

1 PRESCRIBING INFORMATION

2 **ADVAIR DISKUS<sup>®</sup> 100/50**

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

4  
5 **ADVAIR DISKUS<sup>®</sup> 250/50**

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

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8 **ADVAIR DISKUS<sup>®</sup> 500/50**

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

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

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13 **For Oral Inhalation Only**

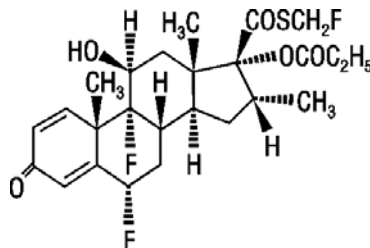
14 **WARNING**

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

25 **DESCRIPTION**

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

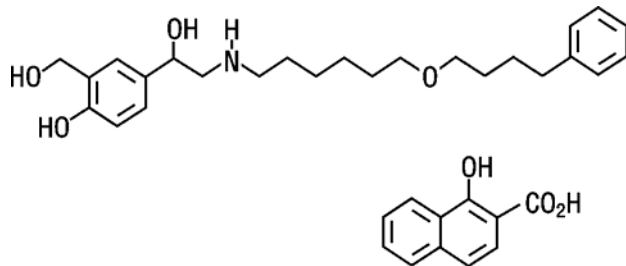
28 One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having  
29 the chemical name *S*-(fluoromethyl) 6 $\alpha$ ,9-difluoro-11 $\beta$ ,17-dihydroxy-16 $\alpha$ -methyl-3-  
30 oxoandrosta-1,4-diene-17 $\beta$ -carbothioate, 17-propionate and the following chemical structure:



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 beta<sub>2</sub>-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- $\alpha^1$ -[[[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 [FEV<sub>1</sub>] 20% to 30% of predicted), mean peak inspiratory  
62 flow (PIF) through a DISKUS<sup>®</sup> 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 beta<sub>2</sub>-adrenergic agonist. In vitro studies  
96 and in vivo pharmacologic studies demonstrate that salmeterol is selective for  
97 beta<sub>2</sub>-adrenoceptors compared with isoproterenol, which has approximately equal agonist  
98 activity on beta<sub>1</sub>- and beta<sub>2</sub>-adrenoceptors. In vitro studies show salmeterol to be at least 50 times  
99 more selective for beta<sub>2</sub>-adrenoceptors than albuterol. Although beta<sub>2</sub>-adrenoceptors are the  
100 predominant adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-adrenoceptors are the  
101 predominant receptors in the heart, there are also beta<sub>2</sub>-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 beta<sub>2</sub>-agonists  
104 may have cardiac effects.

105 The pharmacologic effects of beta<sub>2</sub>-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 D<sub>2</sub>, 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:** Following administration of ADVAIR DISKUS to  
117 healthy adult subjects, peak plasma concentrations of fluticasone propionate were achieved in 1  
118 to 2 hours and those of salmeterol were achieved in about 5 minutes.

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

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

131 **Special Populations: Population Pharmacokinetics:** A population  
132 pharmacokinetic analysis was performed for fluticasone propionate and salmeterol utilizing data  
133 from 9 controlled clinical trials that included 350 patients with asthma aged 4 to 77 years who  
134 received treatment with ADVAIR DISKUS, the combination of HFA-propelled fluticasone  
135 propionate and salmeterol inhalation aerosol ([ADVAIR<sup>®</sup> HFA](#)), fluticasone propionate inhalation  
136 powder ([FLOVENT<sup>®</sup> DISKUS<sup>®</sup>](#)), HFA-propelled fluticasone propionate inhalation aerosol  
137 ([FLOVENT<sup>®</sup> HFA](#)), or CFC-propelled fluticasone propionate inhalation aerosol. The population  
138 pharmacokinetic analyses for fluticasone propionate and salmeterol showed no clinically relevant  
139 effects of age, gender, race, body weight, body mass index, or percent of predicted FEV<sub>1</sub> on  
140 apparent clearance and apparent volume of distribution.

141 When the population pharmacokinetic analysis for fluticasone propionate was divided into  
142 subgroups based on fluticasone propionate strength, formulation, and age (adolescents/adults and  
143 children), there were some differences in fluticasone propionate exposure. Higher fluticasone  
144 propionate exposure from ADVAIR DISKUS 100/50 compared with FLOVENT DISKUS  
145 100 mcg was observed in adolescents and adults (ratio 1.52 [90% CI 1.08, 2.13]); [However, in  
146 clinical studies of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and  
147 FLOVENT DISKUS 100 mcg in adolescents and adults, no differences in systemic effects of](#)

148 corticosteroid treatment (e.g., HPA axis effects) were observed while similar fluticasone  
149 propionate exposure was observed from ADVAIR DISKUS 500/50 and FLOVENT DISKUS  
150 500 mcg (ratio 0.83 [90% CI 0.65, 1.07]) in adolescents and adults.

151 Steady-state systemic exposure to salmeterol when delivered as ADVAIR DISKUS 100/50,  
152 ADVAIR DISKUS 250/50, or ~~ADVAIR HFA 115/21~~ the combination of HFA-propelled  
153 fluticasone propionate and salmeterol inhalation aerosol 110/21 was evaluated in 127 patients  
154 aged 4 to 57 years. The geometric mean AUC was 325 pg•hr/mL [90% CI 309, 341] in  
155 adolescents and adults.

156 **Gender:** The population pharmacokinetic analysis involved 202 males and 148 females  
157 with asthma who received fluticasone propionate alone or in combination with salmeterol and  
158 showed no gender differences for fluticasone propionate pharmacokinetics.

159 The population pharmacokinetic analysis involved 76 males and 51 females with asthma who  
160 received salmeterol in combination with fluticasone propionate and showed no gender  
161 differences for salmeterol pharmacokinetics.

162 **Pediatric Patients:** The population pharmacokinetic analysis included 160 patients  
163 with asthma aged 4 to 11 years who received ADVAIR DISKUS 100/5050 ~~or~~ and FLOVENT  
164 DISKUS 100 mcg. Higher fluticasone propionate exposure (AUC) was observed in children  
165 from ADVAIR DISKUS 100/50 compared to FLOVENT DISKUS 100 mcg (ratio 1.20 [90% CI  
166 1.06, 1.37]). Higher fluticasone propionate exposure (AUC) from ADVAIR DISKUS 100/50  
167 was observed in children compared to adolescents and adults (ratio 1.63 [90% CI 1.35, 1.96]).  
168 However, in clinical studies of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50  
169 and FLOVENT DISKUS 100 mcg in both adolescents and adults and in children, no differences  
170 in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed.

171 Exposure to salmeterol was higher in children compared to adolescents and adults who  
172 received ADVAIR DISKUS 100/50 (ratio 1.23 [90% CI 1.10, 1.38]). However, in clinical  
173 studies of up to 12 weeks' duration with ADVAIR DISKUS 100/50 in both adolescents and  
174 adults and in children, no differences in systemic effects of beta<sub>2</sub>-agonist treatment (e.g.,  
175 cardiovascular effects, tremor) were observed.

176 **Hepatic and Renal Impairment:** Formal pharmacokinetic studies using ADVAIR  
177 DISKUS have not been conducted in patients with hepatic or renal impairment. However, since  
178 both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism,  
179 impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol  
180 in plasma. Therefore, patients with hepatic disease should be closely monitored.

181 **Drug Interactions:** In the repeat- and single-dose studies, there was no evidence of  
182 significant drug interaction in systemic exposure between fluticasone propionate and salmeterol  
183 when given as ADVAIR DISKUS. The population pharmacokinetic analysis from 9 controlled  
184 clinical trials in 350 patients with asthma showed no significant effects on fluticasone propionate  
185 or salmeterol pharmacokinetics following co-administration with beta<sub>2</sub>-agonists, corticosteroids,  
186 antihistamines, or theophyllines.

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

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

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

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

204 The percentage of fluticasone propionate bound to human plasma proteins averages 91%.  
205 Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly  
206 bound to human transcortin.

207 **Metabolism:** The total clearance of fluticasone propionate is high (average,  
208 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only  
209 circulating metabolite detected in man is the 17 $\beta$ -carboxylic acid derivative of fluticasone  
210 propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had  
211 less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of  
212 human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other  
213 metabolites detected in vitro using cultured human hepatoma cells have not been detected in  
214 man.

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

219 **Special Populations: Gender:** Full pharmacokinetic profiles were obtained from  
220 9 female and 16 male patients with asthma given fluticasone propionate inhalation powder  
221 500 mcg twice daily using the DISKUS device and from 14 female and 43 male patients with  
222 COPD given 250 or 500 mcg twice daily. No overall differences in fluticasone propionate  
223 pharmacokinetics were observed.

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

226 **Drug Interactions:** Fluticasone propionate is a substrate of cytochrome P450 3A4.  
227 Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor  
228 ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18  
229 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was  
230 coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate  
231 concentrations following fluticasone propionate aqueous nasal spray alone were undetectable  
232 (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels ( $C_{max}$ )  
233 averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and  $AUC_{(0-\tau)}$  averaged 8.43 pg•hr/mL (range,  
234 4.2 to 18.8 pg•hr/mL). Fluticasone propionate  $C_{max}$  and  $AUC_{(0-\tau)}$  increased to 318 pg/mL (range,  
235 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively,  
236 after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This  
237 significant increase in plasma fluticasone propionate exposure resulted in a significant decrease  
238 (86%) in serum cortisol AUC.

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

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

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

251 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low  
252 or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder  
253 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol  
254 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7  
255 patients with asthma; plasma concentrations were very low, with mean peak concentrations of  
256 167 pg/mL at 20 minutes and no accumulation with repeated doses.

257 **Distribution:** The percentage of salmeterol bound to human plasma proteins averages  
258 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much  
259 higher concentrations than those achieved following therapeutic doses of salmeterol.

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

263 **Elimination:** In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as  
264 salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was

265 eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination  
266 half-life was about 5.5 hours (1 volunteer only).

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

269 **Pharmacodynamics: ADVAIR DISKUS: Adult and Adolescent Patients:** Since  
270 systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose,  
271 higher doses were used to produce measurable effects. Four (4) studies were conducted in  
272 healthy adult subjects: (1) a single-dose crossover study using 2 inhalations of ADVAIR  
273 DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given  
274 concurrently, or fluticasone propionate powder 500 mcg given alone, (2) a cumulative dose study  
275 using 50 to 400 mcg of salmeterol powder given alone or as ADVAIR DISKUS 500/50, (3) a  
276 repeat-dose study for 11 days using 2 inhalations twice daily of ADVAIR DISKUS 250/50,  
277 fluticasone propionate powder 250 mcg, or salmeterol powder 50 mcg, and (4) a single-dose  
278 study using 5 inhalations of ADVAIR DISKUS 100/50, fluticasone propionate powder 100 mcg  
279 alone, or placebo. In these studies no significant differences were observed in the  
280 pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and  
281 glucose) whether the salmeterol was given as ADVAIR DISKUS, concurrently with fluticasone  
282 propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic  
283 effects of salmeterol were not altered by the presence of fluticasone propionate in ADVAIR  
284 DISKUS. The potential effect of salmeterol on the effects of fluticasone propionate on the  
285 hypothalamic-pituitary-adrenal (HPA) axis was also evaluated in these studies. No significant  
286 differences across treatments were observed in 24-hour urinary cortisol excretion and, where  
287 measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone  
288 propionate were not altered by the presence of salmeterol in ADVAIR DISKUS in healthy  
289 subjects.

290 **Asthma:** In clinical studies with ADVAIR DISKUS in adult and adolescent patients 12  
291 years of age and older with asthma, no significant differences were observed in the systemic  
292 pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and  
293 glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adolescent and  
294 adult patients with asthma given either ADVAIR DISKUS 100/50 or ADVAIR DISKUS  
295 250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose  
296 and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

297 In a 28-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 500/50  
298 twice daily was compared with the concurrent use of salmeterol powder 50 mcg plus fluticasone  
299 propionate powder 500 mcg from separate inhalers or fluticasone propionate powder 500 mcg  
300 alone. No significant differences across treatments were observed in plasma cortisol AUC after  
301 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

302 In a 12-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 250/50  
303 twice daily was compared with fluticasone propionate powder 250 mcg alone, salmeterol powder  
304 50 mcg alone, and placebo. For most patients, the ability to increase cortisol production in



305 response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with  
306 ADVAIR DISKUS. One patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal  
307 response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who  
308 received placebo, 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients  
309 who received salmeterol.

310 In a repeat-dose, 3-way crossover study, 1 inhalation twice daily of ADVAIR DISKUS  
311 100/50, FLOVENT DISKUS 100 mcg, or placebo was administered to 20 adolescent and adult  
312 patients with asthma. After 28 days of treatment, geometric mean serum cortisol AUC over  
313 12 hours showed no significant difference between ADVAIR DISKUS and FLOVENT DISKUS  
314 or between either active treatment and placebo.

315 **Chronic Obstructive Pulmonary Disease:** In clinical studies with ADVAIR  
316 DISKUS in patients with COPD associated with chronic bronchitis, no significant differences  
317 were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR DISKUS, the  
318 individual components of ADVAIR DISKUS, and placebo. In a study of ADVAIR DISKUS  
319 250/50, 8 patients (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in the  
320 fluticasone propionate 250 mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the  
321 placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5)  
322 of these 8 patients had a prolonged QTc interval at baseline.

323 In a 24-week study, 130 patients with COPD associated with chronic bronchitis received  
324 continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of  
325 twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate powder  
326 500 mcg, salmeterol powder 50 mcg, or placebo. No significant differences in ventricular or  
327 supraventricular arrhythmias and heart rate were observed among the groups treated with  
328 ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the  
329 fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the  
330 group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of  
331 nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone  
332 propionate 500 mcg treatment groups).

333 Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in  
334 101 patients with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate  
335 powder 250 mcg, salmeterol powder 50 mcg, or placebo. For most patients, the ability to  
336 increase cortisol production in response to stress, as assessed by short cosyntropin stimulation,  
337 remained intact with ADVAIR DISKUS 250/50. One (1) patient (3%) who received ADVAIR  
338 DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL  
339 assessed by high-performance liquid chromatography) after dosing, compared with 2 patients  
340 (9%) who received fluticasone propionate 250 mcg, 2 patients (7%) who received salmeterol  
341 50 mcg, and 1 patient (4%) who received placebo following 24 weeks of treatment or early  
342 discontinuation from study.

343 **Pediatric Patients:** In a 12-week study in patients with asthma aged 4 to 11 years who  
344 were receiving inhaled corticosteroids at study entry, ADVAIR DISKUS 100/50 twice daily was

345 compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via  
346 the DISKUS. The values for 24-hour urinary cortisol excretion at study entry and after 12 weeks  
347 of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol  
348 excretion was also similar between the 2 groups.

349 **Fluticasone Propionate: Asthma:** In clinical trials with fluticasone propionate inhalation  
350 powder using doses up to and including 250 mcg twice daily, occasional abnormal short  
351 cosyntropin tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted  
352 both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence  
353 of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out  
354 with the DISKHALER<sup>®</sup> inhalation device in 64 patients with mild, persistent asthma (mean  
355 FEV<sub>1</sub> 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo,  
356 no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin  
357 infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1  
358 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing  
359 at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had  
360 an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or  
361 2 years.

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

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

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

382 **Chronic Obstructive Pulmonary Disease:** In 24-week clinical studies in patients  
383 with COPD associated with chronic bronchitis, the incidence of clinically significant  
384 electrocardiogram (ECG) abnormalities (myocardial ischemia, ventricular hypertrophy, clinically

385 significant conduction abnormalities, clinically significant arrhythmias) was lower for patients  
386 who received salmeterol (1%, 9 of 688 patients who received either salmeterol 50 mcg or  
387 ADVAIR DISKUS) compared with placebo (3%, 10 of 370 patients).

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

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

## 399 **CLINICAL TRIALS**

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

406 **Studies Comparing ADVAIR DISKUS to Fluticasone Propionate Alone or**  
407 **Salmeterol Alone:** Three (3) double-blind, parallel-group clinical trials were conducted with  
408 ADVAIR DISKUS in 1,208 adolescent and adult patients ( $\geq 12$  years, baseline FEV<sub>1</sub> 63% to 72%  
409 of predicted normal) with asthma that was not optimally controlled on their current therapy. All  
410 treatments were inhalation powders, given as 1 inhalation from the DISKUS device twice daily,  
411 and other maintenance therapies were discontinued.

412 **Study 1: Clinical Trial With ADVAIR DISKUS 100/50:** This placebo-controlled,  
413 12-week, US study compared ADVAIR DISKUS 100/50 with its individual components,  
414 fluticasone propionate 100 mcg and salmeterol 50 mcg. The study was stratified according to  
415 baseline asthma maintenance therapy; patients were using either inhaled corticosteroids  
416 (N = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg;  
417 fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg)  
418 or salmeterol (N = 106). Baseline FEV<sub>1</sub> measurements were similar across treatments: ADVAIR  
419 DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and  
420 placebo, 2.15 L.

421 Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were  
422 utilized for this placebo-controlled study. Worsening asthma was defined as a clinically  
423 important decrease in FEV<sub>1</sub> or peak expiratory flow (PEF), increase in use of VENTOLIN<sup>®</sup>

424 (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency  
425 intervention or hospitalization due to asthma, or requirement for asthma medication not allowed  
426 by the protocol. As shown in Table 1, statistically significantly fewer patients receiving  
427 ADVAIR DISKUS 100/50 were withdrawn due to worsening asthma compared with fluticasone  
428 propionate, salmeterol, and placebo.

429

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

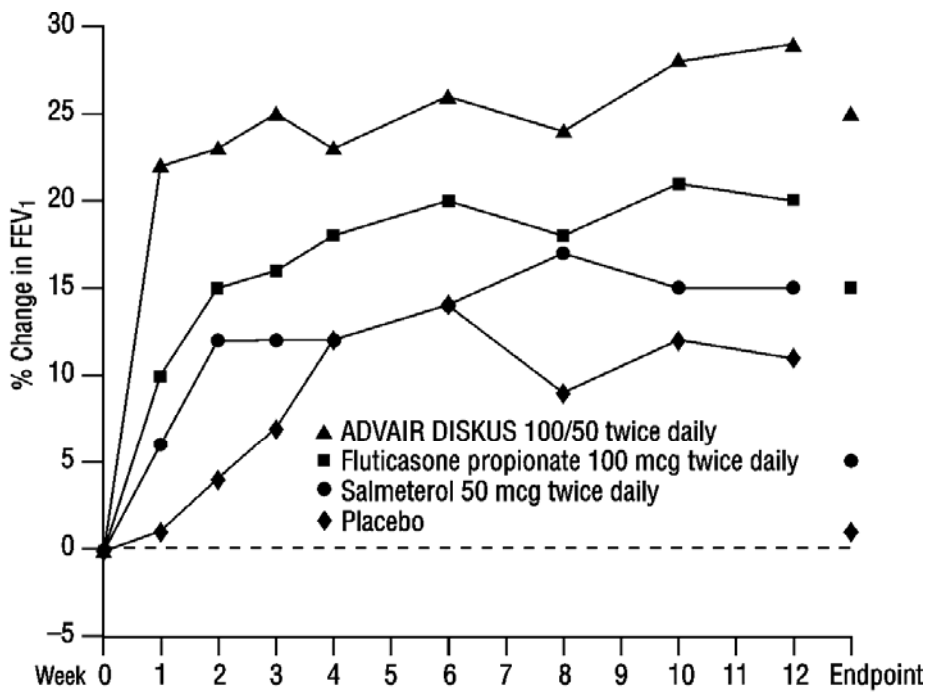
ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
3%	11%	35%	49%

432

433 The FEV<sub>1</sub> results are displayed in Figure 1. Because this trial used predetermined criteria for  
434 worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV<sub>1</sub>  
435 results at Endpoint (last available FEV<sub>1</sub> result) are also provided. Patients receiving ADVAIR  
436 DISKUS 100/50 had significantly greater improvements in FEV<sub>1</sub> (0.51 L, 25%) compared with  
437 fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L,  
438 1%). These improvements in FEV<sub>1</sub> with ADVAIR DISKUS were achieved regardless of baseline  
439 asthma maintenance therapy (inhaled corticosteroids or salmeterol).

440

441 **Figure 1. Mean Percent Change From Baseline in FEV<sub>1</sub> in Patients With Asthma**  
 442 **Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**  
 443



	Week 0	Week 6	Week 12	Endpoint
	N	N	N	N
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

444  
 445  
 446 The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in  
 447 Table 2.

448  
 449 **Table 2. Peak Expiratory Flow Results for Patients With Asthma Previously Treated With**  
 450 **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

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

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

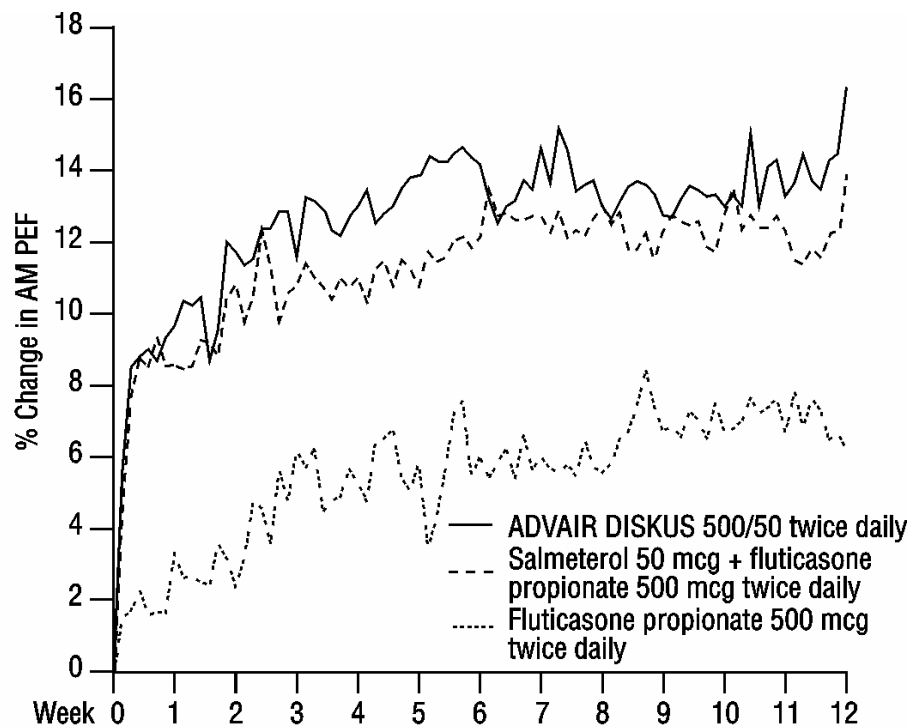
**Study 2: Clinical Trial With ADVAIR DISKUS 250/50:** This placebo-controlled, 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components, fluticasone propionate 250 mcg and salmeterol 50 mcg in 349 patients with asthma using inhaled corticosteroids (daily doses of beclomethasone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

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

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

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

492 **Figure 2. Mean Percent Change From Baseline in Morning Peak Expiratory Flow in**  
 493 **Patients With Asthma Previously Treated With Inhaled Corticosteroids (Study 3)**  
 494



	<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

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 496  
 497 **Onset of Action and Progression of Improvement in Asthma Control:** The  
 498 onset of action and progression of improvement in asthma control were evaluated in the 2  
 499 placebo-controlled US trials. Following the first dose, the median time to onset of clinically  
 500 significant bronchodilatation ( $\geq 15\%$  improvement in FEV<sub>1</sub>) in most patients was seen within 30  
 501 to 60 minutes. Maximum improvement in FEV<sub>1</sub> generally occurred within 3 hours, and clinically  
 502 significant improvement was maintained for 12 hours (see Figure 3).

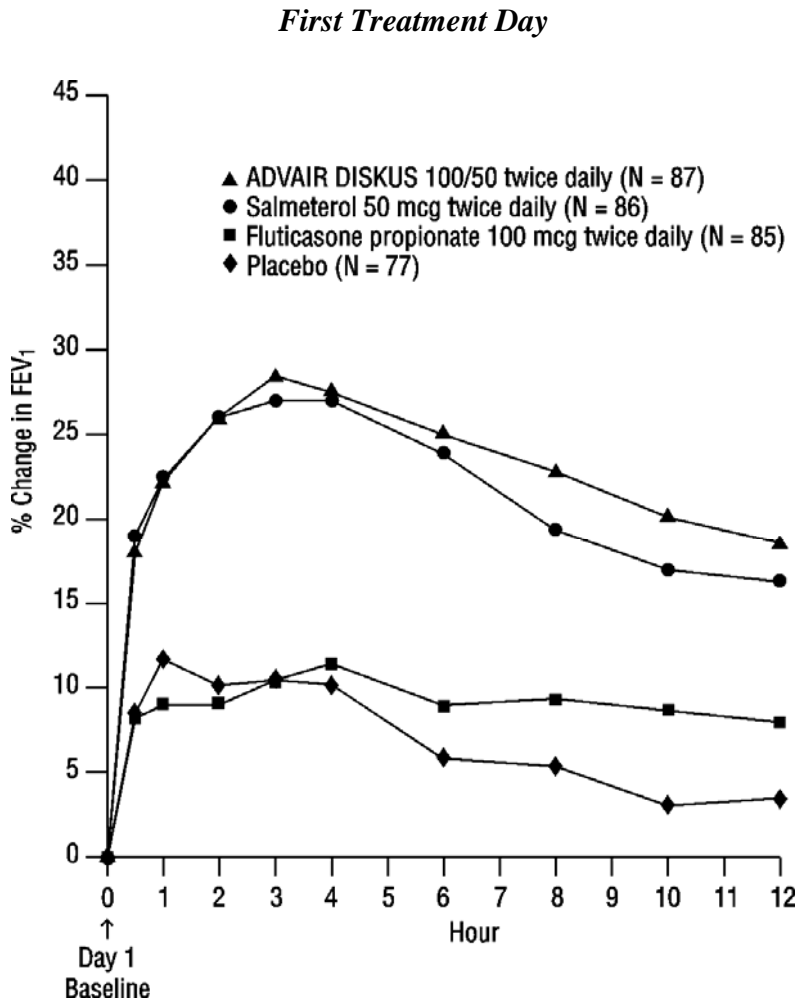
503 Following the initial dose, predose FEV<sub>1</sub> relative to Day 1 baseline improved markedly over  
 504 the first week of treatment and continued to improve over the 12 weeks of treatment in both  
 505 studies.

506 No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR  
 507 DISKUS 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV<sub>1</sub> following  
 508 12 weeks of therapy.

509

510 **Figure 3. Percent Change in Serial 12-hour FEV<sub>1</sub> in**  
511 **Patients With Asthma Previously Using Either Inhaled**  
512 **Corticosteroids or Salmeterol (Study 1)**

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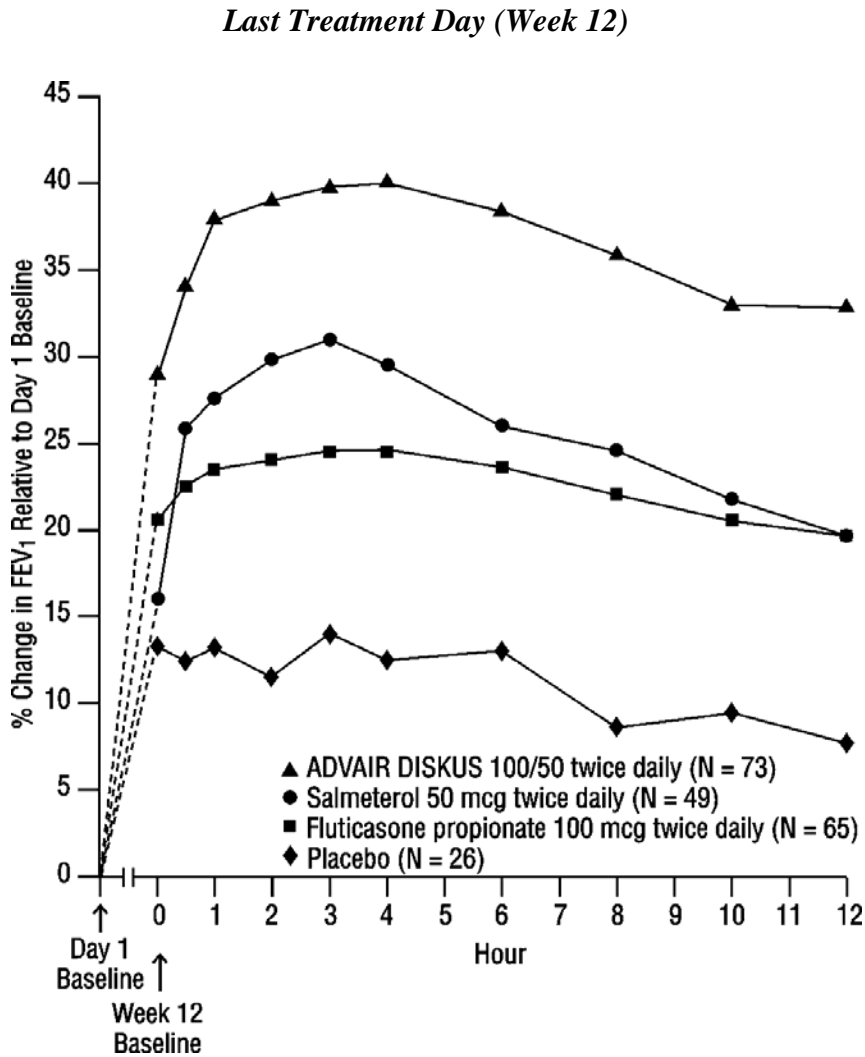


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518 **Figure 4. Percent Change in Serial 12-hour FEV<sub>1</sub> in Patients**  
 519 **With Asthma Previously Using Either Inhaled Corticosteroids**  
 520 **or Salmeterol (Study 1)**

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

529 **Pediatric Patients:** In a 12-week US study, ADVAIR DISKUS 100/50 twice daily was  
 530 compared with fluticasone propionate inhalation powder 100 mcg twice daily in 203 children  
 531 with asthma aged 4 to 11 years. At study entry, the children were symptomatic on low doses of  
 532 inhaled corticosteroids (beclomethasone dipropionate 252 to 336 mcg/day; budesonide 200 to  
 533 400 mcg/day; flunisolide 1,000 mcg/day; triamcinolone acetonide 600 to 1,000 mcg/day; or  
 534 fluticasone propionate 88 to 250 mcg/day). The primary objective of this study was to determine  
 535 the safety of ADVAIR DISKUS 100/50 compared with fluticasone propionate inhalation powder

536 100 mcg in this age-group; however, the study also included secondary efficacy measures of  
537 pulmonary function. Morning predose FEV<sub>1</sub> was obtained at baseline and Endpoint (last  
538 available FEV<sub>1</sub> result) in children aged 6 to 11 years. In patients receiving ADVAIR DISKUS  
539 100/50, FEV<sub>1</sub> increased from 1.70 L at baseline (N = 79) to 1.88 L at Endpoint (N = 69)  
540 compared with an increase from 1.65 L at baseline (N = 83) to 1.77 L at Endpoint (N = 75) in  
541 patients receiving fluticasone propionate 100 mcg.

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

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

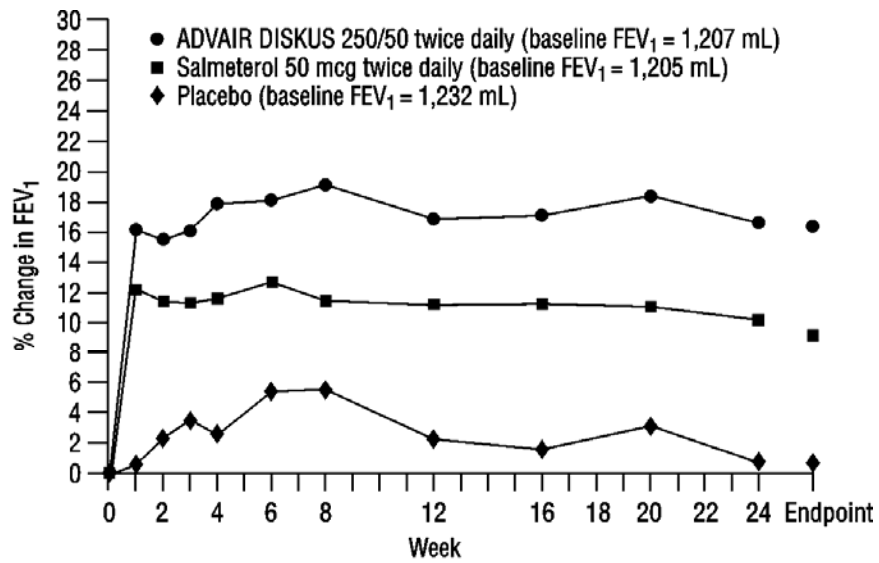
555 Figures 5 and 6 display predose and 2-hour postdose FEV<sub>1</sub> results. To account for patient  
556 withdrawals during the study, FEV<sub>1</sub> at Endpoint (last evaluable FEV<sub>1</sub>) was evaluated. Patients  
557 receiving ADVAIR DISKUS 250/50 had significantly greater improvements in predose FEV<sub>1</sub> at  
558 Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL,  
559 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung  
560 function with ADVAIR DISKUS (Figure 5). Patients receiving ADVAIR DISKUS 250/50 had  
561 significantly greater improvements in postdose FEV<sub>1</sub> at Endpoint (281 mL, 27%) compared with  
562 fluticasone propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the  
563 contribution of salmeterol to the improvement in lung function with ADVAIR DISKUS  
564 (Figure 6).

565 A similar degree of improvement in lung function was also observed with ADVAIR DISKUS  
566 500/50 twice daily.

567

568 **Figure 5. Predose FEV<sub>1</sub>: Mean Percent Change From Baseline in Patients With**  
 569 **COPD Associated With Chronic Bronchitis**

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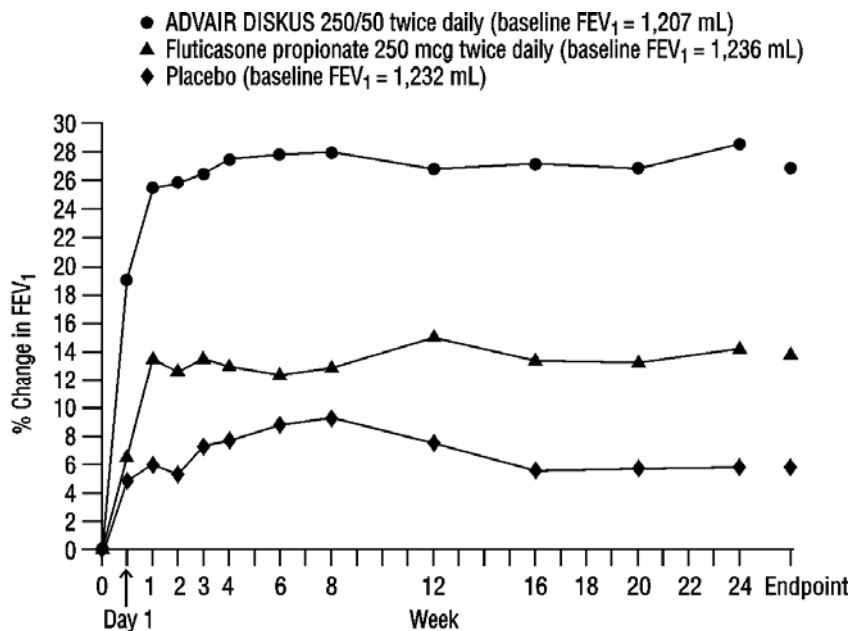


	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 250/50	178	144	124	171
Salmeterol 50 mcg	177	135	119	168
Placebo	185	139	125	172

571

572

573 **Figure 6. Two-Hour Postdose FEV<sub>1</sub>: Mean Percent Changes From Baseline Over**  
 574 **Time in Patients With COPD Associated With Chronic Bronchitis**  
 575



	<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

576  
 577  
 578 Patients treated with ADVAIR DISKUS 250/50 or ADVAIR DISKUS 500/50 did not have a  
 579 significant reduction in chronic bronchitis symptoms (as measured by the Chronic Bronchitis  
 580 Symptom Questionnaire) or in COPD exacerbations compared to patients treated with placebo  
 581 over the 24 weeks of therapy. The improvement in lung function with ADVAIR DISKUS 500/50  
 582 was similar to the improvement seen with ADVAIR DISKUS 250/50. Since there is evidence of  
 583 more systemic exposure to fluticasone propionate from this higher dose and no documented  
 584 advantage for efficacy, ADVAIR DISKUS 500/50 is not recommended for use in COPD.

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

587 **INDICATIONS AND USAGE**

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

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

596 patients whose asthma can be successfully managed by inhaled corticosteroids along with  
597 occasional use of inhaled, short-acting beta<sub>2</sub>-agonists.

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

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

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

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

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

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

612 **CONTRAINDICATIONS**

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

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

618 **WARNINGS**

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

625 A large placebo-controlled US study that compared the safety of salmeterol with placebo,  
626 each added to usual asthma therapy, showed an increase in asthma-related deaths in patients  
627 receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a  
628 randomized, double-blind study that enrolled long-acting beta<sub>2</sub>-agonist-naïve patients with  
629 asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily  
630 over 28 weeks compared to placebo when added to usual asthma therapy. A planned interim  
631 analysis was conducted when approximately half of the intended number of patients had been  
632 enrolled (N = 26,355), which led to premature termination of the study. The results of the interim  
633 analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events  
634 (see Table 3 and Figure 7). In the total population, a higher rate of asthma-related death occurred

635 in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%; relative risk  
 636 4.37 [95% CI 1.25, 15.34]).

637 Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death  
 638 occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo  
 639 (0.07% vs. 0.01%; relative risk 5.82 [95% CI 0.70, 48.37]). In African Americans also,  
 640 asthma-related death occurred at a higher rate in patients treated with salmeterol than those  
 641 treated with placebo (0.31% vs. 0.04%; relative risk 7.26 [95% CI 0.89, 58.94]). Although the  
 642 relative risks of asthma-related death were similar in Caucasians and African Americans, the  
 643 estimate of excess deaths in patients treated with salmeterol was greater in African Americans  
 644 because there was a higher overall rate of asthma-related death in African American patients (see  
 645 Table 3). Given the similar basic mechanisms of action of beta<sub>2</sub>-agonists, it is possible that the  
 646 findings seen in the SMART study represent a class effect.

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

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

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

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

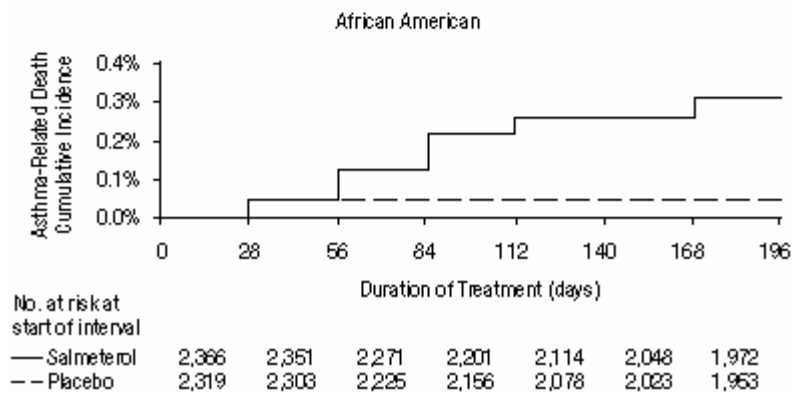
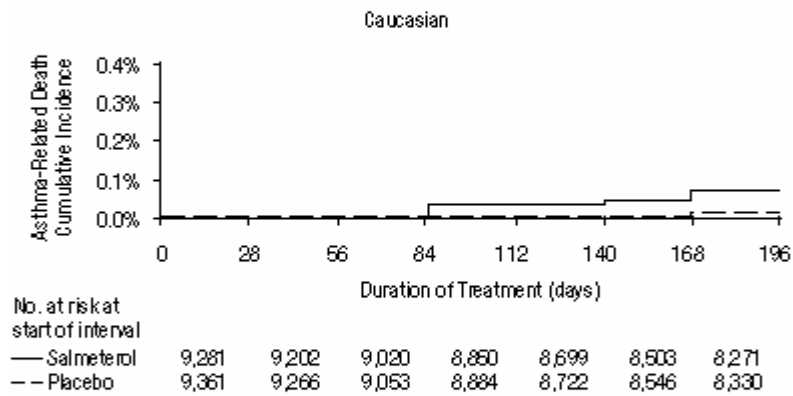
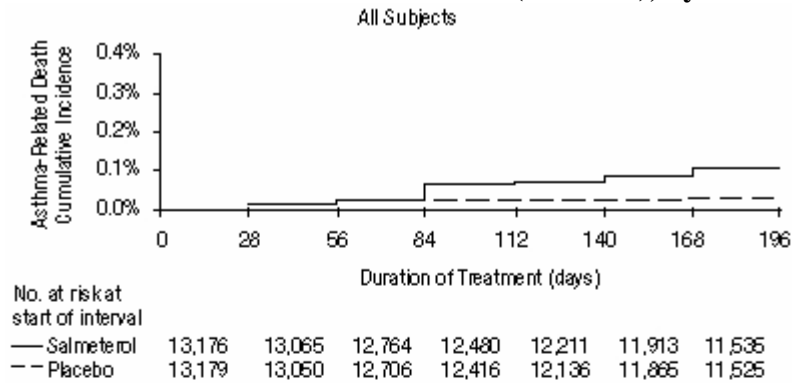
655 † Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the  
 656 rate in the placebo group. The relative risk indicates how many more times likely an  
 657 asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week  
 658 treatment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

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

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

663 § The Total Population includes the following ethnic origins listed on the case report form:  
664 Caucasian, African American, Hispanic, Asian, and “Other.” In addition, the Total Population  
665 includes those patients whose ethnic origin was not reported. The results for Caucasian and  
666 African American subpopulations are shown above. No asthma-related deaths occurred in the  
667 Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149),  
668 or “Other” (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death  
669 occurred in the placebo group in the subpopulation whose ethnic origin was not reported  
670 (salmeterol n = 130, placebo n = 127).  
671

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



674  
675

676 A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide  
 677 Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate  
 678 of asthma-related death was numerically, though not statistically significantly, greater in patients  
 679 with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol  
 680 (180 mcg 4 times daily) added to usual asthma therapy.



681 **The SNS and SMART studies enrolled patients with asthma. No studies have been**  
682 **conducted that were adequate to determine whether the rate of death in patients with**  
683 **COPD is increased by long-acting beta<sub>2</sub> adrenergic agonists.**

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

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

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

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

708 3. Increasing use of inhaled, short-acting beta<sub>2</sub>-agonists is a marker of deteriorating asthma. The  
709 physician and patient should be alert to such changes. The patient's condition may deteriorate  
710 acutely over a period of hours or chronically over several days or longer. If the patient's inhaled,  
711 short-acting beta<sub>2</sub>-agonist becomes less effective, the patient needs more inhalations than usual,  
712 or the patient develops a significant decrease in lung function, this may be a marker of  
713 destabilization of the disease. In this setting, the patient requires immediate reevaluation with  
714 reassessment of the treatment regimen, giving special consideration to the possible need for  
715 replacing the current strength of ADVAIR DISKUS with a higher strength, adding additional  
716 inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 1  
717 inhalation twice daily (morning and evening) of ADVAIR DISKUS.

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

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

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

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

738 5. ADVAIR DISKUS should not be used in conjunction with an inhaled, long-acting beta<sub>2</sub>-  
739 agonist. Patients who are receiving ADVAIR DISKUS twice daily should not use additional  
740 salmeterol or other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for prevention of  
741 exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma or the  
742 maintenance treatment of bronchospasm associated with COPD. Additional benefit would not be  
743 gained from using supplemental salmeterol or formoterol for prevention of EIB since ADVAIR  
744 DISKUS already contains an inhaled, long-acting beta<sub>2</sub>-agonist.

745 6. The recommended dosage should not be exceeded. ADVAIR DISKUS should not be used  
746 more often or at higher doses than recommended. Fatalities have been reported in association  
747 with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol  
748 (12 to 20 times the recommended dose) have been associated with clinically significant  
749 prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias.

750 7. Paradoxical bronchospasm. As with other inhaled asthma and COPD medications, ADVAIR  
751 DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical  
752 bronchospasm occurs following dosing with ADVAIR DISKUS, it should be treated  
753 immediately with an inhaled, short-acting bronchodilator, ADVAIR DISKUS should be  
754 discontinued immediately, and alternative therapy should be instituted.

755 8. Immediate hypersensitivity reactions. Immediate hypersensitivity reactions may occur after  
756 administration of ADVAIR DISKUS, as demonstrated by cases of urticaria, angioedema, rash,  
757 and bronchospasm.

758 9. Upper airway symptoms. Symptoms of laryngeal spasm, irritation, or swelling, such as stridor  
759 and choking, have been reported in patients receiving fluticasone propionate and salmeterol,  
760 components of ADVAIR DISKUS.

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

770 11. Discontinuation of systemic corticosteroids. Transfer of patients from systemic  
771 corticosteroid therapy to ADVAIR DISKUS may unmask conditions previously suppressed by  
772 the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and  
773 eosinophilic conditions.

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

786 13. Drug interaction with ritonavir. A drug interaction study in healthy subjects has shown that  
787 ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma  
788 fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations  
789 (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Fluticasone Propionate: Drug*  
790 *Interactions* and PRECAUTIONS: Drug Interactions: *Inhibitors of Cytochrome P450*). During  
791 postmarketing use, there have been reports of clinically significant drug interactions in patients  
792 receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects  
793 including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone  
794 propionate and ritonavir is not recommended unless the potential benefit to the patient  
795 outweighs the risk of systemic corticosteroid side effects.

## 796 **PRECAUTIONS**

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

800 discontinuation of ADVAIR DISKUS. ADVAIR DISKUS, like all medications containing  
801 sympathomimetic amines, should be used with caution in patients with cardiovascular disorders,  
802 especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with  
803 convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to  
804 sympathomimetic amines.

805 As has been described with other beta-adrenergic agonist bronchodilators, clinically  
806 significant changes in electrocardiograms (ECGs) have been seen infrequently in individual  
807 patients in controlled clinical studies with ADVAIR DISKUS and salmeterol. Clinically  
808 significant changes in systolic and/or diastolic blood pressure and pulse rate have been seen  
809 infrequently in individual patients in controlled clinical studies with salmeterol, a component of  
810 ADVAIR DISKUS.

811 **Metabolic and Other Effects:** Long-term use of orally inhaled corticosteroids may affect  
812 normal bone metabolism, resulting in a loss of bone mineral density (BMD). A 2-year study of  
813 160 patients (females 18 to 40 and males 18 to 50 years of age) with asthma receiving  
814 chlorofluorocarbon-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice  
815 daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and  
816 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar  
817 region L1 through L4. Long-term treatment effects of fluticasone propionate on BMD in the  
818 COPD population have not been studied.

819 In patients with major risk factors for decreased bone mineral content, such as tobacco use,  
820 advanced age, sedentary lifestyle, poor nutrition, family history of osteoporosis, or chronic use of  
821 drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), ADVAIR DISKUS  
822 may pose an additional risk. Since patients with COPD often have multiple risk factors for  
823 reduced BMD, assessment of BMD is recommended, including prior to instituting ADVAIR  
824 DISKUS 250/50 and periodically thereafter. If significant reductions in BMD are seen and  
825 ADVAIR DISKUS 250/50 is still considered medically important for that patient's COPD  
826 therapy, use of medication to treat or prevent osteoporosis should be strongly considered.  
827 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of  
828 COPD associated with chronic bronchitis, and higher doses, including ADVAIR DISKUS  
829 500/50, are not recommended.

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

834 Lower respiratory tract infections, including pneumonia, have been reported following the  
835 inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR  
836 DISKUS.

837 Doses of the related beta<sub>2</sub>-adrenoceptor agonist albuterol, when administered intravenously,  
838 have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic  
839 agonist medications may produce significant hypokalemia in some patients, possibly through

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

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

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

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

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

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

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

871 A 52-week, placebo-controlled study to assess the potential growth effects of fluticasone  
872 propionate inhalation powder (FLOVENT<sup>®</sup> ROTADISK<sup>®</sup>) at 50 and 100 mcg twice daily was  
873 conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to  
874 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were  
875 6.32 cm/year in the placebo group (N = 76), 6.07 cm/year in the 50-mcg group (N = 98), and  
876 5.66 cm/year in the 100-mcg group (N = 89). An imbalance in the proportion of children entering  
877 puberty between groups and a higher dropout rate in the placebo group due to poorly controlled  
878 asthma may be confounding factors in interpreting these data. A separate subset analysis of  
879 children who remained prepubertal during the study revealed growth rates at 52 weeks of

880 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and  
881 5.67 cm/year in the 100-mcg group (n = 79). In children 8.5 years of age, the mean age of  
882 children in this study, the range for expected growth velocity is: boys – 3<sup>rd</sup>  
883 percentile = 3.8 cm/year, 50<sup>th</sup> percentile = 5.4 cm/year, and 97<sup>th</sup> percentile = 7.0 cm/year; girls –  
884 3<sup>rd</sup> percentile = 4.2 cm/year, 50<sup>th</sup> percentile = 5.7 cm/year, and 97<sup>th</sup> percentile = 7.3 cm/year.

885 The clinical relevance of these growth data is not certain. Physicians should closely follow the  
886 growth of children and adolescents taking corticosteroids by any route, and weigh the benefits of  
887 corticosteroid therapy against the possibility of growth suppression if growth appears slowed.  
888 Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively  
889 controls their asthma.

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

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

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

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

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

920 FEV<sub>1</sub>) was observed in clinical trials and higher doses of corticosteroids increase the risk of  
921 systemic effects.

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

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

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

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

- 936 1. **Patients should be informed that salmeterol, one of the active ingredients in ADVAIR**  
937 **DISKUS, may increase the risk of asthma-related death.** They should also be informed  
938 that data are not adequate to determine whether the concurrent use of inhaled corticosteroids,  
939 such as fluticasone propionate, the other component of ADVAIR DISKUS, or other  
940 asthma-controller therapy modifies this risk.
- 941 2. ADVAIR DISKUS is not meant to relieve acute asthma symptoms and extra doses should  
942 not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting  
943 beta<sub>2</sub>-agonist such as albuterol (the physician should provide the patient with such  
944 medication and instruct the patient in how it should be used). ADVAIR DISKUS is not  
945 meant to relieve acute asthma symptoms or exacerbations of COPD.
- 946 3. The physician should be notified immediately if any of the following signs of seriously  
947 worsening asthma occur:
  - 948 • decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonists;
  - 949 • need for more inhalations than usual of inhaled, short-acting beta<sub>2</sub>-agonists;
  - 950 • significant decrease in lung function as outlined by the physician.
- 951 4. Patients should not stop therapy with ADVAIR DISKUS without physician/provider  
952 guidance since symptoms may recur after discontinuation.
- 953 5. Patients should be cautioned regarding common adverse effects associated with  
954 beta<sub>2</sub>-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 955 6. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of  
956 ADVAIR DISKUS, may increase the risk of some eye problems (cataracts or glaucoma).  
957 Regular eye examinations should be considered.

- 958 7. Patients who are at an increased risk for decreased BMD should be advised that the use of  
959 corticosteroids may pose an additional risk and should be told to monitor and, where  
960 appropriate, seek treatment for this condition.
- 961 8. When patients are prescribed ADVAIR DISKUS, other medications for asthma and COPD  
962 should be used only as directed by their physicians.
- 963 9. ADVAIR DISKUS should not be used with a spacer device.
- 964 10. Patients who are pregnant or nursing should contact their physicians about the use of  
965 ADVAIR DISKUS.
- 966 11. Patients should use ADVAIR DISKUS at regular intervals as directed. Results of clinical  
967 trials indicate significant improvement may occur within the first 30 minutes of taking the  
968 first dose; however, the full benefit may not be achieved until treatment has been  
969 administered for 1 week or longer. The patient should not use more than the prescribed  
970 dosage but should contact the physician if symptoms do not improve or if the condition  
971 worsens.
- 972 12. The bronchodilation from a single dose of ADVAIR DISKUS may last up to 12 hours or  
973 longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not  
974 be exceeded. Patients who are receiving ADVAIR DISKUS twice daily should not use  
975 salmeterol or other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for prevention of  
976 EIB or maintenance treatment of asthma or the maintenance treatment of bronchospasm in  
977 COPD.
- 978 13. Patients should be warned to avoid exposure to chickenpox or measles and, if they are  
979 exposed, to consult their physicians without delay.
- 980 14. Effective and safe use of ADVAIR DISKUS includes an understanding of the way that it  
981 should be used:
- 982 • Never exhale into the DISKUS.
  - 983 • Never attempt to take the DISKUS apart.
  - 984 • Always activate and use the DISKUS in a level, horizontal position.
  - 985 • After inhalation, rinse the mouth with water without swallowing.
  - 986 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
  - 987 • Always keep the DISKUS in a dry place.
  - 988 • Discard **1 month** after removal from the moisture-protective foil overwrap pouch or after  
989 all blisters have been used (when the dose indicator reads “0”), whichever comes first.
- 990 15. For the proper use of ADVAIR DISKUS and to attain maximum improvement, the patient  
991 should read and carefully follow the Instructions for Using ADVAIR DISKUS in the  
992 Medication Guide accompanying the product.
- 993 16. Most patients are able to taste or feel a dose delivered from ADVAIR DISKUS. However,  
994 whether or not patients are able to sense delivery of a dose, you should instruct them not to  
995 exceed the recommended dose of 1 inhalation each morning and evening, approximately 12  
996 hours apart. You should instruct them to contact you or the pharmacist if they have questions.



997 **Drug Interactions:** ADVAIR DISKUS has been used concomitantly with other drugs,  
998 including short-acting beta<sub>2</sub>-agonists, methylxanthines, and intranasal corticosteroids, commonly  
999 used in patients with asthma or COPD, without adverse drug reactions. No formal drug  
1000 interaction studies have been performed with ADVAIR DISKUS.

1001 **Short-Acting Beta<sub>2</sub>-Agonists:** In clinical trials with patients with asthma, the mean daily  
1002 need for albuterol by 166 adult and adolescent patients 12 years of age and older using ADVAIR  
1003 DISKUS was approximately 1.3 inhalations/day, and ranged from 0 to 9 inhalations/day. Five  
1004 percent (5%) of patients using ADVAIR DISKUS in these trials averaged 6 or more inhalations  
1005 per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse  
1006 reactions was observed among patients who averaged 6 or more inhalations per day.

1007 In a COPD clinical trial, the mean daily need for albuterol for patients using ADVAIR  
1008 DISKUS 250/50 was 4.1 inhalations/day. Twenty-six percent (26%) of patients using ADVAIR  
1009 DISKUS 250/50 averaged 6 or more inhalations per day over the course of the 24-week trial. No  
1010 increase in frequency of cardiovascular adverse reactions was observed among patients who  
1011 averaged 6 or more inhalations of albuterol per day.

1012 **Methylxanthines:** The concurrent use of intravenously or orally administered  
1013 methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent patients 12 years of  
1014 age and older receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials  
1015 with patients with asthma, 39 patients receiving ADVAIR DISKUS 100/50, 250/50, or 500/50  
1016 twice daily concurrently with a theophylline product had adverse event rates similar to those in  
1017 304 patients receiving ADVAIR DISKUS without theophylline. Similar results were observed in  
1018 patients receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily  
1019 concurrently with a theophylline product (n = 39) or without theophylline (n = 132).

1020 In a COPD clinical trial, 17 patients receiving ADVAIR DISKUS 250/50 twice daily  
1021 concurrently with a theophylline product had adverse event rates similar to those in 161 patients  
1022 receiving ADVAIR DISKUS without theophylline. Based on the available data, the concomitant  
1023 administration of methylxanthines with ADVAIR DISKUS did not alter the observed adverse  
1024 event profile.

1025 **Fluticasone Propionate Nasal Spray:** In adult and adolescent patients 12 years of age  
1026 and older taking ADVAIR DISKUS in clinical trials, no difference in the profile of adverse  
1027 events or HPA axis effects was noted between patients taking FLONASE<sup>®</sup> (fluticasone  
1028 propionate) Nasal Spray, 50 mcg concurrently (n = 46) and those who were not (n = 130).

1029 **Monoamine Oxidase Inhibitors and Tricyclic Antidepressants:** ADVAIR DISKUS  
1030 should be administered with extreme caution to patients being treated with monoamine oxidase  
1031 inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents,  
1032 because the action of salmeterol, a component of ADVAIR DISKUS, on the vascular system  
1033 may be potentiated by these agents.

1034 **Beta-Adrenergic Receptor Blocking Agents:** Beta-blockers not only block the  
1035 pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, but  
1036 may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma

1037 should not normally be treated with beta-blockers. However, under certain circumstances, there  
1038 may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with  
1039 asthma. In this setting, cardioselective beta-blockers could be considered, although they should  
1040 be administered with caution.

1041 **Diuretics:** The ECG changes and/or hypokalemia that may result from the administration of  
1042 nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by  
1043 beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although  
1044 the clinical relevance of these effects is not known, caution is advised in the coadministration of  
1045 beta-agonists with nonpotassium-sparing diuretics.

1046 **Inhibitors of Cytochrome P450:** Fluticasone propionate is a substrate of cytochrome  
1047 P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy  
1048 subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can  
1049 significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced  
1050 serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics:  
1051 *Fluticasone Propionate: Drug Interactions*). During postmarketing use, there have been reports  
1052 of clinically significant drug interactions in patients receiving fluticasone propionate and  
1053 ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal  
1054 suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not  
1055 recommended unless the potential benefit to the patient outweighs the risk of systemic  
1056 corticosteroid side effects.

1057 In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a  
1058 single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of  
1059 ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate  
1060 exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.  
1061 Caution should be exercised when ADVAIR DISKUS is coadministered with ketoconazole and  
1062 other known potent cytochrome P450 3A4 inhibitors.

1063 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate:**  
1064 Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to  
1065 1,000 mcg/kg (approximately 4 and 10 times, respectively, the maximum recommended daily  
1066 inhalation dose in adults and children on a mcg/m<sup>2</sup> basis) for 78 weeks or in rats at inhalation  
1067 doses up to 57 mcg/kg (less than and approximately equivalent to, respectively, the maximum  
1068 recommended daily inhalation dose in adults and children on a mcg/m<sup>2</sup> basis) for 104 weeks.

1069 Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in  
1070 vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in  
1071 vitro or in the mouse micronucleus test.

1072 No evidence of impairment of fertility was observed in reproductive studies conducted in  
1073 male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum  
1074 recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis). Prostate weight was  
1075 significantly reduced at a subcutaneous dose of 50 mcg/kg.

1076 **Salmeterol:** In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of  
1077 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose  
1078 in adults and children based on comparison of the plasma area under the curves [AUCs]) caused  
1079 a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular  
1080 hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of  
1081 leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg  
1082 (approximately 3 times the maximum recommended daily inhalation doses in adults and children  
1083 based on comparison of the AUCs).

1084 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol  
1085 caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at  
1086 doses of 0.68 mg/kg and above (approximately 55 and 25 times, respectively, the maximum  
1087 recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis). No tumors were  
1088 seen at 0.21 mg/kg (approximately 15 and 8 times, respectively, the maximum recommended  
1089 daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis). These findings in rodents are  
1090 similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of  
1091 these findings to human use is unknown.

1092 Salmeterol produced no detectable or reproducible increases in microbial and mammalian  
1093 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo  
1094 in a rat micronucleus test. No effects on fertility were identified in male and female rats treated  
1095 with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum  
1096 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis).

1097 **Pregnancy: Teratogenic Effects: ADVAIR DISKUS:** Pregnancy Category C. From the  
1098 reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using  
1099 combinations of fluticasone propionate and salmeterol compared to toxicity data from the  
1100 components administered separately. In mice combining 150 mcg/kg subcutaneously of  
1101 fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a  
1102 mcg/m<sup>2</sup> basis) with 10 mg/kg orally of salmeterol (approximately 410 times the maximum  
1103 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis) was teratogenic. Cleft palate,  
1104 fetal death, increased implantation loss and delayed ossification were seen. These observations  
1105 are characteristic of glucocorticoids. No developmental toxicity was observed at combination  
1106 doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum  
1107 recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) and up to 1.4 mg/kg orally of  
1108 salmeterol (approximately 55 times the maximum recommended daily inhalation dose in adults  
1109 on a mg/m<sup>2</sup> basis). In rats, no teratogenicity was observed at combination doses up to 30 mcg/kg  
1110 subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation  
1111 dose in adults on a mcg/m<sup>2</sup> basis) and up to 1 mg/kg of salmeterol (approximately 80 times the  
1112 maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Combining  
1113 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum recommended  
1114 daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) with 10 mg/kg orally of salmeterol  
1115 (approximately 810 times the maximum recommended daily inhalation dose in adults on a

1116 mg/m<sup>2</sup> basis) produced maternal toxicity, decreased placental weight, decreased fetal weight,  
1117 umbilical hernia, delayed ossification, and changes in the occipital bone. There are no adequate  
1118 and well-controlled studies with ADVAIR DISKUS in pregnant women. ADVAIR DISKUS  
1119 should be used during pregnancy only if the potential benefit justifies the potential risk to the  
1120 fetus.

1121 **Fluticasone Propionate:** Pregnancy Category C. Subcutaneous studies in the mouse  
1122 and rat at 45 and 100 mcg/kg (less than or equivalent to the maximum recommended daily  
1123 inhalation dose in adults on a mcg/m<sup>2</sup> basis), respectively, revealed fetal toxicity characteristic of  
1124 potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft  
1125 palate, and retarded cranial ossification.

1126 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of  
1127 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
1128 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg  
1129 (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
1130 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this  
1131 study, consistent with the established low bioavailability following oral administration (see  
1132 CLINICAL PHARMACOLOGY).

1133 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose  
1134 of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a  
1135 mcg/m<sup>2</sup> basis), administration of a subcutaneous or an oral dose of 100 mcg/kg to rats  
1136 (approximately equivalent to the maximum recommended daily inhalation dose in adults on a  
1137 mcg/m<sup>2</sup> basis), and administration of an oral dose of 300 mcg/kg to rabbits (approximately 5  
1138 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis).

1139 There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate  
1140 should be used during pregnancy only if the potential benefit justifies the potential risk to the  
1141 fetus.

1142 Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to  
1143 physiologic, doses suggests that rodents are more prone to teratogenic effects from  
1144 corticosteroids than humans. In addition, because there is a natural increase in corticosteroid  
1145 production during pregnancy, most women will require a lower exogenous corticosteroid dose  
1146 and many will not need corticosteroid treatment during pregnancy.

1147 **Salmeterol:** Pregnancy Category C. No teratogenic effects occurred in rats at oral doses  
1148 up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in  
1149 adults on a mg/m<sup>2</sup> basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and  
1150 above (approximately 50 times the maximum recommended daily inhalation dose in adults based  
1151 on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting  
1152 from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate,  
1153 sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones.  
1154 No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the  
1155 maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

1156 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal  
1157 bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the maximum  
1158 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Extensive use of other  
1159 beta-agonists has provided no evidence that these class effects in animals are relevant to their use  
1160 in humans. There are no adequate and well-controlled studies with salmeterol in pregnant  
1161 women. Salmeterol should be used during pregnancy only if the potential benefit justifies the  
1162 potential risk to the fetus.

1163 Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice  
1164 and rats (approximately 410 and 810 times, respectively, the maximum recommended daily  
1165 inhalation dose in adults on a mg/m<sup>2</sup> basis).

1166 **Use in Labor and Delivery:** There are no well-controlled human studies that have  
1167 investigated effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the  
1168 potential for beta-agonist interference with uterine contractility, use of ADVAIR DISKUS during  
1169 labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

1170 **Nursing Mothers:** Plasma levels of salmeterol, a component of ADVAIR DISKUS, after  
1171 inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There  
1172 are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known  
1173 whether fluticasone propionate, a component of ADVAIR DISKUS, is excreted in human breast  
1174 milk. However, other corticosteroids have been detected in human milk. Subcutaneous  
1175 administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the  
1176 maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) resulted in  
1177 measurable radioactivity in milk.

1178 Since there are no data from controlled trials on the use of ADVAIR DISKUS by nursing  
1179 mothers, a decision should be made whether to discontinue nursing or to discontinue ADVAIR  
1180 DISKUS, taking into account the importance of ADVAIR DISKUS to the mother.

1181 Caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.

1182 **Pediatric Use:** Use of ADVAIR DISKUS 100/50 in patients 4 to 11 years of age is supported  
1183 by extrapolation of efficacy data from older patients and by safety and efficacy data from a study  
1184 of ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years (see CLINICAL  
1185 TRIALS: Asthma: *Pediatric Patients* and ADVERSE REACTIONS: Asthma: *Pediatric*  
1186 *Patients*). The safety and effectiveness of ADVAIR DISKUS in children with asthma under  
1187 4 years of age have not been established.

1188 Controlled clinical studies have shown that orally inhaled corticosteroids may cause a  
1189 reduction in growth velocity in pediatric patients. This effect has been observed in the absence of  
1190 laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive  
1191 indicator of systemic corticosteroid exposure in pediatric patients than some commonly used  
1192 tests of HPA axis function. The long-term effects of this reduction in growth velocity associated  
1193 with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The  
1194 potential for “catch-up” growth following discontinuation of treatment with orally inhaled  
1195 corticosteroids has not been adequately studied.

1196 Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS,  
1197 may cause a reduction in growth velocity in children and adolescents (see PRECAUTIONS:  
1198 General: *Metabolic and Other Effects*). The growth of pediatric patients receiving orally inhaled  
1199 corticosteroids, including ADVAIR DISKUS, should be monitored. If a child or adolescent on  
1200 any corticosteroid appears to have growth suppression, the possibility that he/she is particularly  
1201 sensitive to this effect of corticosteroids should be considered. The potential growth effects of  
1202 prolonged treatment should be weighed against the clinical benefits obtained. To minimize the  
1203 systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, each patient  
1204 should be titrated to the lowest strength that effectively controls his/her asthma (see DOSAGE  
1205 AND ADMINISTRATION: Asthma).

1206 **Geriatric Use:** Of the total number of patients in clinical studies of ADVAIR DISKUS for  
1207 asthma, 44 were 65 years of age or older and 3 were 75 years of age or older. Of the total  
1208 number of patients in a clinical study of ADVAIR DISKUS 250/50 for COPD, 85 were 65 years  
1209 of age or older and 31 were 75 years of age or older. For both diseases, no overall differences in  
1210 safety were observed between these patients and younger patients, and other reported clinical  
1211 experience, including studies of the individual components, has not identified differences in  
1212 responses between the elderly and younger patients, but greater sensitivity of some older  
1213 individuals cannot be ruled out. As with other products containing beta<sub>2</sub>-agonists, special caution  
1214 should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant  
1215 cardiovascular disease that could be adversely affected by beta<sub>2</sub>-agonists. Based on available  
1216 data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR  
1217 DISKUS in geriatric patients is warranted.

## 1218 **ADVERSE REACTIONS**

1219 **Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, may increase the risk of**  
1220 **asthma-related death. Data from a large, placebo-controlled US study that compared the**  
1221 **safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma**  
1222 **therapy showed an increase in asthma-related deaths in patients receiving salmeterol (see**  
1223 **WARNINGS). Salmeterol is a component of ADVAIR DISKUS. However, the data from**  
1224 **this study are not adequate to determine whether concurrent use of inhaled corticosteroids,**  
1225 **such as fluticasone propionate, the other component of ADVAIR DISKUS, or other asthma**  
1226 **controller therapy modifies the risk of asthma-related death.**

1227 **Asthma: Adult and Adolescent Patients 12 Years of Age and Older:** The incidence of  
1228 common adverse events in Table 4 is based upon 2 placebo-controlled, 12-week, US clinical  
1229 studies (Studies 1 and 2). A total of 705 adolescent and adult patients (349 females and 356  
1230 males) previously treated with salmeterol or inhaled corticosteroids were treated twice daily with  
1231 ADVAIR DISKUS (100/50- or 250/50-mcg doses), fluticasone propionate inhalation powder  
1232 (100- or 250-mcg doses), salmeterol inhalation powder 50 mcg, or placebo.  
1233

1234 **Table 4. Overall Adverse Events With  $\geq 3\%$  Incidence in US Controlled Clinical Trials With**  
 1235 **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

1236  
 1237 Table 4 includes all events (whether considered drug-related or nondrug-related by the  
 1238 investigator) that occurred at a rate of 3% or greater in either of the groups receiving ADVAIR  
 1239 DISKUS and were more common than in the placebo group. In considering these data,  
 1240 differences in average duration of exposure should be taken into account. Rare cases of

1241 immediate and delayed hypersensitivity reactions, including rash and other rare events of  
1242 angioedema and bronchospasm, have been reported.

1243 These adverse reactions were mostly mild to moderate in severity.

1244 Other adverse events that occurred in the groups receiving ADVAIR DISKUS in these studies  
1245 with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1246 **Blood and Lymphatic:** Lymphatic signs and symptoms.

1247 **Cardiovascular:** Palpitations.

1248 **Drug Interaction, Overdose, and Trauma:** Muscle injuries, fractures, wounds and  
1249 lacerations, contusions and hematomas, burns.

1250 **Ear, Nose, and Throat:** Rhinorrhea/postnasal drip; ear, nose, and throat infections; ear  
1251 signs and symptoms; nasal signs and symptoms; nasal sinus disorders; rhinitis; sneezing; nasal  
1252 irritation; blood in nasal mucosa.

1253 **Eye:** Keratitis and conjunctivitis, viral eye infections, eye redness.

1254 **Gastrointestinal:** Dental discomfort and pain, gastrointestinal signs and symptoms,  
1255 gastrointestinal infections, gastroenteritis, gastrointestinal disorders, oral ulcerations, oral  
1256 erythema and rashes, constipation, appendicitis, oral discomfort and pain.

1257 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1258 **Lower Respiratory:** Lower respiratory signs and symptoms, pneumonia, lower  
1259 respiratory infections.

1260 **Musculoskeletal:** Arthralgia and articular rheumatism; muscle stiffness, tightness, and  
1261 rigidity; bone and cartilage disorders.

1262 **Neurology:** Sleep disorders, tremors, hypnagogic effects, compressed nerve syndromes.

1263 **Non-Site Specific:** Allergies and allergic reactions, congestion, viral infections, pain,  
1264 chest symptoms, fluid retention, bacterial infections, wheeze and hives, unusual taste.

1265 **Skin:** Viral skin infections, urticaria, skin flakiness and acquired ichthyosis, disorders of  
1266 sweat and sebum, sweating.

1267 The incidence of common adverse events reported in Study 3, a 28-week, non-US clinical  
1268 study of 503 patients previously treated with inhaled corticosteroids who were treated twice daily  
1269 with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and  
1270 salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation  
1271 powder 500 mcg was similar to the incidences reported in Table 4.

1272 **Pediatric Patients: Pediatric Study:** ADVAIR DISKUS 100/50 was well tolerated in  
1273 clinical trials conducted in children with asthma aged 4 to 11 years. The incidence of common  
1274 adverse events in Table 5 is based upon a 12-week US study in 203 patients with asthma aged 4  
1275 to 11 years (74 females and 129 males) who were receiving inhaled corticosteroids at study entry  
1276 and were randomized to either ADVAIR DISKUS 100/50 or fluticasone propionate inhalation  
1277 powder 100 mcg twice daily.

1278



1279 **Table 5. Overall Adverse Events With  $\geq 3\%$  Incidence With ADVAIR DISKUS 100/50**  
 1280 **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

1281  
 1282 Table 5 includes all events (whether considered drug-related or nondrug-related by the  
 1283 investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS  
 1284 100/50.

1285 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The  
 1286 incidence of common adverse events in Table 6 is based upon 1 placebo-controlled, 24-week, US  
 1287 clinical trial in patients with COPD associated with chronic bronchitis. A total of 723 adult  
 1288 patients (266 females and 457 males) were treated twice daily with ADVAIR DISKUS 250/50,  
 1289 fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder 50 mcg, or  
 1290 placebo.

1291

1292 **Table 6. Overall Adverse Events With  $\geq 3\%$  Incidence With ADVAIR DISKUS 250/50 in**  
 1293 **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

1294  
 1295 Table 6 includes all events (whether considered drug-related or nondrug-related by the  
 1296 investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS  
 1297 250/50 and were more common than in the placebo group.

1298 These adverse reactions were mostly mild to moderate in severity.

1299 Other adverse events that occurred in the groups receiving ADVAIR DISKUS 250/50 with an  
 1300 incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1301 **Cardiovascular:** Syncope.

1302 **Drug Interaction, Overdose, and Trauma:** Postoperative complications.

1303 **Ear, Nose, and Throat:** Ear, nose, and throat infections; ear signs and symptoms;  
 1304 laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection.

1305 **Endocrine and Metabolic:** Hypothyroidism.

1306 **Eye:** Dry eyes, eye infections.

1307 **Gastrointestinal:** Constipation, gastrointestinal signs and symptoms, oral lesions.

1308 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1309 **Lower Respiratory:** Breathing disorders, lower respiratory signs and symptoms.  
1310 **Non-Site Specific:** Bacterial infections, candidiasis unspecified site, edema and swelling,  
1311 nonspecific conditions, viral infections.  
1312 **Psychiatry:** Situational disorders.  
1313 **Observed During Clinical Practice:** In addition to adverse events reported from clinical  
1314 trials, the following events have been identified during worldwide use of any formulation of  
1315 ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are  
1316 reported voluntarily from a population of unknown size, estimates of frequency cannot be made.  
1317 These events have been chosen for inclusion due to either their seriousness, frequency of  
1318 reporting, or causal connection to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol  
1319 or a combination of these factors.  
1320 In extensive US and worldwide postmarketing experience with salmeterol, a component of  
1321 ADVAIR DISKUS, serious exacerbations of asthma, including some that have been fatal, have  
1322 been reported. In most cases, these have occurred in patients with severe asthma and/or in some  
1323 patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also  
1324 occurred in a few patients with less severe asthma. It was not possible from these reports to  
1325 determine whether salmeterol contributed to these events.  
1326 **Cardiovascular:** Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular  
1327 tachycardia), ventricular tachycardia.  
1328 **Ear, Nose, and Throat:** Aphonia, earache, facial and oropharyngeal edema, paranasal sinus  
1329 pain, throat soreness.  
1330 **Endocrine and Metabolic:** Cushing syndrome, Cushingoid features, growth velocity  
1331 reduction in children/adolescents, hypercorticism, hyperglycemia, weight gain, osteoporosis.  
1332 **Eye:** Cataracts, glaucoma.  
1333 **Gastrointestinal:** Abdominal pain, dyspepsia, xerostomia.  
1334 **Musculoskeletal:** Back pain, cramps, muscle spasm, myositis.  
1335 **Neurology:** Paresthesia, restlessness.  
1336 **Non-Site Specific:** Immediate and delayed hypersensitivity reaction (including very rare  
1337 anaphylactic reaction), pallor. Very rare anaphylactic reaction in patients with severe milk  
1338 protein allergy.  
1339 **Psychiatry:** Agitation, aggression, depression.  
1340 **Respiratory:** Chest congestion; chest tightness; dyspnea; immediate bronchospasm;  
1341 influenza; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory  
1342 symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.  
1343 **Skin:** Contact dermatitis, contusions, ecchymoses, photodermatitis.  
1344 **Urogenital:** Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal  
1345 candidiasis, vaginitis, vulvovaginitis.  
1346 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a  
1347 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some  
1348 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a

1349 condition that is often treated with systemic corticosteroid therapy. These events usually, but not  
1350 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy  
1351 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions  
1352 have also been reported with other inhaled corticosteroids in this clinical setting. While  
1353 ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid  
1354 therapy, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary  
1355 symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal  
1356 relationship between fluticasone propionate and these underlying conditions has not been  
1357 established (see PRECAUTIONS: General: *Eosinophilic Conditions*).

## 1358 **OVERDOSAGE**

1359 **ADVAIR DISKUS:** No deaths occurred in rats given an inhaled single-dose combination of  
1360 salmeterol 3.6 mg/kg (approximately 290 and 140 times, respectively, the maximum  
1361 recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis) and 1.9 mg/kg of  
1362 fluticasone propionate (approximately 15 and 35 times, respectively, the maximum  
1363 recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis).

1364 **Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in  
1365 signs/symptoms of hypercorticism (see PRECAUTIONS: General: *Metabolic and Other*  
1366 *Effects*). Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate  
1367 inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate inhalation  
1368 aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of  
1369 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated.  
1370 Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to  
1371 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or  
1372 moderate severity, and incidences were similar in active and placebo treatment groups. In mice,  
1373 the oral median lethal dose was >1,000 mg/kg (>4,100 and >9,600 times, respectively, the  
1374 maximum recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis). In rats  
1375 the subcutaneous median lethal dose was >1,000 mg/kg (>8,100 and >19,200 times,  
1376 respectively, the maximum recommended daily inhalation dose in adults and children on a  
1377 mg/m<sup>2</sup> basis).

1378 **Salmeterol:** The expected signs and symptoms with overdosage of salmeterol are those of  
1379 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and  
1380 symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or  
1381 hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache,  
1382 tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and  
1383 insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the  
1384 pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia  
1385 and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead  
1386 to clinically significant prolongation of the QTc interval, which can produce ventricular  
1387 arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

1388 As with all sympathomimetic medications, cardiac arrest and even death may be associated  
1389 with abuse of salmeterol.

1390 Treatment consists of discontinuation of salmeterol together with appropriate symptomatic  
1391 therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing  
1392 in mind that such medication can produce bronchospasm. There is insufficient evidence to  
1393 determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is  
1394 recommended in cases of overdosage.

1395 No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg  
1396 (approximately 240 and 110 times, respectively, the maximum recommended daily inhalation  
1397 dose in adults and children on a mg/m<sup>2</sup> basis) and in dogs at an inhalation dose of 0.7 mg/kg  
1398 (approximately 190 and 90 times, respectively, the maximum recommended daily inhalation  
1399 dose in adults and children on a mg/m<sup>2</sup> basis). By the oral route, no deaths occurred in mice at  
1400 150 mg/kg (approximately 6,100 and 2,900 times, respectively, the maximum recommended  
1401 daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis) and in rats at 1,000 mg/kg  
1402 (approximately 81,000 and 38,000 times, respectively, the maximum recommended daily  
1403 inhalation dose in adults and children on a mg/m<sup>2</sup> basis).

#### 1404 **DOSAGE AND ADMINISTRATION**

1405 ADVAIR DISKUS should be administered by the orally inhaled route only (see Instructions  
1406 for Using ADVAIR DISKUS in the Medication Guide accompanying the product). After  
1407 inhalation, the patient should rinse the mouth with water without swallowing. ADVAIR DISKUS  
1408 should not be used for transferring patients from systemic corticosteroid therapy.

1409 **Asthma:** Long-acting beta<sub>2</sub>-adrenergic agonists, such as salmeterol, one of the active  
1410 ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death (see  
1411 WARNINGS). Therefore, when treating patients with asthma, physicians should only prescribe  
1412 ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications  
1413 (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants  
1414 initiation of treatment with 2 maintenance therapies. ADVAIR DISKUS is not indicated in  
1415 patients whose asthma can be successfully managed by inhaled corticosteroids along with  
1416 occasional use of inhaled, short-acting beta<sub>2</sub>-agonists.

1417 ADVAIR DISKUS is available in 3 strengths, ADVAIR DISKUS 100/50, ADVAIR DISKUS  
1418 250/50, and ADVAIR DISKUS 500/50, containing 100, 250, and 500 mcg of fluticasone  
1419 propionate, respectively, and 50 mcg of salmeterol per inhalation.

1420 ADVAIR DISKUS should be administered twice daily every day. More frequent  
1421 administration (more than twice daily) or a higher number of inhalations (more than 1 inhalation  
1422 twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some  
1423 patients are more likely to experience adverse effects with higher doses of salmeterol. The safety  
1424 and efficacy of ADVAIR DISKUS when administered in excess of recommended doses have not  
1425 been established.

1426 If symptoms arise in the period between doses, an inhaled, short-acting beta<sub>2</sub>-agonist should  
1427 be taken for immediate relief.

1428 Patients who are receiving ADVAIR DISKUS twice daily should not use additional  
1429 salmeterol or other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for prevention of EIB,  
1430 or for any other reason.

1431 ***Adult and Adolescent Patients 12 Years of Age and Older:*** For patients 12 years of  
1432 age and older, the dosage is 1 inhalation twice daily (morning and evening, approximately  
1433 12 hours apart).

1434 The recommended starting dosages for ADVAIR DISKUS for patients 12 years of age and  
1435 older are based upon patients' current asthma therapy.

- 1436 • For patients not adequately controlled on an inhaled corticosteroid, Table 7 provides the  
1437 recommended starting dosage.
- 1438 • For patients not currently on inhaled corticosteroids whose disease severity clearly warrants  
1439 initiation of treatment with 2 maintenance therapies, the recommended starting dosage is  
1440 ADVAIR DISKUS 100/50 or 250/50 twice daily (see INDICATIONS AND USAGE).

1441 The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

1442 **For all patients it is desirable to titrate to the lowest effective strength after adequate**  
1443 **asthma stability is achieved.**

1444

1445 **Table 7. Recommended Dosages of ADVAIR DISKUS for Patients With Asthma Aged**  
 1446 **12 Years and Older Not Adequately Controlled on Inhaled Corticosteroids**

Current <b>Daily Dose</b> 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
	,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

1447 \* ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid  
 1448 therapy.

1449  
 1450 Improvement in asthma control following inhaled administration of ADVAIR DISKUS can  
 1451 occur within 30 minutes of beginning treatment, although maximum benefit may not be  
 1452 achieved for 1 week or longer after starting treatment. Individual patients will experience a  
 1453 variable time to onset and degree of symptom relief.

1454 For patients who do not respond adequately to the starting dosage after 2 weeks of therapy,  
 1455 replacing the current strength of ADVAIR DISKUS with a higher strength may provide  
 1456 additional improvement in asthma control.

1457 If a previously effective dosage regimen of ADVAIR DISKUS fails to provide adequate  
 1458 improvement in asthma control, the therapeutic regimen should be reevaluated and additional  
 1459 therapeutic options, e.g., replacing the current strength of ADVAIR DISKUS with a higher

1460 strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be  
1461 considered.

1462 **Pediatric Patients:** For patients aged 4 to 11 years who are symptomatic on an inhaled  
1463 corticosteroid the dosage is 1 inhalation of ADVAIR DISKUS 100/50 twice daily (morning and  
1464 evening, approximately 12 hours apart).

1465 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The  
1466 dosage for adults is 1 inhalation (250/50 mcg) twice daily (morning and evening, approximately  
1467 12 hours apart).

1468 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of  
1469 COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50,  
1470 are not recommended, as no additional improvement in lung function was observed in clinical  
1471 trials and higher doses of corticosteroids increase the risk of systemic effects.

1472 If shortness of breath occurs in the period between doses, an inhaled, short-acting  
1473 beta<sub>2</sub>-agonist should be taken for immediate relief.

1474 Patients who are receiving ADVAIR DISKUS twice daily should not use additional  
1475 salmeterol or other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for the maintenance  
1476 treatment of COPD or for any other reason.

1477 **Geriatric Use:** In studies where geriatric patients (65 years of age or older, see  
1478 PRECAUTIONS: Geriatric Use) have been treated with ADVAIR DISKUS, efficacy and safety  
1479 did not differ from that in younger patients. Based on available data for ADVAIR DISKUS and  
1480 its active components, no dosage adjustment is recommended.

## 1481 **HOW SUPPLIED**

1482 ADVAIR DISKUS 100/50 is supplied as a disposable purple device containing 60 blisters.  
1483 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective  
1484 foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional  
1485 pack of 1 disposable purple device containing 28 blisters. The DISKUS inhalation device is  
1486 packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0695-02).

1487 ADVAIR DISKUS 250/50 is supplied as a disposable purple device containing 60 blisters.  
1488 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective  
1489 foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional  
1490 pack of 1 disposable purple device containing 28 blisters. The DISKUS inhalation device is  
1491 packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0696-02).

1492 ADVAIR DISKUS 500/50 is supplied as a disposable purple device containing 60 blisters.  
1493 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective  
1494 foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional  
1495 pack of 1 disposable purple device containing 28 blisters. The DISKUS inhalation device is  
1496 packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0697-02).

1497 **Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F), in a dry place**  
1498 **away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation**



1499 **device is not reusable. The device should be discarded 1 month after removal from the**  
1500 **moisture-protective foil pouch or after all blisters have been used (when the dose indicator**  
1501 **reads “0”), whichever comes first. Do not attempt to take the device apart.**

1502  
1503



1504  
1505 GlaxoSmithKline  
1506 Research Triangle Park, NC 27709

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1509  
1510 [September](#)~~March~~ 2006 RL-

1511

1512 **MEDICATION GUIDE**

1513

1514 **ADVAIR [ad'vair] DISKUS 100/50<sup>®</sup>**  
1515 **(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)**

1516 **ADVAIR DISKUS 250/50<sup>®</sup>**  
1517 **(fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder)**

1518 **ADVAIR DISKUS 500/50<sup>®</sup>**  
1519 **(fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder)**

1520

1521 Read the Medication Guide that comes with ADVAIR DISKUS before you start using it and  
1522 each time you get a refill. There may be new information. This Medication Guide does not take  
1523 the place of talking to your healthcare provider about your medical condition or treatment.

1524

1525 **What is the most important information I should know about ADVAIR DISKUS?**

- 1526 • **ADVAIR DISKUS contains 2 medicines:**
- 1527 • **fluticasone propionate (the same medicine found in FLOVENT<sup>®</sup>),** an inhaled  
1528 corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the  
1529 lungs. Inflammation in the lungs can lead to asthma symptoms.
  - 1530 • **salmeterol (the same medicine found in SEREVENT<sup>®</sup>),** a long-acting beta<sub>2</sub>-agonist  
1531 medicine or LABA. LABA medicines are used in patients with asthma and chronic  
1532 obstructive pulmonary disease (COPD). LABA medicines help the muscles around the  
1533 airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness  
1534 of breath. These symptoms can happen when the muscles around the airways tighten.

1535 This makes it hard to breathe. In severe cases, wheezing can stop your breathing and  
1536 cause death if not treated right away.

1537

1538 • **In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in**  
1539 **ADVAIR DISKUS), may increase the chance of death from asthma problems.** In a large  
1540 asthma study, more patients who used salmeterol died from asthma problems compared with  
1541 patients who did not use salmeterol. It is not known whether fluticasone propionate, the other  
1542 medicine in ADVAIR DISKUS, changes your chance of death from asthma problems seen  
1543 with salmeterol. Talk with your healthcare provider about this risk and the benefits of  
1544 treating your asthma with ADVAIR DISKUS.

1545

1546 • **ADVAIR DISKUS does not relieve sudden symptoms. Always have a short-acting**  
1547 **beta<sub>2</sub>-agonist medicine with you to treat sudden symptoms. If you do not have an**  
1548 **inhaled, short-acting bronchodilator, contact your healthcare provider to have one**  
1549 **prescribed for you.**

1550

1551 • **Do not stop using ADVAIR DISKUS unless told to do so by your healthcare provider**  
1552 **because your symptoms might get worse.**

1553

1554 • **ADVAIR DISKUS should be used only if your healthcare provider decides that another**  
1555 **asthma-controller medicine alone does not control your asthma or that you need 2**  
1556 **asthma-controller medicines.**

1557

1558 • **Call your healthcare provider if breathing problems worsen over time while using**  
1559 **ADVAIR DISKUS. You may need different treatment.**

1560

1561 • **Get emergency medical care if:**

1562

- **breathing problems worsen quickly, and**

1563

- **you use your short-acting beta<sub>2</sub>-agonist medicine, but it does not relieve your**  
1564 **breathing problems.**

1565

1566 **What is ADVAIR DISKUS?**

1567 ADVAIR DISKUS combines an inhaled corticosteroid medicine, fluticasone propionate (the  
1568 same medicine found in FLOVENT) and a long-acting beta<sub>2</sub>-agonist medicine, salmeterol (the  
1569 same medicine found in SEREVENT). ADVAIR DISKUS is used for asthma and chronic  
1570 obstructive pulmonary disease (COPD) as follows:

1571

1572 **Asthma**

1573 ADVAIR DISKUS is used long term, twice a day to control symptoms of asthma and to prevent  
1574 symptoms such as wheezing in adults and children ages 4 and older.

1575  
1576 **ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). Because**  
1577 **LABA medicines, such as salmeterol, may increase the chance of death from asthma**  
1578 **problems, ADVAIR DISKUS is not for adults and children with asthma who:**  
1579     • are well controlled with another asthma-controller medicine, such as a low to medium  
1580     dose of an inhaled corticosteroid medicine  
1581     • only need short-acting beta<sub>2</sub>-agonist medicines once in awhile

1582  
1583 **Chronic Obstructive Pulmonary Disease (COPD)**  
1584 ADVAIR DISKUS is used long term, twice a day in controlling symptoms of COPD and  
1585 preventing wheezing in adults with COPD.

1586  
1587 **What should I tell my healthcare provider before using ADVAIR DISKUS?**  
1588 **Tell your healthcare provider about all of your health conditions, including if you:**

- 1589 • **have heart problems**
- 1590 • **have high blood pressure**
- 1591 • **have seizures**
- 1592 • **have thyroid problems**
- 1593 • **have diabetes**
- 1594 • **have liver problems**
- 1595 • **have osteoporosis**
- 1596 • **have an immune system problem**
- 1597 • **are pregnant or planning to become pregnant.** It is not known if ADVAIR DISKUS may  
1598 harm your unborn baby.
- 1599 • **are breastfeeding.** It is not known if ADVAIR DISKUS passes into your milk and if it can  
1600 harm your baby.
- 1601 • **are allergic to ADVAIR DISKUS, any other medicines, or food products**
- 1602 • **are exposed to chickenpox or measles**

1603  
1604 Tell your healthcare provider about all the medicines you take including prescription and  
1605 non-prescription medicines, vitamins, and herbal supplements. ADVAIR DISKUS and certain  
1606 other medicines may interact with each other. This may cause serious side effects. Especially,  
1607 tell your healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR<sup>®</sup> (ritonavir  
1608 capsules) Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA<sup>®</sup> (lopinavir/ritonavir)  
1609 Tablets contain ritonavir.

1610  
1611 Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist  
1612 each time you get a new medicine.

1613  
1614 **How do I use ADVAIR DISKUS?**

1615 **See the step-by-step instructions for using the ADVAIR DISKUS at the end of this**  
1616 **Medication Guide.** Do not use the ADVAIR DISKUS unless your healthcare provider has  
1617 taught you and you understand everything. Ask your healthcare provider or pharmacist if you  
1618 have any questions.

1619

1620 • Children should use ADVAIR DISKUS with an adult’s help, as instructed by the child’s  
1621 healthcare provider.

1622

1623 • Use ADVAIR DISKUS exactly as prescribed. **Do not use ADVAIR DISKUS more often**  
1624 **than prescribed.** ADVAIR DISKUS comes in 3 strengths. Your healthcare provider will  
1625 prescribe the one that is best for your condition.

1626

1627 • The usual dosage of ADVAIR DISKUS is 1 inhalation twice a day (morning and evening).  
1628 The 2 doses should be about 12 hours apart. Rinse your mouth with water after using  
1629 ADVAIR DISKUS.

1630

1631 • If you miss a dose of ADVAIR DISKUS, just skip that dose. Take your next dose at your  
1632 usual time. Do not take 2 doses at one time.

1633

1634 • Do not use a spacer device with ADVAIR DISKUS.

1635

1636 • Do not breathe into ADVAIR DISKUS.

1637

1638 • **While you are using ADVAIR DISKUS twice a day, do not use other medicines that**  
1639 **contain a long-acting beta<sub>2</sub>-agonist or LABA for any reason. Other LABA medicines**  
1640 **include SEREVENT<sup>®</sup> DISKUS<sup>®</sup> (salmeterol xinafoate inhalation powder) or**  
1641 **FORADIL<sup>®</sup> AEROLIZER<sup>™</sup> (formoterol fumarate inhalation powder).**

1642

1643 • Do not change or stop any of your medicines used to control or treat your breathing  
1644 problems. Your healthcare provider will adjust your medicines as needed.

1645

1646 • Make sure you always have a short-acting beta<sub>2</sub>-agonist medicine with you. Use your  
1647 short-acting beta<sub>2</sub>-agonist medicine if you have breathing problems between doses of  
1648 ADVAIR DISKUS.

1649

1650 • **Call your healthcare provider or get medical care right away if:**

1651 • your breathing problems worsen with ADVAIR DISKUS

1652 • you need to use your short-acting beta<sub>2</sub>-agonist medicine more often than usual

1653 • your short-acting beta<sub>2</sub>-agonist medicine does not work as well for you at relieving

1654 symptoms

- 1655 • you need to use 4 or more inhalations of your short-acting beta<sub>2</sub>-agonist medicine for 2 or  
1656 more days in a row
- 1657 • you use 1 whole canister of your short-acting beta<sub>2</sub>-agonist medicine in 8 weeks' time
- 1658 • your peak flow meter results decrease. Your healthcare provider will tell you the numbers  
1659 that are right for you.
- 1660 • you have asthma and your symptoms do not improve after using ADVAIR DISKUS  
1661 regularly for 1 week

1662

1663 **What are the possible side effects with ADVAIR DISKUS?**

- 1664 • **ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). In**  
1665 **patients with asthma, LABA medicines, such as salmeterol, may increase the chance of**  
1666 **death from asthma problems.** See “What is the most important information I should know  
1667 about ADVAIR DISKUS?”

1668

1669 **Other possible side effects with ADVAIR DISKUS include:**

- 1670 • **serious allergic reactions including rash; hives; swelling of the face, mouth, and tongue;**  
1671 **and breathing problems.** Call your healthcare provider or get emergency medical care if  
1672 you get any symptoms of a serious allergic reaction.
- 1673 • **increased blood pressure**
- 1674 • **a fast and irregular heartbeat**
- 1675 • **chest pain**
- 1676 • **headache**
- 1677 • **tremor**
- 1678 • **nervousness**
- 1679 • **immune system effects and a higher chance for infections**
- 1680 • **lower bone mineral density.** This may be a problem for people who already have a higher  
1681 chance for low bone density (osteoporosis).
- 1682 • **eye problems including glaucoma and cataracts.** You should have regular eye exams  
1683 while using ADVAIR DISKUS.
- 1684 • **slowed growth in children.** A child's growth should be checked often.
- 1685 • **throat irritation**

1686

1687 Tell your healthcare provider about any side effect that bothers you or that does not go away.

1688

1689 These are not all the side effects with ADVAIR DISKUS. Ask your healthcare provider or  
1690 pharmacist for more information.

1691

1692 **How do I store ADVAIR DISKUS?**

- 1693 • Store ADVAIR DISKUS at room temperature between 68° to 77° F (20° to 25° C). Keep in a  
1694 dry place away from heat and sunlight.

- 1695 • Safely discard ADVAIR DISKUS 1 month after you remove it from the foil pouch, or after  
1696 the dose indicator reads “0”, whichever comes first.
- 1697 • **Keep ADVAIR DISKUS and all medicines out of the reach of children.**

1698

1699 **General Information about ADVAIR DISKUS**

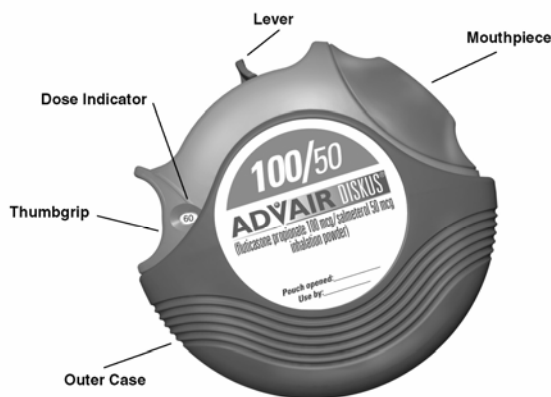
1700 Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not  
1701 use ADVAIR DISKUS for a condition for which it was not prescribed. Do not give your  
1702 ADVAIR DISKUS to other people, even if they have the same condition. It may harm them.

1703 This Medication Guide summarizes the most important information about ADVAIR DISKUS. If  
1704 you would like more information, talk with your healthcare provider or pharmacist. You can ask  
1705 your healthcare provider or pharmacist for information about ADVAIR DISKUS that was  
1706 written for healthcare professionals. You can also contact the company that makes ADVAIR  
1707 DISKUS (toll free) at 1-888-825-5249 or at www.advair.com.

1708

1709 **Instructions for Using ADVAIR DISKUS**

1710 Follow the instructions below for using your ADVAIR DISKUS. **You will breathe in (inhale)**  
1711 **the medicine from the DISKUS.** If you have any questions, ask your healthcare provider or  
1712 pharmacist.



1713

1714 Take the ADVAIR DISKUS out of the box and foil overwrap pouch. Write the **“Pouch opened”**  
1715 and **“Use by”** dates on the label on top of the DISKUS. **The “Use by” date is 1 month from**  
1716 **date of opening the pouch.**

- 1717 • The DISKUS will be in the closed position when the pouch is opened.
- 1718 • The **dose indicator** on the top of the DISKUS tells you how many doses are left. The  
1719 dose indicator number will decrease each time you use the DISKUS. After you have used  
1720 55 doses from the DISKUS, the numbers 5 to 0 will appear in **red** to warn you that there  
1721 are only a few doses left (*see Figure 1*). If you are using a “sample” DISKUS, the  
1722 numbers 5 to 0 will appear in red after 23 doses.



*Figure 1*

1723

1724

1725 Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.

1726 1. **OPEN**

1727 Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**. Push  
1728 your thumb away from you as far as it will go until the mouthpiece appears and snaps into  
1729 position (*see Figure 2*).



*Figure 2*

1730

1731

1732 2. **CLICK**

1733 Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the **lever**  
1734 away from you as far as it will go until it **clicks** (see *Figure 3*). The DISKUS is now ready to  
1735 use.



1736

1737

*Figure 3*

1738 Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a  
1739 decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the**  
1740 **DISKUS is ready:**

1741

- **Do not close the DISKUS.**
- **Do not tilt the DISKUS.**
- **Do not play with the lever.**
- **Do not move the lever more than once.**

1742

1743

1744

1745

1746 3. **INHALE**

1747 Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the  
1748 DISKUS level and away from your mouth (see *Figure 4*). **Remember, never breathe out**  
1749 **into the DISKUS mouthpiece.**





**Figure 4**

1750  
1751

1752 Put the mouthpiece to your lips (*see Figure 5*). Breathe in quickly and deeply through the  
1753 DISKUS. Do not breathe in through your nose.



**Figure 5**

1754  
1755

1756 Remove the DISKUS from your mouth. Hold your breath for about 10 seconds, or for as long  
1757 as is comfortable. Breathe out slowly.

1758 The DISKUS delivers your dose of medicine as a very fine powder. Most patients can taste  
1759 or feel the powder. Do not use another dose from the DISKUS if you do not feel or taste the  
1760 medicine.

1761 Rinse your mouth with water after breathing-in the medicine. Spit the water out. Do not  
1762 swallow.

1763 4. **Close the DISKUS when you are finished taking a dose so that the DISKUS will be**  
1764 **ready for you to take your next dose.** Put your thumb on the thumbgrip and slide the  
1765 thumbgrip back towards you as far as it will go (*see Figure 6*). The DISKUS will click shut.  
1766 The lever will automatically return to its original position. The DISKUS is now ready for you  
1767 to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4.)



1768  
1769 *Figure 6*

1770 **Remember:**

- 1771 • Never breathe into the DISKUS.
- 1772 • Never take the DISKUS apart.
- 1773 • Always ready and use the DISKUS in a level, flat position.
- 1774 • Do not use the DISKUS with a spacer device.
- 1775 • After each dose, rinse your mouth with water and spit the water out. Do not swallow.
- 1776 • Never wash the mouthpiece or any part of the DISKUS. **Keep it dry.**
- 1777 • Always keep the DISKUS in a dry place.
- 1778 • Never take an extra dose, even if you did not taste or feel the medicine.

1779 **Rx only**



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1794  
1795 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**