should Not Be Exceeded. ADVAIR DISKUS should not be used
717 more often or at higher doses than recommended. Fatalities have been reported in association
718 with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol
719 (12 to 20 times the recommended dose) have been associated with clinically significant
720 prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias.

721 7. Paradoxical Bronchospasm. As with other inhaled asthma and COPD medications, ADVAIR
722 DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical
723 bronchospasm occurs following dosing with ADVAIR DISKUS, it should be treated
724 immediately with an inhaled, short-acting bronchodilator, ADVAIR DISKUS should be
725 discontinued immediately, and alternative therapy should be instituted.

726 8. Immediate Hypersensitivity Reactions. Immediate hypersensitivity reactions may occur after
727 administration of ADVAIR DISKUS, as demonstrated by cases of urticaria, angioedema, rash,
728 and bronchospasm.

729 9. Upper Airway Symptoms. Symptoms of laryngeal spasm, irritation, or swelling, such as
730 stridor and choking, have been reported in patients receiving fluticasone propionate and
731 salmeterol, components of ADVAIR DISKUS.

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

741 11. Discontinuation of Systemic Corticosteroids. Transfer of patients from systemic
742 corticosteroid therapy to ADVAIR DISKUS may unmask conditions previously suppressed by
743 the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and
744 eosinophilic conditions.

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

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

767 **PRECAUTIONS**

768 **General: Cardiovascular Effects:** Cardiovascular and central nervous system effects seen
769 with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can
770 occur after use of salmeterol, a component of ADVAIR DISKUS, and may require

771 discontinuation of ADVAIR DISKUS. ADVAIR DISKUS, like all medications containing
772 sympathomimetic amines, should be used with caution in patients with cardiovascular disorders,
773 especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with
774 convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to
775 sympathomimetic amines.

776 As has been described with other beta-adrenergic agonist bronchodilators, clinically
777 significant changes in electrocardiograms (ECGs) have been seen infrequently in individual
778 patients in controlled clinical studies with ADVAIR DISKUS and salmeterol. Clinically
779 significant changes in systolic and/or diastolic blood pressure and pulse rate have been seen
780 infrequently in individual patients in controlled clinical studies with salmeterol, a component of
781 ADVAIR DISKUS.

782 **Metabolic and Other Effects:** Long-term use of orally inhaled corticosteroids may affect
783 normal bone metabolism, resulting in a loss of bone mineral density (BMD). A 2-year study of
784 160 patients (females 18 to 40 and males 18 to 50 years of age) with asthma receiving
785 chlorofluorocarbon-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice
786 daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and
787 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar
788 region L1 through L4. Long-term treatment effects of fluticasone propionate on BMD in the
789 COPD population have not been studied.

790 In patients with major risk factors for decreased bone mineral content, such as tobacco use,
791 advanced age, sedentary lifestyle, poor nutrition, family history of osteoporosis, or chronic use of
792 drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), ADVAIR DISKUS
793 may pose an additional risk. Since patients with COPD often have multiple risk factors for
794 reduced BMD, assessment of BMD is recommended, including prior to instituting ADVAIR
795 DISKUS 250/50 and periodically thereafter. If significant reductions in BMD are seen and
796 ADVAIR DISKUS 250/50 is still considered medically important for that patient's COPD
797 therapy, use of medication to treat or prevent osteoporosis should be strongly considered.
798 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of
799 COPD associated with chronic bronchitis, and higher doses, including ADVAIR DISKUS
800 500/50, are not recommended.

801 Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with
802 asthma and COPD following the long-term administration of inhaled corticosteroids, including
803 fluticasone propionate, a component of ADVAIR DISKUS; therefore, regular eye examinations
804 should be considered.

805 Lower respiratory tract infections, including pneumonia, have been reported following the
806 inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR
807 DISKUS.

808 Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously,
809 have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic
810 agonist medications may produce significant hypokalemia in some patients, possibly through

811 intracellular shunting, which has the potential to produce adverse cardiovascular effects. The
812 decrease in serum potassium is usually transient, not requiring supplementation.

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

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

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

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

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

838 A reduction of growth velocity in children and adolescents may occur as a result of poorly
839 controlled asthma or from the therapeutic use of corticosteroids, including inhaled
840 corticosteroids. The effects of long-term treatment of children and adolescents with inhaled
841 corticosteroids, including fluticasone propionate, on final adult height are not known.

842 A 52-week, placebo-controlled study to assess the potential growth effects of fluticasone
843 propionate inhalation powder (FLOVENT[®] ROTADISK[®]) at 50 and 100 mcg twice daily was
844 conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to
845 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were
846 6.32 cm/year in the placebo group (N = 76), 6.07 cm/year in the 50-mcg group (N = 98), and
847 5.66 cm/year in the 100-mcg group (N = 89). An imbalance in the proportion of children entering
848 puberty between groups and a higher dropout rate in the placebo group due to poorly controlled
849 asthma may be confounding factors in interpreting these data. A separate subset analysis of
850 children who remained prepubertal during the study revealed growth rates at 52 weeks of

851 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and
852 5.67 cm/year in the 100-mcg group (n = 79). In children 8.5 years of age, the mean age of
853 children in this study, the range for expected growth velocity is: boys – 3rd
854 percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls –
855 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year.

856 The clinical significance of these growth data is not certain. Physicians should closely follow
857 the growth of children and adolescents taking corticosteroids by any route, and weigh the
858 benefits of corticosteroid therapy against the possibility of growth suppression if growth appears
859 slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that
860 effectively controls their asthma.

861 The long-term effects of ADVAIR DISKUS in human subjects are not fully known. In
862 particular, the effects resulting from chronic use of fluticasone propionate on developmental or
863 immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients
864 have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or
865 longer. In clinical studies in patients with asthma treated for 2 years with inhaled fluticasone
866 propionate, no apparent differences in the type or severity of adverse reactions were observed
867 after long- versus short-term treatment.

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

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

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

887 **Chronic Obstructive Pulmonary Disease:** ADVAIR DISKUS 250/50 twice daily is the
888 only dosage recommended for the treatment of airflow obstruction in patients with COPD
889 associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not
890 recommended, as no additional improvement in lung function (defined by predose and postdose

891 FEV₁) was observed in clinical trials and higher doses of corticosteroids increase the risk of
892 systemic effects.

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

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

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

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

- 907 1. **Patients should be informed that salmeterol, one of the active ingredients in ADVAIR**
908 **DISKUS, may increase the risk of asthma-related death.** They should also be informed
909 that data are not adequate to determine whether the concurrent use of inhaled corticosteroids,
910 such as fluticasone propionate, the other component of ADVAIR DISKUS, or other
911 asthma-controller therapy modifies this risk.
- 912 2. ADVAIR DISKUS is not meant to relieve acute asthma symptoms and extra doses should
913 not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting
914 beta₂-agonist such as albuterol (the physician should provide the patient with such
915 medication and instruct the patient in how it should be used). ADVAIR DISKUS is not
916 meant to relieve acute asthma symptoms or exacerbations of COPD.
- 917 3. The physician should be notified immediately if any of the following signs of seriously
918 worsening asthma occur:
 - 919 • decreasing effectiveness of inhaled, short-acting beta₂-agonists;
 - 920 • need for more inhalations than usual of inhaled, short-acting beta₂-agonists;
 - 921 • significant decrease in lung function as outlined by the physician.
- 922 4. Patients should not stop therapy with ADVAIR DISKUS without physician/provider
923 guidance since symptoms may recur after discontinuation.
- 924 5. Patients should be cautioned regarding common adverse effects associated with
925 beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 926 6. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of
927 ADVAIR DISKUS, may increase the risk of some eye problems (cataracts or glaucoma).
928 Regular eye examinations should be considered.

- 929 7. Patients who are at an increased risk for decreased BMD should be advised that the use of
930 corticosteroids may pose an additional risk and should be told to monitor and, where
931 appropriate, seek treatment for this condition.
- 932 8. When patients are prescribed ADVAIR DISKUS, other medications for asthma and COPD
933 should be used only as directed by their physicians.
- 934 9. ADVAIR DISKUS should not be used with a spacer device.
- 935 10. Patients who are pregnant or nursing should contact their physicians about the use of
936 ADVAIR DISKUS.
- 937 11. Patients should use ADVAIR DISKUS at regular intervals as directed. Results of clinical
938 trials indicate significant improvement may occur within the first 30 minutes of taking the
939 first dose; however, the full benefit may not be achieved until treatment has been
940 administered for 1 week or longer. The patient should not use more than the prescribed
941 dosage but should contact the physician if symptoms do not improve or if the condition
942 worsens.
- 943 12. The bronchodilation from a single dose of ADVAIR DISKUS may last up to 12 hours or
944 longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not
945 be exceeded. Patients who are receiving ADVAIR DISKUS twice daily should not use
946 salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of
947 EIB or maintenance treatment of asthma or the maintenance treatment of bronchospasm in
948 COPD.
- 949 13. Patients should be warned to avoid exposure to chickenpox or measles and, if they are
950 exposed, to consult their physicians without delay.
- 951 14. Effective and safe use of ADVAIR DISKUS includes an understanding of the way that it
952 should be used:
- 953 • Never exhale into the DISKUS.
 - 954 • Never attempt to take the DISKUS apart.
 - 955 • Always activate and use the DISKUS in a level, horizontal position.
 - 956 • After inhalation, rinse the mouth with water without swallowing.
 - 957 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
 - 958 • Always keep the DISKUS in a dry place.
 - 959 • Discard **1 month** after removal from the moisture-protective foil overwrap pouch or after
960 all blisters have been used (when the dose indicator reads “0”), whichever comes first.
- 961 15. For the proper use of ADVAIR DISKUS and to attain maximum improvement, the patient
962 should read and carefully follow the Instructions for Using ADVAIR DISKUS in the
963 Medication Guide accompanying the product.
- 964 16. Most patients are able to taste or feel a dose delivered from ADVAIR DISKUS. However,
965 whether or not patients are able to sense delivery of a dose, you should instruct them not to
966 exceed the recommended dose of 1 inhalation each morning and evening, approximately 12
967 hours apart. You should instruct them to contact you or the pharmacist if they have questions.

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

972 **Short-Acting Beta₂-Agonists:** In clinical trials with patients with asthma, the mean daily
973 need for albuterol by 166 adult and adolescent patients 12 years of age and older using ADVAIR
974 DISKUS was approximately 1.3 inhalations/day, and ranged from 0 to 9 inhalations/day. Five
975 percent (5%) of patients using ADVAIR DISKUS in these trials averaged 6 or more inhalations
976 per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse
977 reactions was observed among patients who averaged 6 or more inhalations per day.

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

983 **Methylxanthines:** The concurrent use of intravenously or orally administered
984 methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent patients 12 years of
985 age and older receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials
986 with patients with asthma, 39 patients receiving ADVAIR DISKUS 100/50, 250/50, or 500/50
987 twice daily concurrently with a theophylline product had adverse event rates similar to those in
988 304 patients receiving ADVAIR DISKUS without theophylline. Similar results were observed in
989 patients receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily
990 concurrently with a theophylline product (N = 39) or without theophylline (N = 132).

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

996 **Fluticasone Propionate Nasal Spray:** In adult and adolescent patients 12 years of age
997 and older taking ADVAIR DISKUS in clinical trials, no difference in the profile of adverse
998 events or HPA axis effects was noted between patients taking FLONASE[®] (fluticasone
999 propionate) Nasal Spray, 50 mcg concurrently (N = 46) and those who were not (N = 130).

1000 **Monoamine Oxidase Inhibitors and Tricyclic Antidepressants:** ADVAIR DISKUS
1001 should be administered with extreme caution to patients being treated with monoamine oxidase
1002 inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents,
1003 because the action of salmeterol, a component of ADVAIR DISKUS, on the vascular system
1004 may be potentiated by these agents.

1005 **Beta-Adrenergic Receptor Blocking Agents:** Beta-blockers not only block the
1006 pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, but
1007 may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma

1008 should not normally be treated with beta-blockers. However, under certain circumstances, there
1009 may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with
1010 asthma. In this setting, cardioselective beta-blockers could be considered, although they should
1011 be administered with caution.

1012 **Diuretics:** The ECG changes and/or hypokalemia that may result from the administration of
1013 nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by
1014 beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although
1015 the clinical significance of these effects is not known, caution is advised in the coadministration
1016 of beta-agonists with nonpotassium-sparing diuretics.

1017 **Inhibitors of Cytochrome P450:** Fluticasone propionate is a substrate of cytochrome
1018 P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy
1019 subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can
1020 significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced
1021 serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics:
1022 *Fluticasone Propionate: Drug Interactions*). During postmarketing use, there have been reports
1023 of clinically significant drug interactions in patients receiving fluticasone propionate and
1024 ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal
1025 suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not
1026 recommended unless the potential benefit to the patient outweighs the risk of systemic
1027 corticosteroid side effects.

1028 In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a
1029 single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of
1030 ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate
1031 exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.
1032 Caution should be exercised when ADVAIR DISKUS is coadministered with ketoconazole and
1033 other known potent cytochrome P450 3A4 inhibitors.

1034 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate:**
1035 Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to
1036 1,000 mcg/kg (approximately 4 and 10 times, respectively, the maximum recommended daily
1037 inhalation dose in adults and children on a mcg/m² basis) for 78 weeks or in rats at inhalation
1038 doses up to 57 mcg/kg (less than and approximately equivalent to, respectively, the maximum
1039 recommended daily inhalation dose in adults and children on a mcg/m² basis) for 104 weeks.

1040 Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in
1041 vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in
1042 vitro or in the mouse micronucleus test.

1043 No evidence of impairment of fertility was observed in reproductive studies conducted in
1044 male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum
1045 recommended daily inhalation dose in adults on a mcg/m² basis). Prostate weight was
1046 significantly reduced at a subcutaneous dose of 50 mcg/kg.

1047 **Salmeterol:** In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of
1048 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose
1049 in adults and children based on comparison of the plasma area under the curves [AUCs]) caused
1050 a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular
1051 hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of
1052 leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg
1053 (approximately 3 times the maximum recommended daily inhalation doses in adults and children
1054 based on comparison of the AUCs).

1055 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol
1056 caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at
1057 doses of 0.68 mg/kg and above (approximately 55 and 25 times, respectively, the maximum
1058 recommended daily inhalation dose in adults and children on a mg/m² basis). No tumors were
1059 seen at 0.21 mg/kg (approximately 15 and 8 times, respectively, the maximum recommended
1060 daily inhalation dose in adults and children on a mg/m² basis). These findings in rodents are
1061 similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of
1062 these findings to human use is unknown.

1063 Salmeterol produced no detectable or reproducible increases in microbial and mammalian
1064 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo
1065 in a rat micronucleus test. No effects on fertility were identified in male and female rats treated
1066 with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum
1067 recommended daily inhalation dose in adults on a mg/m² basis).

1068 **Pregnancy: Teratogenic Effects: ADVAIR DISKUS:** Pregnancy Category C. From the
1069 reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using
1070 combinations of fluticasone propionate and salmeterol compared to toxicity data from the
1071 components administered separately. In mice combining 150 mcg/kg subcutaneously of
1072 fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a
1073 mcg/m² basis) with 10 mg/kg orally of salmeterol (approximately 410 times the maximum
1074 recommended daily inhalation dose in adults on a mg/m² basis) was teratogenic. Cleft palate,
1075 fetal death, increased implantation loss and delayed ossification were seen. These observations
1076 are characteristic of glucocorticoids. No developmental toxicity was observed at combination
1077 doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum
1078 recommended daily inhalation dose in adults on a mcg/m² basis) and up to 1.4 mg/kg orally of
1079 salmeterol (approximately 55 times the maximum recommended daily inhalation dose in adults
1080 on a mg/m² basis). In rats, no teratogenicity was observed at combination doses up to 30 mcg/kg
1081 subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation
1082 dose in adults on a mcg/m² basis) and up to 1 mg/kg of salmeterol (approximately 80 times the
1083 maximum recommended daily inhalation dose in adults on a mg/m² basis). Combining
1084 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum recommended
1085 daily inhalation dose in adults on a mcg/m² basis) with 10 mg/kg orally of salmeterol
1086 (approximately 810 times the maximum recommended daily inhalation dose in adults on a

1087 mg/m² basis) produced maternal toxicity, decreased placental weight, decreased fetal weight,
1088 umbilical hernia, delayed ossification, and changes in the occipital bone. There are no adequate
1089 and well-controlled studies with ADVAIR DISKUS in pregnant women. ADVAIR DISKUS
1090 should be used during pregnancy only if the potential benefit justifies the potential risk to the
1091 fetus.

1092 **Fluticasone Propionate:** Pregnancy Category C. Subcutaneous studies in the mouse
1093 and rat at 45 and 100 mcg/kg (less than or equivalent to the maximum recommended daily
1094 inhalation dose in adults on a mcg/m² basis), respectively, revealed fetal toxicity characteristic of
1095 potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft
1096 palate, and retarded cranial ossification.

1097 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of
1098 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m²
1099 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg
1100 (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m²
1101 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this
1102 study, consistent with the established low bioavailability following oral administration (see
1103 CLINICAL PHARMACOLOGY).

1104 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose
1105 of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a
1106 mcg/m² basis), administration of a subcutaneous or an oral dose of 100 mcg/kg to rats
1107 (approximately equivalent to the maximum recommended daily inhalation dose in adults on a
1108 mcg/m² basis), and administration of an oral dose of 300 mcg/kg to rabbits (approximately 5
1109 times the maximum recommended daily inhalation dose in adults on a mcg/m² basis).

1110 There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate
1111 should be used during pregnancy only if the potential benefit justifies the potential risk to the
1112 fetus.

1113 Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to
1114 physiologic, doses suggests that rodents are more prone to teratogenic effects from
1115 corticosteroids than humans. In addition, because there is a natural increase in corticosteroid
1116 production during pregnancy, most women will require a lower exogenous corticosteroid dose
1117 and many will not need corticosteroid treatment during pregnancy.

1118 **Salmeterol:** Pregnancy Category C. No teratogenic effects occurred in rats at oral doses
1119 up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in
1120 adults on a mg/m² basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and
1121 above (approximately 50 times the maximum recommended daily inhalation dose in adults based
1122 on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting
1123 from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate,
1124 sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones.
1125 No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the
1126 maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

1127 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal
1128 bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the maximum
1129 recommended daily inhalation dose in adults on a mg/m² basis). Extensive use of other
1130 beta-agonists has provided no evidence that these class effects in animals are relevant to their use
1131 in humans. There are no adequate and well-controlled studies with salmeterol in pregnant
1132 women. Salmeterol should be used during pregnancy only if the potential benefit justifies the
1133 potential risk to the fetus.

1134 Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice
1135 and rats (approximately 410 and 810 times, respectively, the maximum recommended daily
1136 inhalation dose in adults on a mg/m² basis).

1137 **Use in Labor and Delivery:** There are no well-controlled human studies that have
1138 investigated effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the
1139 potential for beta-agonist interference with uterine contractility, use of ADVAIR DISKUS during
1140 labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

1141 **Nursing Mothers:** Plasma levels of salmeterol, a component of ADVAIR DISKUS, after
1142 inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There
1143 are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known
1144 whether fluticasone propionate, a component of ADVAIR DISKUS, is excreted in human breast
1145 milk. However, other corticosteroids have been detected in human milk. Subcutaneous
1146 administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the
1147 maximum recommended daily inhalation dose in adults on a mcg/m² basis) resulted in
1148 measurable radioactivity in milk.

1149 Since there are no data from controlled trials on the use of ADVAIR DISKUS by nursing
1150 mothers, a decision should be made whether to discontinue nursing or to discontinue ADVAIR
1151 DISKUS, taking into account the importance of ADVAIR DISKUS to the mother.

1152 Caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.

1153 **Pediatric Use:** Use of ADVAIR DISKUS 100/50 in patients 4 to 11 years of age is supported
1154 by extrapolation of efficacy data from older patients and by safety and efficacy data from a study
1155 of ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years (see CLINICAL
1156 TRIALS: Asthma: *Pediatric Patients* and ADVERSE REACTIONS: Asthma: *Pediatric*
1157 *Patients*). The safety and effectiveness of ADVAIR DISKUS in children with asthma under
1158 4 years of age have not been established.

1159 Controlled clinical studies have shown that orally inhaled corticosteroids may cause a
1160 reduction in growth velocity in pediatric patients. This effect has been observed in the absence of
1161 laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive
1162 indicator of systemic corticosteroid exposure in pediatric patients than some commonly used
1163 tests of HPA axis function. The long-term effects of this reduction in growth velocity associated
1164 with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The
1165 potential for “catch-up” growth following discontinuation of treatment with orally inhaled
1166 corticosteroids has not been adequately studied.

1167 Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS,
1168 may cause a reduction in growth velocity in children and adolescents (see PRECAUTIONS:
1169 General: *Metabolic and Other Effects*). The growth of pediatric patients receiving orally inhaled
1170 corticosteroids, including ADVAIR DISKUS, should be monitored. If a child or adolescent on
1171 any corticosteroid appears to have growth suppression, the possibility that he/she is particularly
1172 sensitive to this effect of corticosteroids should be considered. The potential growth effects of
1173 prolonged treatment should be weighed against the clinical benefits obtained. To minimize the
1174 systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, each patient
1175 should be titrated to the lowest strength that effectively controls his/her asthma (see DOSAGE
1176 AND ADMINISTRATION: Asthma).

1177 **Geriatric Use:** Of the total number of patients in clinical studies of ADVAIR DISKUS for
1178 asthma, 44 were 65 years of age or older and 3 were 75 years of age or older. Of the total
1179 number of patients in a clinical study of ADVAIR DISKUS 250/50 for COPD, 85 were 65 years
1180 of age or older and 31 were 75 years of age or older. For both diseases, no overall differences in
1181 safety were observed between these patients and younger patients, and other reported clinical
1182 experience, including studies of the individual components, has not identified differences in
1183 responses between the elderly and younger patients, but greater sensitivity of some older
1184 individuals cannot be ruled out. As with other products containing beta₂-agonists, special caution
1185 should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant
1186 cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available
1187 data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR
1188 DISKUS in geriatric patients is warranted.

1189 **ADVERSE REACTIONS**

1190 **Long-acting beta₂-adrenergic agonists, such as salmeterol, may increase the risk of**
1191 **asthma-related death. Data from a large, placebo-controlled US study that compared the**
1192 **safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma**
1193 **therapy showed an increase in asthma-related deaths in patients receiving salmeterol (see**
1194 **WARNINGS). Salmeterol is a component of ADVAIR DISKUS. However, the data from**
1195 **this study are not adequate to determine whether concurrent use of inhaled corticosteroids,**
1196 **such as fluticasone propionate, the other component of ADVAIR DISKUS, or other asthma**
1197 **controller therapy modifies the risk of asthma-related death.**

1198 **Asthma: Adult and Adolescent Patients 12 Years of Age and Older:** The incidence of
1199 common adverse events in Table 4 is based upon 2 placebo-controlled, 12-week, US clinical
1200 studies (Studies 1 and 2). A total of 705 adolescent and adult patients (349 females and 356
1201 males) previously treated with salmeterol or inhaled corticosteroids were treated twice daily with
1202 ADVAIR DISKUS (100/50- or 250/50-mcg doses), fluticasone propionate inhalation powder
1203 (100- or 250-mcg doses), salmeterol inhalation powder 50 mcg, or placebo.
1204

1205 **Table 4. Overall Adverse Events With $\geq 3\%$ Incidence in US Controlled Clinical Trials With**
 1206 **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, & 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

1207
 1208 Table 4 includes all events (whether considered drug-related or nondrug-related by the
 1209 investigator) that occurred at a rate of 3% or greater in either of the groups receiving ADVAIR
 1210 DISKUS and were more common than in the placebo group. In considering these data,
 1211 differences in average duration of exposure should be taken into account. Rare cases of

1212 immediate and delayed hypersensitivity reactions, including rash and other rare events of
1213 angioedema and bronchospasm, have been reported.

1214 These adverse reactions were mostly mild to moderate in severity.

1215 Other adverse events that occurred in the groups receiving ADVAIR DISKUS in these studies
1216 with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1217 **Blood and Lymphatic:** Lymphatic signs and symptoms.

1218 **Cardiovascular:** Palpitations.

1219 **Drug Interaction, Overdose, and Trauma:** Muscle injuries, fractures, wounds and
1220 lacerations, contusions and hematomas, burns.

1221 **Ear, Nose, and Throat:** Rhinorrhea/postnasal drip; ear, nose, and throat infections; ear
1222 signs and symptoms; nasal signs and symptoms; nasal sinus disorders; rhinitis; sneezing; nasal
1223 irritation; blood in nasal mucosa.

1224 **Eye:** Keratitis and conjunctivitis, viral eye infections, eye redness.

1225 **Gastrointestinal:** Dental discomfort and pain, gastrointestinal signs and symptoms,
1226 gastrointestinal infections, gastroenteritis, gastrointestinal disorders, oral ulcerations, oral
1227 erythema and rashes, constipation, appendicitis, oral discomfort and pain.

1228 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1229 **Lower Respiratory:** Lower respiratory signs and symptoms, pneumonia, lower
1230 respiratory infections.

1231 **Musculoskeletal:** Arthralgia and articular rheumatism; muscle stiffness, tightness, and
1232 rigidity; bone and cartilage disorders.

1233 **Neurology:** Sleep disorders, tremors, hypnagogic effects, compressed nerve syndromes.

1234 **Non-Site Specific:** Allergies and allergic reactions, congestion, viral infections, pain,
1235 chest symptoms, fluid retention, bacterial infections, wheeze and hives, unusual taste.

1236 **Skin:** Viral skin infections, urticaria, skin flakiness and acquired ichthyosis, disorders of
1237 sweat and sebum, sweating.

1238 The incidence of common adverse events reported in Study 3, a 28-week, non-US clinical
1239 study of 503 patients previously treated with inhaled corticosteroids who were treated twice daily
1240 with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and
1241 salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation
1242 powder 500 mcg was similar to the incidences reported in Table 4.

1243 **Pediatric Patients: Pediatric Study:** ADVAIR DISKUS 100/50 was well tolerated in
1244 clinical trials conducted in children with asthma aged 4 to 11 years. The incidence of common
1245 adverse events in Table 5 is based upon a 12-week US study in 203 patients with asthma aged 4
1246 to 11 years (74 females and 129 males) who were receiving inhaled corticosteroids at study entry
1247 and were randomized to either ADVAIR DISKUS 100/50 or fluticasone propionate inhalation
1248 powder 100 mcg twice daily.

1249

1250 **Table 5. Overall Adverse Events With $\geq 3\%$ Incidence With ADVAIR DISKUS 100/50**
 1251 **in Patients 4 to 11 Years of Age With Asthma**

Adverse Event	ADVAIR DISKUS 100/50 (N = 101) %	Fluticasone Propionate 100 mcg (N = 102) %
Ear, nose, & throat		
Upper respiratory tract infection	10	17
Throat irritation	8	7
Ear, nose, & throat infections	4	<1
Epistaxis	4	<1
Pharyngitis/throat infection	3	2
Ear signs & symptoms	3	<1
Sinusitis	3	0
Neurology		
Headache	20	20
Gastrointestinal		
Gastrointestinal discomfort & pain	7	5
Nausea & vomiting	5	3
Candidiasis mouth/throat	4	<1
Non-site specific		
Fever	5	13
Chest symptoms	3	<1
Average duration of exposure (days)	74.8	78.8

1252
 1253 Table 5 includes all events (whether considered drug-related or nondrug-related by the
 1254 investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS
 1255 100/50.

1256 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The
 1257 incidence of common adverse events in Table 6 is based upon 1 placebo-controlled, 24-week, US
 1258 clinical trial in patients with COPD associated with chronic bronchitis. A total of 723 adult
 1259 patients (266 females and 457 males) were treated twice daily with ADVAIR DISKUS 250/50,
 1260 fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder 50 mcg, or
 1261 placebo.
 1262

1263
1264

Table 6. Overall Adverse Events With ≥3% Incidence With ADVAIR DISKUS 250/50 in Patients With Chronic Obstructive Pulmonary Disease Associated With Chronic 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, & 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

1265

1266 Table 6 includes all events (whether considered drug-related or nondrug-related by the
1267 investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS
1268 250/50 and were more common than in the placebo group.

1269 These adverse reactions were mostly mild to moderate in severity.

1270 Other adverse events that occurred in the groups receiving ADVAIR DISKUS 250/50 with an
1271 incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1272 **Cardiovascular:** Syncope.

1273 **Drug Interaction, Overdose, and Trauma:** Postoperative complications.

1274 **Ear, Nose, and Throat:** Ear, nose, and throat infections; ear signs and symptoms;
1275 laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection.

1276 **Endocrine and Metabolic:** Hypothyroidism.

1277 **Eye:** Dry eyes, eye infections.

1278 **Gastrointestinal:** Constipation, gastrointestinal signs and symptoms, oral lesions.

1279 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1280 **Lower Respiratory:** Breathing disorders, lower respiratory signs and symptoms.
1281 **Non-Site Specific:** Bacterial infections, candidiasis unspecified site, edema and swelling,
1282 nonspecific conditions, viral infections.
1283 **Psychiatry:** Situational disorders.
1284 **Observed During Clinical Practice:** In addition to adverse events reported from clinical
1285 trials, the following events have been identified during worldwide use of any formulation of
1286 ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are
1287 reported voluntarily from a population of unknown size, estimates of frequency cannot be made.
1288 These events have been chosen for inclusion due to either their seriousness, frequency of
1289 reporting, or causal connection to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol
1290 or a combination of these factors.
1291 In extensive US and worldwide postmarketing experience with salmeterol, a component of
1292 ADVAIR DISKUS, serious exacerbations of asthma, including some that have been fatal, have
1293 been reported. In most cases, these have occurred in patients with severe asthma and/or in some
1294 patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also
1295 occurred in a few patients with less severe asthma. It was not possible from these reports to
1296 determine whether salmeterol contributed to these events.
1297 **Cardiovascular:** Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular
1298 tachycardia), ventricular tachycardia.
1299 **Ear, Nose, and Throat:** Aphonia, earache, facial and oropharyngeal edema, paranasal sinus
1300 pain, throat soreness.
1301 **Endocrine and Metabolic:** Cushing syndrome, Cushingoid features, growth velocity
1302 reduction in children/adolescents, hypercorticism, hyperglycemia, weight gain, osteoporosis.
1303 **Eye:** Cataracts, glaucoma.
1304 **Gastrointestinal:** Abdominal pain, dyspepsia, xerostomia.
1305 **Musculoskeletal:** Back pain, cramps, muscle spasm, myositis.
1306 **Neurology:** Paresthesia, restlessness.
1307 **Non-Site Specific:** Immediate and delayed hypersensitivity reaction (including very rare
1308 anaphylactic reaction), pallor. Very rare anaphylactic reaction in patients with severe milk
1309 protein allergy.
1310 **Psychiatry:** Agitation, aggression, depression.
1311 **Respiratory:** Chest congestion; chest tightness; dyspnea; immediate bronchospasm;
1312 influenza; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory
1313 symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.
1314 **Skin:** Contact dermatitis, contusions, ecchymoses, photodermatitis.
1315 **Urogenital:** Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal
1316 candidiasis, vaginitis, vulvovaginitis.
1317 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a
1318 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some
1319 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a

1320 condition that is often treated with systemic corticosteroid therapy. These events usually, but not
1321 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy
1322 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions
1323 have also been reported with other inhaled corticosteroids in this clinical setting. While
1324 ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid
1325 therapy, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary
1326 symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal
1327 relationship between fluticasone propionate and these underlying conditions has not been
1328 established (see PRECAUTIONS: General: *Eosinophilic Conditions*).

1329 **OVERDOSAGE**

1330 **ADVAIR DISKUS:** No deaths occurred in rats given an inhaled single-dose combination of
1331 salmeterol 3.6 mg/kg (approximately 290 and 140 times, respectively, the maximum
1332 recommended daily inhalation dose in adults and children on a mg/m² basis) and 1.9 mg/kg of
1333 fluticasone propionate (approximately 15 and 35 times, respectively, the maximum
1334 recommended daily inhalation dose in adults and children on a mg/m² basis).

1335 **Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in
1336 signs/symptoms of hypercorticism (see PRECAUTIONS: General: *Metabolic and Other*
1337 *Effects*). Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate
1338 inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate inhalation
1339 aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of
1340 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated.
1341 Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to
1342 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or
1343 moderate severity, and incidences were similar in active and placebo treatment groups. In mice,
1344 the oral median lethal dose was >1,000 mg/kg (>4,100 and >9,600 times, respectively, the
1345 maximum recommended daily inhalation dose in adults and children on a mg/m² basis). In rats
1346 the subcutaneous median lethal dose was >1,000 mg/kg (>8,100 and >19,200 times,
1347 respectively, the maximum recommended daily inhalation dose in adults and children on a
1348 mg/m² basis).

1349 **Salmeterol:** The expected signs and symptoms with overdosage of salmeterol are those of
1350 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and
1351 symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or
1352 hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache,
1353 tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and
1354 insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the
1355 pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia
1356 and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead
1357 to clinically significant prolongation of the QTc interval, which can produce ventricular
1358 arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

1359 As with all sympathomimetic medications, cardiac arrest and even death may be associated
1360 with abuse of salmeterol.

1361 Treatment consists of discontinuation of salmeterol together with appropriate symptomatic
1362 therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing
1363 in mind that such medication can produce bronchospasm. There is insufficient evidence to
1364 determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is
1365 recommended in cases of overdosage.

1366 No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg
1367 (approximately 240 and 110 times, respectively, the maximum recommended daily inhalation
1368 dose in adults and children on a mg/m² basis) and in dogs at an inhalation dose of 0.7 mg/kg
1369 (approximately 190 and 90 times, respectively, the maximum recommended daily inhalation
1370 dose in adults and children on a mg/m² basis). By the oral route, no deaths occurred in mice at
1371 150 mg/kg (approximately 6,100 and 2,900 times, respectively, the maximum recommended
1372 daily inhalation dose in adults and children on a mg/m² basis) and in rats at 1,000 mg/kg
1373 (approximately 81,000 and 38,000 times, respectively, the maximum recommended daily
1374 inhalation dose in adults and children on a mg/m² basis).

1375 **DOSAGE AND ADMINISTRATION**

1376 ADVAIR DISKUS should be administered by the orally inhaled route only (see Instructions
1377 for Using ADVAIR DISKUS in the Medication Guide accompanying the product). After
1378 inhalation, the patient should rinse the mouth with water without swallowing. ADVAIR DISKUS
1379 should not be used for transferring patients from systemic corticosteroid therapy.

1380 **Asthma:** Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active
1381 ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death (see
1382 WARNINGS). Therefore, when treating patients with asthma, physicians should only prescribe
1383 ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications
1384 (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants
1385 initiation of treatment with 2 maintenance therapies. ADVAIR DISKUS is not indicated in
1386 patients whose asthma can be successfully managed by inhaled corticosteroids along with
1387 occasional use of inhaled, short-acting beta₂-agonists.

1388 ADVAIR DISKUS is available in 3 strengths, ADVAIR DISKUS 100/50, ADVAIR DISKUS
1389 250/50, and ADVAIR DISKUS 500/50, containing 100, 250, and 500 mcg of fluticasone
1390 propionate, respectively, and 50 mcg of salmeterol per inhalation.

1391 ADVAIR DISKUS should be administered twice daily every day. More frequent
1392 administration (more than twice daily) or a higher number of inhalations (more than 1 inhalation
1393 twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some
1394 patients are more likely to experience adverse effects with higher doses of salmeterol. The safety
1395 and efficacy of ADVAIR DISKUS when administered in excess of recommended doses have not
1396 been established.

1397 If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should
1398 be taken for immediate relief.

1399 Patients who are receiving ADVAIR DISKUS twice daily should not use additional
1400 salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for prevention of EIB,
1401 or for any other reason.

1402 ***Adult and Adolescent Patients 12 Years of Age and Older:*** For patients 12 years of
1403 age and older, the dosage is 1 inhalation twice daily (morning and evening, approximately
1404 12 hours apart).

1405 The recommended starting dosages for ADVAIR DISKUS for patients 12 years of age and
1406 older are based upon patients' current asthma therapy.

- 1407 • For patients not adequately controlled on an inhaled corticosteroid, Table 7 provides the
1408 recommended starting dosage.
- 1409 • For patients not currently on inhaled corticosteroids whose disease severity clearly warrants
1410 initiation of treatment with 2 maintenance therapies, the recommended starting dosage is
1411 ADVAIR DISKUS 100/50 or 250/50 twice daily (see INDICATIONS AND USAGE).

1412 The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

1413 **For all patients it is desirable to titrate to the lowest effective strength after adequate**
1414 **asthma stability is achieved.**

1415

1416 **Table 7. Recommended Dosages of ADVAIR DISKUS for Patients With Asthma Aged**
 1417 **12 Years and Older Not Adequately Controlled on Inhaled Corticosteroids**

Current Daily Dose of Inhaled Corticosteroid		Recommended Strength and Dosing Schedule of ADVAIR DISKUS
Beclomethasone dipropionate HFA inhalation aerosol	≤160 mcg	100/50 twice daily
	320 mcg	250/50 twice daily
	640 mcg	500/50 twice daily
Budesonide inhalation aerosol	≤400 mcg	100/50 twice daily
	800-1,200 mcg	250/50 twice daily
	1,600 mcg*	500/50 twice daily
Flunisolide inhalation aerosol	≤1,000 mcg	100/50 twice daily
	1,250-2,000 mcg	250/50 twice daily
Flunisolide HFA inhalation aerosol	≤320 mcg	100/50 twice daily
	640 mcg	250/50 twice daily
Fluticasone propionate HFA 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
Mometasone furoate inhalation powder	220 mcg	100/50 twice daily
	440 mcg	250/50 twice daily
	880 mcg	500/50 twice daily
Triamcinolone acetonide inhalation aerosol	≤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.

1418
 1419
 1420
 1421 Improvement in asthma control following inhaled administration of ADVAIR DISKUS can
 1422 occur within 30 minutes of beginning treatment, although maximum benefit may not be
 1423 achieved for 1 week or longer after starting treatment. Individual patients will experience a
 1424 variable time to onset and degree of symptom relief.

1425 For patients who do not respond adequately to the starting dosage after 2 weeks of therapy,
 1426 replacing the current strength of ADVAIR DISKUS with a higher strength may provide
 1427 additional improvement in asthma control.

1428 If a previously effective dosage regimen of ADVAIR DISKUS fails to provide adequate
 1429 improvement in asthma control, the therapeutic regimen should be reevaluated and additional
 1430 therapeutic options, e.g., replacing the current strength of ADVAIR DISKUS with a higher

1431 strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be
1432 considered.

1433 **Pediatric Patients:** For patients aged 4 to 11 years who are symptomatic on an inhaled
1434 corticosteroid the dosage is 1 inhalation of ADVAIR DISKUS 100/50 twice daily (morning and
1435 evening, approximately 12 hours apart).

1436 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The
1437 dosage for adults is 1 inhalation (250/50 mcg) twice daily (morning and evening, approximately
1438 12 hours apart).

1439 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of
1440 COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50,
1441 are not recommended, as no additional improvement in lung function was observed in clinical
1442 trials and higher doses of corticosteroids increase the risk of systemic effects.

1443 If shortness of breath occurs in the period between doses, an inhaled, short-acting
1444 beta₂-agonist should be taken for immediate relief.

1445 Patients who are receiving ADVAIR DISKUS twice daily should not use additional
1446 salmeterol or other inhaled, long-acting beta₂-agonists (e.g., formoterol) for the maintenance
1447 treatment of COPD or for any other reason.

1448 **Geriatric Use:** In studies where geriatric patients (65 years of age or older, see
1449 PRECAUTIONS: Geriatric Use) have been treated with ADVAIR DISKUS, efficacy and safety
1450 did not differ from that in younger patients. Based on available data for ADVAIR DISKUS and
1451 its active components, no dosage adjustment is recommended.

1452 **Directions for Use:** Illustrated Patient's Instructions for Use accompany each package of
1453 ADVAIR DISKUS.

1454 **HOW SUPPLIED**

1455 ADVAIR DISKUS 100/50 is supplied as a disposable, purple device containing 60 blisters.
1456 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective
1457 foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional
1458 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS
1459 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch
1460 (NDC 0173-0695-02).

1461 ADVAIR DISKUS 250/50 is supplied as a disposable, purple device containing 60 blisters.
1462 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective
1463 foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional
1464 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS
1465 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch
1466 (NDC 0173-0696-02).

1467 ADVAIR DISKUS 500/50 is supplied as a disposable, purple device containing 60 blisters.
1468 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective
1469 foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional

1470 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS
1471 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch
1472 (NDC 0173-0697-02).

1473 **Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F), in a dry place**
1474 **away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation**
1475 **device is not reusable. The device should be discarded 1 month after removal from the**
1476 **moisture-protective foil overwrap pouch or after all blisters have been used (when the dose**
1477 **indicator reads “0”), whichever comes first. Do not attempt to take the device apart.**

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1482 Research Triangle Park, NC 27709

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MEDICATION GUIDE

ADVAIR [*ad'vair*] DISKUS[®]

(fluticasone propionate and salmeterol inhalation powder)

1492

1493 **ADVAIR DISKUS**

1494 (fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

1495

1496 **ADVAIR DISKUS**

1497 (fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder)

1498

1499 **ADVAIR DISKUS**

1500 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder)

1501

1502 Read the Medication Guide that comes with ADVAIR DISKUS before you start using it and
1503 each time you get a refill. There may be new information. This Medication Guide does not take
1504 the place of talking to your healthcare provider about your medical condition or treatment.

1505

1506 **What is the most important information I should know about ADVAIR DISKUS?**

- 1507
 - **ADVAIR DISKUS contains 2 medicines:**

- 1508
- **fluticasone propionate (the same medicine found in FLOVENT)**, an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
- 1509
- 1510
- 1511
- **salmeterol (the same medicine found in SEREVENT)**, a long-acting beta₂-agonist medicine or LABA. LABA medicines are used in patients with asthma and chronic obstructive pulmonary disease (COPD). LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.
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- **In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in ADVAIR DISKUS), may increase the chance of death from asthma problems.** In a large asthma study, more patients who used salmeterol died from asthma problems compared with patients who did not use salmeterol. It is not known whether fluticasone propionate, the other medicine in ADVAIR DISKUS, changes your chance of death from asthma problems seen with salmeterol. Talk with your healthcare provider about this risk and the benefits of treating your asthma with ADVAIR DISKUS.
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- 1527
- **ADVAIR DISKUS does not relieve sudden symptoms. Always have a short-acting beta₂-agonist medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.**
- 1528
- 1529
- 1530
- 1531
- 1532
- **Do not stop using ADVAIR DISKUS unless told to do so by your healthcare provider because your symptoms might get worse.**
- 1533
- 1534
- 1535
- **ADVAIR DISKUS** should be used only if your healthcare provider decides that another asthma-controller medicine alone does not control your asthma or that you need 2 asthma-controller medicines.
- 1536
- 1537
- 1538
- 1539
- **Call your healthcare provider if breathing problems worsen over time while using ADVAIR DISKUS. You may need different treatment.**
- 1540
- 1541
- 1542
- **Get emergency medical care if:**
 - **breathing problems worsen quickly, and**
 - **you use your short-acting beta₂-agonist medicine, but it does not relieve your breathing problems.**
- 1543
- 1544
- 1545
- 1546
- 1547

1548 **What is ADVAIR DISKUS?**

1549 ADVAIR DISKUS combines an inhaled corticosteroid medicine, fluticasone propionate (the
1550 same medicine found in FLOVENT) and a long-acting beta₂-agonist medicine, salmeterol (the
1551 same medicine found in SEREVENT). ADVAIR DISKUS is used for asthma and chronic
1552 obstructive pulmonary disease (COPD) as follows:

1553

1554 **Asthma**

1555 ADVAIR DISKUS is used long term, twice a day to control symptoms of asthma, and prevent
1556 symptoms such as wheezing in adults and children ages 4 and older.

1557

1558 **ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). Because**
1559 **LABA medicines such as salmeterol may increase the chance of death from asthma**
1560 **problems, ADVAIR DISKUS is not for adults and children with asthma who:**

- 1561 • are well controlled with another asthma-controller medicine such as a low to medium
1562 dose of an inhaled corticosteroid medicine
- 1563 • only need short-acting beta₂-agonist medicines once in awhile

1564

1565 **Chronic Obstructive Pulmonary Disease (COPD)**

1566 ADVAIR DISKUS is used long term, twice a day in controlling symptoms of COPD and
1567 preventing wheezing in adults with COPD.

1568

1569 **What should I tell my healthcare provider before using ADVAIR DISKUS?**

1570 **Tell your healthcare provider about all of your health conditions, including if you:**

- 1571 • **have heart problems**
- 1572 • **have high blood pressure**
- 1573 • **have seizures**
- 1574 • **have thyroid problems**
- 1575 • **have diabetes**
- 1576 • **have liver problems**
- 1577 • **have osteoporosis**
- 1578 • **have an immune system problem**
- 1579 • **are pregnant or planning to become pregnant.** It is not known if ADVAIR DISKUS may
1580 harm your unborn baby.
- 1581 • **are breastfeeding.** It is not known if ADVAIR DISKUS passes into your milk and if it can
1582 harm your baby.
- 1583 • **are allergic to ADVAIR DISKUS, any other medicines, or food products**
- 1584 • **are exposed to chickenpox or measles**

1585

1586 Tell your healthcare provider about all the medicines you take including prescription and non-
1587 prescription medicines, vitamins, and herbal supplements. ADVAIR DISKUS and certain other

1588 medicines may interact with each other. This may cause serious side effects. Especially, tell your
1589 healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR[®] (ritonavir capsules)
1590 Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA[®] (lopinavir/ritonavir) Tablets
1591 contain ritonavir.

1592
1593 Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist
1594 each time you get a new medicine.

1595

1596 **How do I use ADVAIR DISKUS?**

1597 **See the step-by-step instructions for using the ADVAIR DISKUS at the end of this**

1598 **Medication Guide.** Do not use the ADVAIR DISKUS unless your healthcare provider has
1599 taught you and you understand everything. Ask your healthcare provider or pharmacist if you
1600 have any questions.

1601

1602 • Children should use ADVAIR DISKUS with an adult's help, as instructed by the child's
1603 healthcare provider.

1604

1605 • Use ADVAIR DISKUS exactly as prescribed. **Do not use ADVAIR DISKUS more often**
1606 **than prescribed.** ADVAIR DISKUS comes in 3 strengths. Your healthcare provider will
1607 prescribe the one that is best for your condition.

1608

1609 • The usual dose of ADVAIR DISKUS is 1 inhalation twice a day (morning and evening). The
1610 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR
1611 DISKUS.

1612

1613 • If you miss a dose of ADVAIR DISKUS, just skip that dose. Take your next dose at your
1614 usual time. Do not take 2 doses at one time.

1615

1616 • Do not use a spacer device with ADVAIR DISKUS.

1617

1618 • Do not breathe into ADVAIR DISKUS.

1619

1620 • **While you are using ADVAIR DISKUS twice a day, you should not use other medicines**
1621 **that contain a long-acting beta₂-agonist or LABA for any reason. Other LABA**
1622 **medicines include SEREVENT[®] DISKUS[®] (salmeterol xinafoate inhalation powder) or**
1623 **FORADIL[®] AEROLIZER[™] (formoterol fumarate inhalation powder).**

1624

1625 • Do not change or stop any of your medicines used to control or treat your breathing
1626 problems. Your healthcare provider will adjust your medicines as needed.

1627

- 1628 • Make sure you always have a short-acting beta₂-agonist medicine with you. Use your
1629 short-acting beta₂-agonist medicine if you have breathing problems between doses of
1630 ADVAIR DISKUS.
1631
- 1632 • **Call your healthcare provider or get medical care right away if:**
1633 • your breathing problems worsen with ADVAIR DISKUS
1634 • you need to use your short-acting beta₂-agonist medicine more often than usual
1635 • your short-acting beta₂-agonist medicine does not work as well for you at relieving
1636 symptoms
1637 • you need to use 4 or more inhalations of your short-acting beta₂-agonist medicine for 2 or
1638 more days in a row
1639 • you use 1 whole canister of your short-acting beta₂-agonist medicine in 8 weeks' time
1640 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers
1641 that are right for you.
1642 • you have asthma and your symptoms do not improve after using ADVAIR DISKUS
1643 regularly for 1 week
1644

1645 **What are the possible side effects with ADVAIR DISKUS?**

- 1646 • **ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). In**
1647 **patients with asthma, LABA medicines such as salmeterol may increase the chance of**
1648 **death from asthma problems.** See “What is the most important information I should know
1649 about ADVAIR DISKUS?”
1650

1651 **Other possible side effects with ADVAIR DISKUS include:**

- 1652 • **serious allergic reactions including rash, hives, swelling of the face, mouth, and tongue,**
1653 **and breathing problems.** Call your healthcare provider or get emergency medical care if
1654 you get any symptoms of a serious allergic reaction.
1655 • **increased blood pressure**
1656 • **a fast and irregular heartbeat**
1657 • **chest pain**
1658 • **headache**
1659 • **tremor**
1660 • **nervousness**
1661 • **immune system effects and a higher chance for infections**
1662 • **lower bone mineral density.** This may be a problem for people who already have a higher
1663 chance for low bone density (osteoporosis).
1664 • **eye problems including glaucoma and cataracts.** You should have regular eye exams
1665 while using ADVAIR DISKUS.
1666 • **slowed growth in children.** A child's growth should be checked often.
1667 • **throat irritation**

1668
1669 Tell your healthcare provider about any side effect that bothers you or that does not go away.

1670
1671 These are not all the side effects with ADVAIR DISKUS. Ask your healthcare provider or
1672 pharmacist for more information.

1673
1674 **How do I store ADVAIR DISKUS?**

- 1675 • Store ADVAIR DISKUS at room temperature between 68° to 77° F (20° to 25° C). Keep in a
1676 dry place away from heat and sunlight.
- 1677 • Safely discard ADVAIR DISKUS 1 month after you remove it from the foil pouch, or after
1678 the dose indicator reads “0”, whichever comes first.
- 1679 • **Keep ADVAIR DISKUS and all medicines out of the reach of children.**

1680
1681 **General Information about ADVAIR DISKUS**

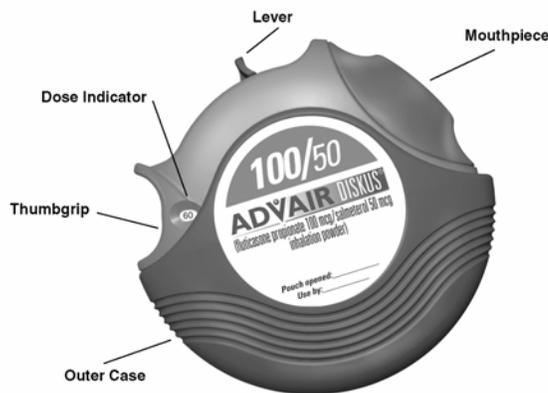
1682 Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not
1683 use ADVAIR DISKUS for a condition for which it was not prescribed. Do not give your
1684 ADVAIR DISKUS to other people, even if they have the same condition. It may harm them.

1685 This Medication Guide summarizes the most important information about ADVAIR DISKUS. If
1686 you would like more information, talk with your healthcare provider or pharmacist. You can ask
1687 your healthcare provider or pharmacist for information about ADVAIR DISKUS that was
1688 written for healthcare professionals. You can also contact the company that makes ADVAIR
1689 DISKUS (toll free) at 1-888-825-5249 or at www.advail.com.

1690
1691 **Instructions for Using ADVAIR DISKUS**

1692 Follow the instructions below for using your ADVAIR DISKUS. **You will breathe-in (inhale)**
1693 **the medicine from the DISKUS.** If you have any questions, ask your healthcare provider or
1694 pharmacist.

1695



1696

1697

1698

How to Use Your ADVAIR DISKUS

1699

Take the ADVAIR DISKUS out of the box and foil overwrap pouch. Write the **“Pouch opened”** and **“Use by”** dates on the label on top of the DISKUS. **The “Use by” date is 1 month from date of opening the pouch.**

1701

1702

- The DISKUS will be in the closed position when the pouch is opened.

1703

- The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose indicator number will decrease each time you use the DISKUS. After you have used 55 doses from the DISKUS, the numbers 5 to 0 will appear in **red** to warn you that there are only a few doses left (*see Figure 1*). If you are using a “sample” DISKUS, the numbers 5 to 0 will appear in red after 23 doses.

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Figure 1

1710

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

1711

1. **OPEN**

1712

Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**.

1713

Push your thumb away from you as far as it will go until the mouthpiece appears and

1714

snaps into position (*see Figure 2*).



Figure 2

1715
1716

1717 2. **CLICK**

1718 Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the
1719 **lever** away from you as far as it will go until it **clicks** (*see Figure 3*). The DISKUS is
1720 now ready to use.



Figure 3

1721
1722

1723 Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a
1724 decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the**
1725 **DISKUS is ready:**

- 1726
- Do not close the DISKUS.

- 1727
- 1728
- 1729
- 1730
- Do not tilt the DISKUS.
 - Do not play with the lever.
 - Do not move the lever more than once.

1731 3. **INHALE**

1732 Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding
1733 the DISKUS level and away from your mouth (*see Figure 4*). **Remember, never**
1734 **breathe out into the DISKUS mouthpiece.**



1735

1736

Figure 4

1737 Put the mouthpiece to your lips (*see Figure 5*). Breathe in quickly and deeply through the
1738 DISKUS. Do not breathe in through your nose.



Figure 5

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

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

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1747

Rinse your mouth with water after breathing-in the medicine. Spit the water out. Do not swallow.

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



Figure 6

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1755

Remember:

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- Never breathe into the DISKUS.
- Never take the DISKUS apart.
- Always ready and use the DISKUS in a level, flat position.
- Do not use the DISKUS with a spacer device.
- After each dose, rinse your mouth with water and spit the water out. Do not swallow.
- Never wash the mouthpiece or any part of the DISKUS. **Keep it dry.**
- Always keep the DISKUS in a dry place.
- Never take an extra dose, even if you did not taste or feel the medicine.

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Rx only



GlaxoSmithKline

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GlaxoSmithKline

Research Triangle Park, NC 27709

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1781 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**