

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)

7  
8 **ADVAIR DISKUS<sup>®</sup> 500/50**

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

10  
11 \*As salmeterol xinafoate salt 72.5 mcg, equivalent to salmeterol base 50 mcg

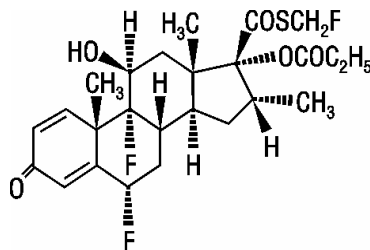
12  
13 **For Oral Inhalation Only**

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

21 **DESCRIPTION**

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

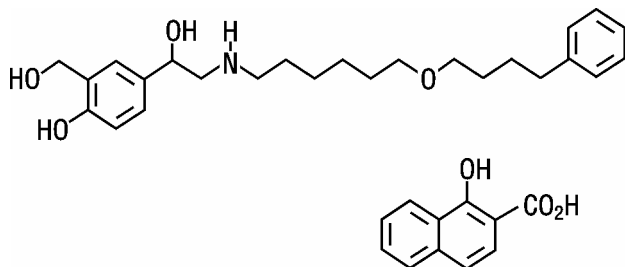
24 One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having  
25 the chemical name *S*-(fluoromethyl) 6 $\alpha$ ,9-difluoro-11 $\beta$ ,17-dihydroxy-16 $\alpha$ -methyl-3-  
26 oxoandrosta-1,4-diene-17 $\beta$ -carbothioate, 17-propionate and the following chemical structure:  
27



28  
29  
30 Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and  
31 the empirical formula is C<sub>25</sub>H<sub>31</sub>F<sub>3</sub>O<sub>5</sub>S. It is practically insoluble in water, freely soluble in  
32 dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

33 The other active component of ADVAIR DISKUS is salmeterol xinafoate, a beta<sub>2</sub>-adrenergic  
34 bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt

35 of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy- $\alpha^1$ -[[[6-(4-phenylbutoxy)  
36 hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has  
37 the following chemical structure:  
38



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

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

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

59 Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to  
60 50 years) patients with asthma inhaling maximally through the DISKUS device show mean PIF  
61 of 122.2 L/min (range, 81.6 to 152.1 L/min). Inhalation profiles for pediatric patients with  
62 asthma inhaling maximally through the DISKUS device show a mean PIF of 75.5 L/min (range,  
63 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  
64 125.6 L/min) for the 8-year-old patient set (N = 20).

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

67 **CLINICAL PHARMACOLOGY**

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

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

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

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

91 **Salmeterol Xinafoate:** Salmeterol is a long-acting beta<sub>2</sub>-adrenergic agonist. In vitro studies  
92 and in vivo pharmacologic studies demonstrate that salmeterol is selective for  
93 beta<sub>2</sub>-adrenoceptors compared with isoproterenol, which has approximately equal agonist  
94 activity on beta<sub>1</sub>- and beta<sub>2</sub>-adrenoceptors. In vitro studies show salmeterol to be at least 50 times  
95 more selective for beta<sub>2</sub>-adrenoceptors than albuterol. Although beta<sub>2</sub>-adrenoceptors are the  
96 predominant adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-adrenoceptors are the  
97 predominant receptors in the heart, there are also beta<sub>2</sub>-adrenoceptors in the human heart  
98 comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors  
99 has not been established, but they raise the possibility that even highly selective beta<sub>2</sub>-agonists  
100 may have cardiac effects.

101 The pharmacologic effects of beta<sub>2</sub>-adrenoceptor agonist drugs, including salmeterol, are at  
102 least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes  
103 the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic  
104 AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition  
105 of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

106 In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast  
107 cell mediators, such as histamine, leukotrienes, and prostaglandin D<sub>2</sub>, from human lung.  
108 Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits  
109 platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when  
110 administered by the inhaled route. In humans, single doses of salmeterol administered via  
111 inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

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

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

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

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

137 **Pediatric Patients:** In a clinical study conducted in patients with asthma aged 4 to  
138 11 years, fluticasone propionate concentrations were obtained in 61 patients at 20 and 40 minutes  
139 after dosing with 50 and 100 mcg of fluticasone propionate inhalation powder twice daily using  
140 the DISKUS. Plasma concentrations were low and ranged from undetectable (about 80% of the  
141 plasma samples) to 88 pg/mL. Mean peak fluticasone propionate plasma concentrations at the  
142 50- and 100-mcg dose levels were 5 and 8 pg/mL, respectively.

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

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

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

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

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

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

166 The percentage of fluticasone propionate bound to human plasma proteins averages 91%.  
167 Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly  
168 bound to human transcortin.

169 **Metabolism:** The total clearance of fluticasone propionate is high (average,  
170 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only  
171 circulating metabolite detected in man is the 17 $\beta$ -carboxylic acid derivative of fluticasone  
172 propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had  
173 less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of  
174 human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other  
175 metabolites detected in vitro using cultured human hepatoma cells have not been detected in  
176 man.

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

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

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

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

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

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

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

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

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

218 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low  
219 or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder  
220 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol  
221 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7  
222 patients with asthma; plasma concentrations were very low, with mean peak concentrations of  
223 167 pg/mL at 20 minutes and no accumulation with repeated doses.

224 **Distribution:** The percentage of salmeterol bound to human plasma proteins averages  
225 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much  
226 higher concentrations than those achieved following therapeutic doses of salmeterol.

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

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

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

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

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

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

262 **Asthma:** In clinical studies with ADVAIR DISKUS in adult and adolescent patients 12  
263 years of age and older with asthma, no significant differences were observed in the systemic

264 pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and  
265 glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adolescent and  
266 adult patients with asthma given either ADVAIR DISKUS 100/50 or ADVAIR DISKUS  
267 250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose  
268 and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

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

274 In a 12-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 250/50  
275 twice daily was compared with fluticasone propionate powder 250 mcg alone, salmeterol powder  
276 50 mcg alone, and placebo. For most patients, the ability to increase cortisol production in  
277 response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with  
278 ADVAIR DISKUS. One patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal  
279 response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who  
280 received placebo, 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients  
281 who received salmeterol.

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

290 In a 24-week study, 130 patients with COPD associated with chronic bronchitis received  
291 continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of  
292 twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate powder  
293 500 mcg, salmeterol powder 50 mcg, or placebo. No significant differences in ventricular or  
294 supraventricular arrhythmias and heart rate were observed among the groups treated with  
295 ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the  
296 fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the  
297 group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of  
298 nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone  
299 propionate 500 mcg treatment groups).

300 Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in  
301 101 patients with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate  
302 powder 250 mcg, salmeterol powder 50 mcg, or placebo. For most patients, the ability to  
303 increase cortisol production in response to stress, as assessed by short cosyntropin stimulation,



304 remained intact with ADVAIR DISKUS 250/50. One (1) patient (3%) who received ADVAIR  
305 DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL  
306 assessed by high-performance liquid chromatography) after dosing, compared with 2 patients  
307 (9%) who received fluticasone propionate 250 mcg, 2 patients (7%) who received salmeterol  
308 50 mcg, and 1 patient (4%) who received placebo following 24 weeks of treatment or early  
309 discontinuation from study.

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

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

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

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

342 **Asthma:** The effects of rising doses of salmeterol and standard inhaled doses of albuterol  
343 were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg

344 administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the  
345 same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and  
346 adult patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent  
347 continuous electrocardiographic monitoring during two 12-hour periods after the first dose and  
348 after 1 month of therapy, and no clinically significant dysrhythmias were noted.

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

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

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

## 366 **CLINICAL TRIALS**

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

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

379 **Study 1: Clinical Trial With ADVAIR DISKUS 100/50:** This placebo-controlled,  
380 12-week, US study compared ADVAIR DISKUS 100/50 with its individual components,  
381 fluticasone propionate 100 mcg and salmeterol 50 mcg. The study was stratified according to  
382 baseline asthma maintenance therapy; patients were using either inhaled corticosteroids

383 (N = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg;  
 384 fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg)  
 385 or salmeterol (N = 106). Baseline FEV<sub>1</sub> measurements were similar across treatments: ADVAIR  
 386 DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and  
 387 placebo, 2.15 L.

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

396

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

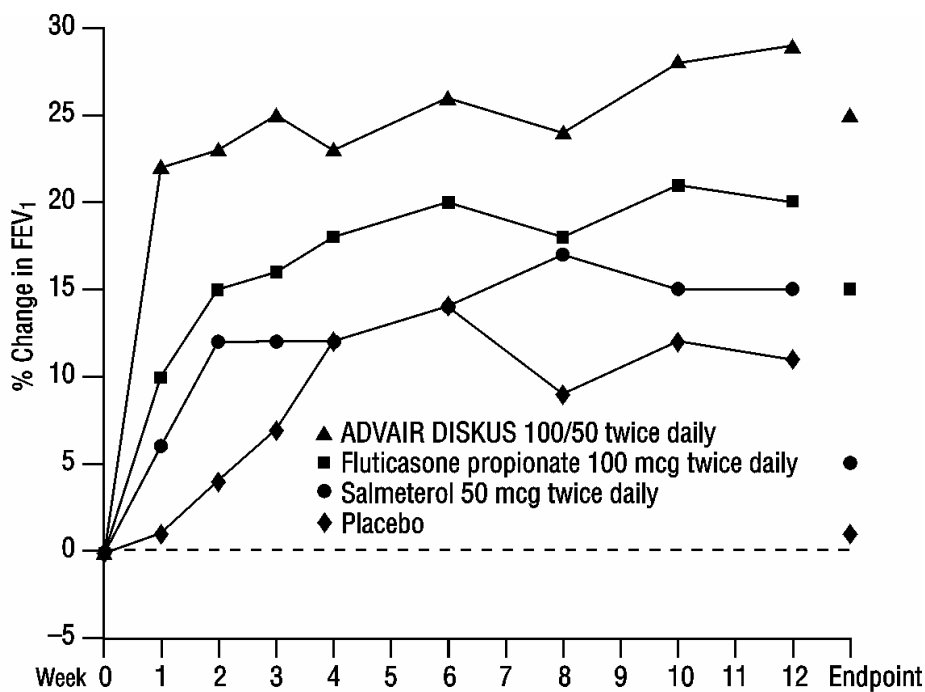
ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
3%	11%	35%	49%

399

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

407

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



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

411  
 412  
 413 The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in  
 414 Table 2.

415  
 416 **Table 2. Peak Expiratory Flow Results for Patients With Asthma Previously Treated With**  
 417 **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

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

419

420 The subjective impact of asthma on patients' perception of health was evaluated through use  
421 of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point  
422 scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR DISKUS  
423 100/50 had clinically meaningful improvements in overall asthma-specific quality of life as  
424 defined by a difference between groups of  $\geq 0.5$  points in change from baseline AQLQ scores  
425 (difference in AQLQ score of 1.25 compared to placebo).

426 **Study 2: Clinical Trial With ADVAIR DISKUS 250/50:** This placebo-controlled,  
427 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components,  
428 fluticasone propionate 250 mcg and salmeterol 50 mcg in 349 patients with asthma using inhaled  
429 corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to  
430 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100  
431 to 1,600 mcg). Baseline FEV<sub>1</sub> measurements were similar across treatments: ADVAIR DISKUS  
432 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

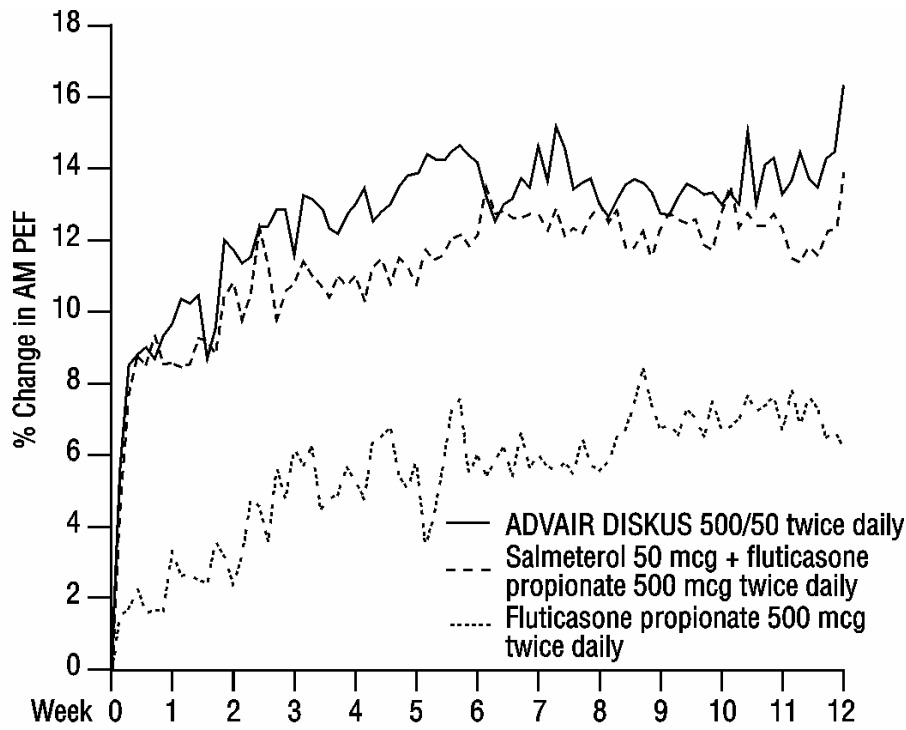
433 Efficacy results in this study were similar to those observed in Study 1. Patients receiving  
434 ADVAIR DISKUS 250/50 had significantly greater improvements in FEV<sub>1</sub> (0.48 L, 23%)  
435 compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and  
436 placebo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

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

452 Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50,  
453 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. As  
454 shown in Figure 2, morning PEF improved significantly with ADVAIR DISKUS 500/50  
455 compared with fluticasone propionate 500 mcg over the 12-week treatment period.  
456 Improvements in morning PEF observed with ADVAIR DISKUS 500/50 were similar to  
457 improvements observed with concurrent therapy.

458

459 **Figure 2. Mean Percent Change From Baseline in Morning Peak Expiratory**  
 460 **Flow in Patients With Asthma Previously Treated With Inhaled Corticosteroids**  
 461 **(Study 3)**  
 462



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

463  
464

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

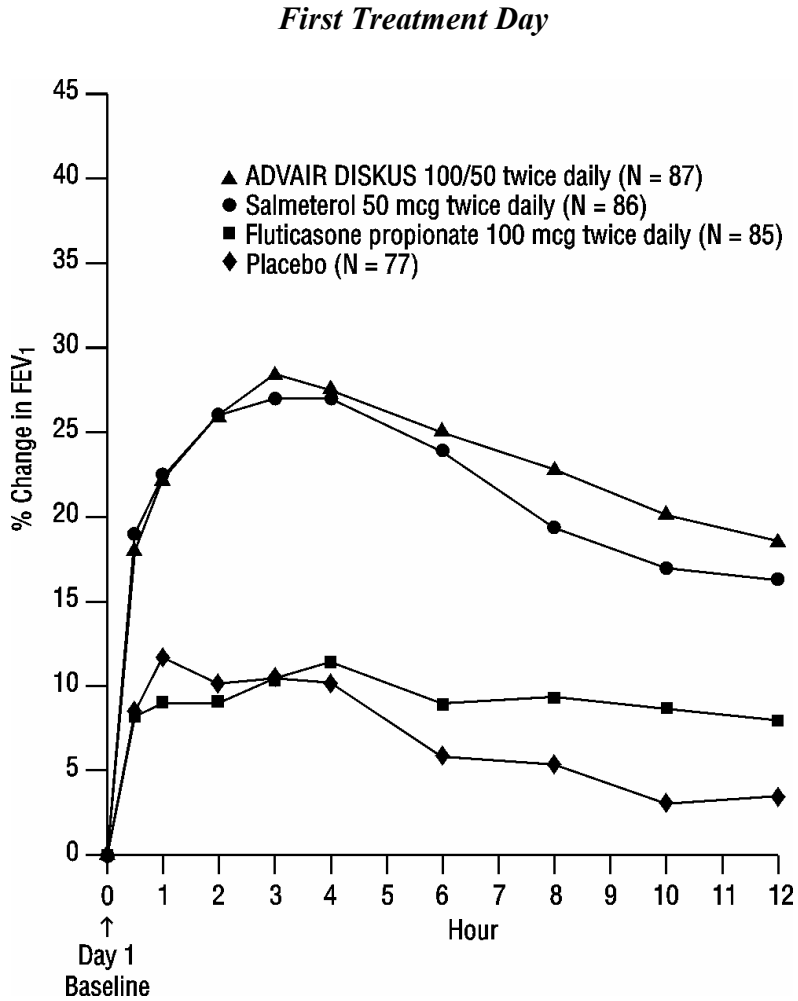
471 Following the initial dose, predose FEV<sub>1</sub> relative to Day 1 baseline improved markedly over  
 472 the first week of treatment and continued to improve over the 12 weeks of treatment in both  
 473 studies.

474 No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR  
 475 DISKUS 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV<sub>1</sub> following  
 476 12 weeks of therapy.

477

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

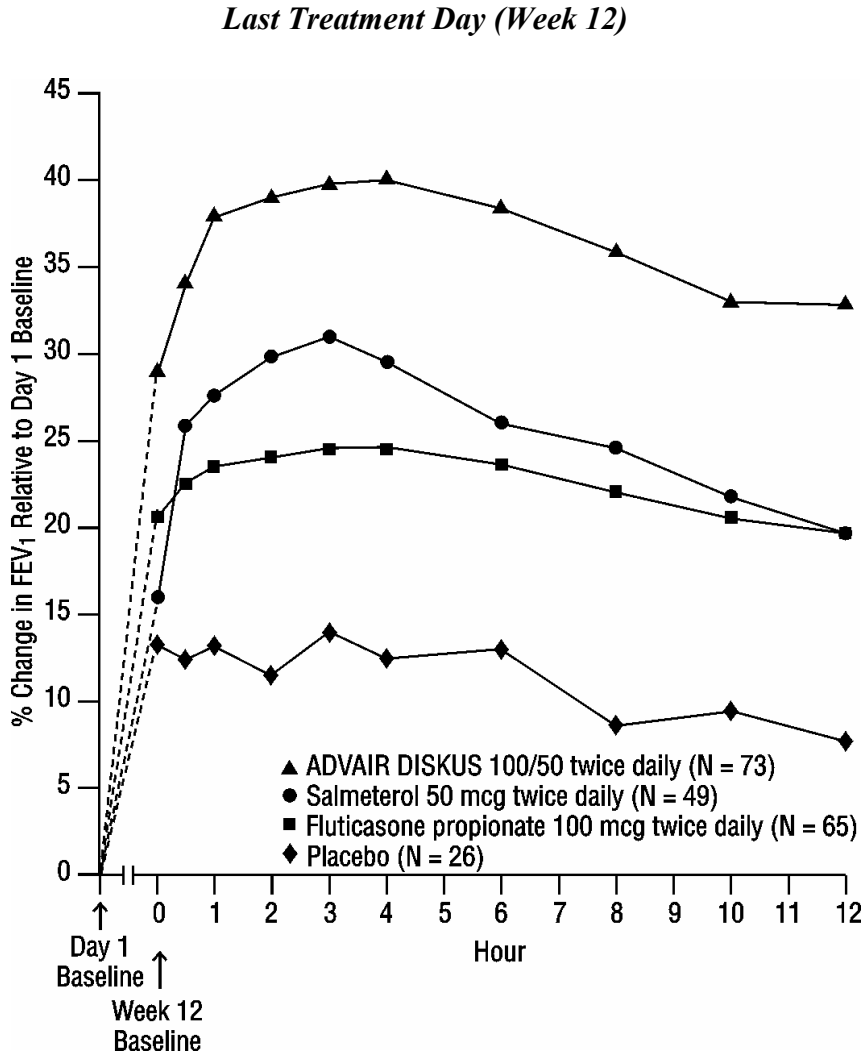
481  
482  
483



484  
485

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

489  
 490  
 491



492  
 493

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

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



504 100 mcg in this age-group; however, the study also included secondary efficacy measures of  
505 pulmonary function. Morning predose FEV<sub>1</sub> was obtained at baseline and Endpoint (last  
506 available FEV<sub>1</sub> result) in children aged 6 to 11 years. In patients receiving ADVAIR DISKUS  
507 100/50, FEV<sub>1</sub> increased from 1.70 L at baseline (N = 79) to 1.88 L at Endpoint (N = 69)  
508 compared with an increase from 1.65 L at baseline (N = 83) to 1.77 L at Endpoint (N = 75) in  
509 patients receiving fluticasone propionate 100 mcg.

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

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

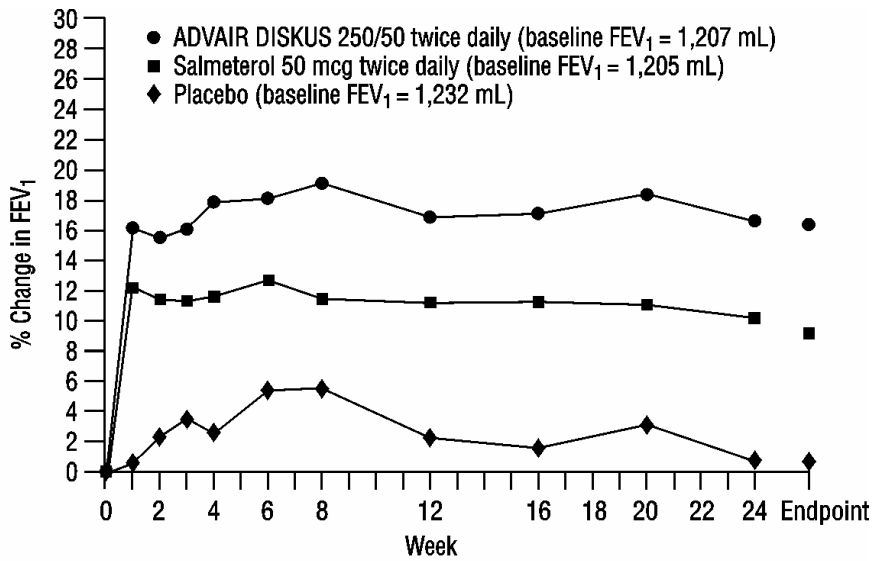
523 Figures 5 and 6 display predose and 2-hour postdose FEV<sub>1</sub> results. To account for patient  
524 withdrawals during the study, FEV<sub>1</sub> at Endpoint (last evaluable FEV<sub>1</sub>) was evaluated. Patients  
525 receiving ADVAIR DISKUS 250/50 had significantly greater improvements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

533 A similar degree of improvement in lung function was also observed with ADVAIR DISKUS  
534 500/50 twice daily.

535

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

538

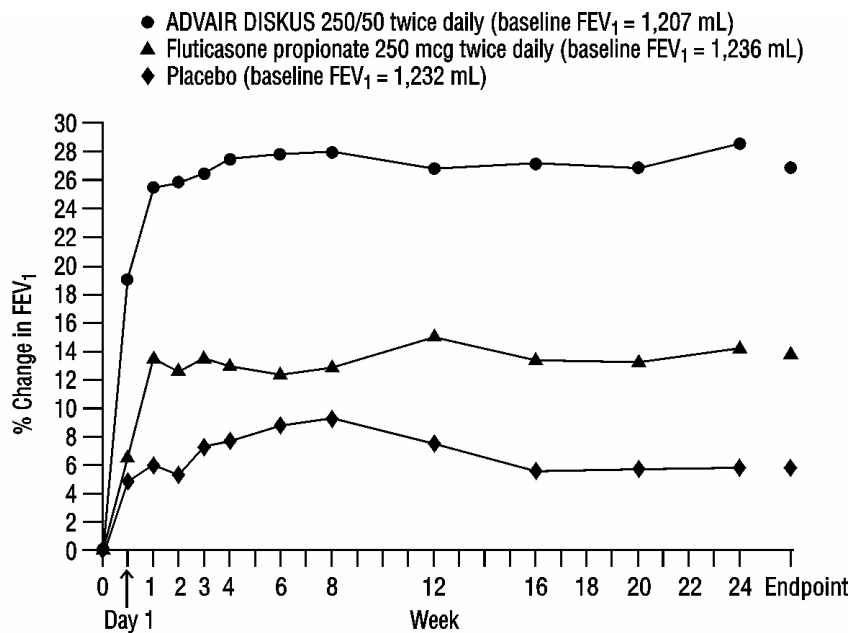


	<u>N</u>	<u>N</u>	<u>N</u>	<u>N</u>
ADVAIR DISKUS 250/50	178	144	124	171
Salmeterol 50 mcg	177	135	119	168
Placebo	185	139	125	172

539

540

541 **Figure 6. Two-Hour Postdose FEV<sub>1</sub>: Mean Percent Changes From Baseline**  
 542 **Over Time in Patients With COPD Associated With Chronic Bronchitis**  
 543



	<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

544  
 545  
 546 Patients treated with ADVAIR DISKUS 250/50 or ADVAIR DISKUS 500/50 did not have a  
 547 significant reduction in chronic bronchitis symptoms (as measured by the Chronic Bronchitis  
 548 Symptom Questionnaire) or in COPD exacerbations compared to patients treated with placebo  
 549 over the 24 weeks of therapy. The improvement in lung function with ADVAIR DISKUS 500/50  
 550 was similar to the improvement seen with ADVAIR DISKUS 250/50. Since there is evidence of  
 551 more systemic exposure to fluticasone propionate from this higher dose and no documented  
 552 advantage for efficacy, ADVAIR DISKUS 500/50 is not recommended for use in COPD.

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

555 **INDICATIONS AND USAGE**

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

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

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

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

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

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

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

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

## 572 **CONTRAINDICATIONS**

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

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

## 578 **WARNINGS**

579 DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS  
580 STOPPED EARLY SUGGEST THAT SALMETEROL, A COMPONENT OF ADVAIR  
581 DISKUS, MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR  
582 ASTHMA-RELATED DEATHS. The Salmeterol Multi-center Asthma Research Trial  
583 (SMART) enrolled long-acting beta<sub>2</sub>-agonist-naïve patients with asthma to assess the safety of  
584 salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared to  
585 placebo, when added to usual asthma therapy. The primary endpoint was the combined number  
586 of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and  
587 mechanical ventilation). Other endpoints included combined asthma-related deaths or  
588 life-threatening experiences and asthma-related deaths

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

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

605 Findings similar to the SMART study findings were reported in a prior 16-week clinical study  
606 performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the  
607 SNS study, the incidence of asthma-related death was numerically, though not statistically,  
608 greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol  
609 (180 mcg 4 times daily) added to usual asthma therapy.

610 Given the similar basic mechanisms of action of beta<sub>2</sub>-agonists, it is possible that the findings  
611 seen in the SMART study may be consistent with a class effect.

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

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

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

633 **2. ADVAIR DISKUS SHOULD NOT BE INITIATED IN PATIENTS DURING RAPIDLY**  
634 **DETERIORATING OR POTENTIALLY LIFE-THREATENING EPISODES OF**  
635 **ASTHMA. Serious acute respiratory events, including fatalities, have been reported both in**  
636 **the United States and worldwide when salmeterol, a component of ADVAIR DISKUS, has**  
637 **been initiated in patients with significantly worsening or acutely deteriorating asthma.** In  
638 most cases, these have occurred in patients with severe asthma (e.g., patients with a history of  
639 corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent  
640 hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients  
641 in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications;  
642 increasing need for inhaled, short-acting beta<sub>2</sub>-agonists; increasing need for systemic

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

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

657 **4. Do Not Use ADVAIR DISKUS to Treat Acute Symptoms:** An inhaled, short-acting  
658 beta<sub>2</sub>-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms of shortness of  
659 breath. When prescribing ADVAIR DISKUS, the physician must also provide the patient with an  
660 inhaled, short-acting beta<sub>2</sub>-agonist (e.g., albuterol) for treatment of shortness of breath that  
661 occurs acutely, despite regular twice-daily (morning and evening) use of ADVAIR DISKUS.

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

667 **5. Watch for Increasing Use of Inhaled, Short-Acting Beta<sub>2</sub>-Agonists, Which Is a Marker of**  
668 **Deteriorating Asthma:** Asthma may deteriorate acutely over a period of hours or chronically over  
669 several days or longer. If the patient's inhaled, short-acting beta<sub>2</sub>-agonist becomes less effective,  
670 the patient needs more inhalations than usual, or the patient develops a significant decrease in  
671 lung function, this may be a marker of destabilization of the disease. In this setting, the patient  
672 requires immediate reevaluation with reassessment of the treatment regimen, giving special  
673 consideration to the possible need for replacing the current strength of ADVAIR DISKUS with a  
674 higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids.  
675 Patients should not use more than 1 inhalation twice daily (morning and evening) of ADVAIR  
676 DISKUS.

677 **6. Do Not Use an Inhaled, Long-Acting Beta<sub>2</sub>-Agonist in Conjunction With ADVAIR DISKUS:**  
678 Patients who are receiving ADVAIR DISKUS twice daily should not use additional salmeterol  
679 or other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for prevention of exercise-induced  
680 bronchospasm (EIB) or the maintenance treatment of asthma or the maintenance treatment of  
681 bronchospasm associated with COPD. Additional benefit would not be gained from using

682 supplemental salmeterol or formoterol for prevention of EIB since ADVAIR DISKUS already  
683 contains an inhaled, long-acting beta<sub>2</sub>-agonist.

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

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

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

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

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

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

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

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

## 725 **PRECAUTIONS**

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

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

740 **Metabolic and Other Effects:** Long-term use of orally inhaled corticosteroids may affect  
741 normal bone metabolism, resulting in a loss of bone mineral density (BMD). A 2-year study of  
742 160 patients (females 18 to 40 and males 18 to 50 years of age) with asthma receiving  
743 chlorofluorocarbon-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice  
744 daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and  
745 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar  
746 region L1 through L4. Long-term treatment effects of fluticasone propionate on BMD in the  
747 COPD population have not been studied.

748 In patients with major risk factors for decreased bone mineral content, such as tobacco use,  
749 advanced age, sedentary lifestyle, poor nutrition, family history of osteoporosis, or chronic use of  
750 drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), ADVAIR DISKUS  
751 may pose an additional risk. Since patients with COPD often have multiple risk factors for  
752 reduced BMD, assessment of BMD is recommended, including prior to instituting ADVAIR  
753 DISKUS 250/50 and periodically thereafter. If significant reductions in BMD are seen and  
754 ADVAIR DISKUS 250/50 is still considered medically important for that patient's COPD  
755 therapy, use of medication to treat or prevent osteoporosis should be strongly considered.  
756 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of  
757 COPD associated with chronic bronchitis, and higher doses, including ADVAIR DISKUS  
758 500/50, are not recommended.

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



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

763 Lower respiratory tract infections, including pneumonia, have been reported following the  
764 inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR  
765 DISKUS.

766 Doses of the related beta<sub>2</sub>-adrenoceptor agonist albuterol, when administered intravenously,  
767 have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic  
768 agonist medications may produce significant hypokalemia in some patients, possibly through  
769 intracellular shunting, which has the potential to produce adverse cardiovascular effects. The  
770 decrease in serum potassium is usually transient, not requiring supplementation.

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

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

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

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

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

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

800 A 52-week, placebo-controlled study to assess the potential growth effects of fluticasone  
801 propionate inhalation powder (FLOVENT<sup>®</sup> ROTADISK<sup>®</sup>) at 50 and 100 mcg twice daily was  
802 conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to  
803 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were  
804 6.32 cm/year in the placebo group (N = 76), 6.07 cm/year in the 50-mcg group (N = 98), and  
805 5.66 cm/year in the 100-mcg group (N = 89). An imbalance in the proportion of children entering  
806 puberty between groups and a higher dropout rate in the placebo group due to poorly controlled  
807 asthma may be confounding factors in interpreting these data. A separate subset analysis of  
808 children who remained prepubertal during the study revealed growth rates at 52 weeks of  
809 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and  
810 5.67 cm/year in the 100-mcg group (n = 79). In children 8.5 years of age, the mean age of  
811 children in this study, the range for expected growth velocity is: boys – 3<sup>rd</sup>  
812 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 –  
813 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.

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

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

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

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

834 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a  
835 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some  
836 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a  
837 condition that is often treated with systemic corticosteroid therapy. These events usually, but not  
838 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy  
839 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions

840 have also been reported with other inhaled corticosteroids in this clinical setting. Physicians  
841 should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac  
842 complications, and/or neuropathy presenting in their patients. A causal relationship between  
843 fluticasone propionate and these underlying conditions has not been established (see ADVERSE  
844 REACTIONS: Observed During Clinical Practice: *Eosinophilic Conditions*).

845 **Chronic Obstructive Pulmonary Disease:** ADVAIR DISKUS 250/50 twice daily is the  
846 only dosage recommended for the treatment of airflow obstruction in patients with COPD  
847 associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50, are not  
848 recommended, as no additional improvement in lung function (defined by predose and postdose  
849 FEV<sub>1</sub>) was observed in clinical trials and higher doses of corticosteroids increase the risk of  
850 systemic effects.

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

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

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

- 862 1. Patients should use ADVAIR DISKUS at regular intervals as directed. Results of clinical  
863 trials indicate significant improvement may occur within the first 30 minutes of taking the  
864 first dose; however, the full benefit may not be achieved until treatment has been  
865 administered for 1 week or longer. The patient should not use more than the prescribed  
866 dosage but should contact the physician if symptoms do not improve or if the condition  
867 worsens.
- 868 2. Most patients are able to taste or feel a dose delivered from ADVAIR DISKUS. However,  
869 whether or not patients are able to sense delivery of a dose, you should instruct them not to  
870 exceed the recommended dose of 1 inhalation each morning and evening, approximately 12  
871 hours apart. You should instruct them to contact you or the pharmacist if they have questions.
- 872 3. The bronchodilation from a single dose of ADVAIR DISKUS may last up to 12 hours or  
873 longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not  
874 be exceeded. Patients who are receiving ADVAIR DISKUS twice daily should not use  
875 salmeterol or other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for prevention of  
876 EIB or maintenance treatment of asthma or the maintenance treatment of bronchospasm in  
877 COPD.
- 878 4. ADVAIR DISKUS is not meant to relieve acute asthma symptoms and extra doses should  
879 not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting

- 880 beta<sub>2</sub>-agonist such as albuterol (the physician should provide the patient with such  
881 medication and instruct the patient in how it should be used). ADVAIR DISKUS is not  
882 meant to relieve acute asthma symptoms or exacerbations of COPD.
- 883 5. Patients should not stop therapy with ADVAIR DISKUS without physician/provider  
884 guidance since symptoms may recur after discontinuation.
- 885 6. The physician should be notified immediately if any of the following situations occur, which  
886 may be a sign of seriously worsening asthma:
- 887 • decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonists;
  - 888 • need for more inhalations than usual of inhaled, short-acting beta<sub>2</sub>-agonists;
  - 889 • significant decrease in lung function as outlined by the physician.
- 890 7. Patients should be cautioned regarding common adverse effects associated with  
891 beta<sub>2</sub>-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 892 8. Patients who are at an increased risk for decreased BMD should be advised that the use of  
893 corticosteroids may pose an additional risk and should be told to monitor and, where  
894 appropriate, seek treatment for this condition.
- 895 9. Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of  
896 ADVAIR DISKUS, may increase the risk of some eye problems (cataracts or glaucoma).  
897 Regular eye examinations should be considered.
- 898 10. When patients are prescribed ADVAIR DISKUS, other medications for asthma and COPD  
899 should be used only as directed by their physicians.
- 900 11. ADVAIR DISKUS should not be used with a spacer device.
- 901 12. Patients who are pregnant or nursing should contact their physicians about the use of  
902 ADVAIR DISKUS.
- 903 13. Effective and safe use of ADVAIR DISKUS includes an understanding of the way that it  
904 should be used:
- 905 • Never exhale into the DISKUS.
  - 906 • Never attempt to take the DISKUS apart.
  - 907 • Always activate and use the DISKUS in a level, horizontal position.
  - 908 • After inhalation, rinse the mouth with water without swallowing.
  - 909 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
  - 910 • Always keep the DISKUS in a dry place.
  - 911 • Discard **1 month** after removal from the moisture-protective foil overwrap pouch or after  
912 all blisters have been used (when the dose indicator reads “0”), whichever comes first.
- 913 14. Patients should be warned to avoid exposure to chickenpox or measles and, if they are  
914 exposed, to consult their physicians without delay.
- 915 15. For the proper use of ADVAIR DISKUS and to attain maximum improvement, the patient  
916 should read and carefully follow the Patient’s Instructions for Use accompanying the  
917 product.
- 918 **Drug Interactions:** ADVAIR DISKUS has been used concomitantly with other drugs,  
919 including short-acting beta<sub>2</sub>-agonists, methylxanthines, and intranasal corticosteroids, commonly

920 used in patients with asthma or COPD, without adverse drug reactions. No formal drug  
921 interaction studies have been performed with ADVAIR DISKUS.

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

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

933 **Methylxanthines:** The concurrent use of intravenously or orally administered  
934 methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent patients 12 years of  
935 age and older receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials  
936 with patients with asthma, 39 patients receiving ADVAIR DISKUS 100/50, 250/50, or 500/50  
937 twice daily concurrently with a theophylline product had adverse event rates similar to those in  
938 304 patients receiving ADVAIR DISKUS without theophylline. Similar results were observed in  
939 patients receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily  
940 concurrently with a theophylline product (N = 39) or without theophylline (N = 132).

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

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

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

955 **Beta-Adrenergic Receptor Blocking Agents:** Beta-blockers not only block the  
956 pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, but  
957 may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma  
958 should not normally be treated with beta-blockers. However, under certain circumstances, there  
959 may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with

960 asthma. In this setting, cardioselective beta-blockers could be considered, although they should  
961 be administered with caution.

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

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

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

984 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate:**  
985 Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to  
986 1,000 mcg/kg (approximately 4 and 10 times, respectively, the maximum recommended daily  
987 inhalation dose in adults and children on a mcg/m<sup>2</sup> basis) for 78 weeks or in rats at inhalation  
988 doses up to 57 mcg/kg (less than and approximately equivalent to, respectively, the maximum  
989 recommended daily inhalation dose in adults and children on a mcg/m<sup>2</sup> basis) for 104 weeks.

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

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

997 **Salmeterol:** In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of  
998 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose  
999 in adults and children based on comparison of the plasma area under the curves [AUCs]) caused

1000 a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular  
1001 hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of  
1002 leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg  
1003 (approximately 3 times the maximum recommended daily inhalation doses in adults and children  
1004 based on comparison of the AUCs).

1005 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol  
1006 caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at  
1007 doses of 0.68 mg/kg and above (approximately 55 and 25 times, respectively, the maximum  
1008 recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis). No tumors were  
1009 seen at 0.21 mg/kg (approximately 15 and 8 times, respectively, the maximum recommended  
1010 daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis). These findings in rodents are  
1011 similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of  
1012 these findings to human use is unknown.

1013 Salmeterol produced no detectable or reproducible increases in microbial and mammalian  
1014 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo  
1015 in a rat micronucleus test. No effects on fertility were identified in male and female rats treated  
1016 with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum  
1017 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis).

1018 **Pregnancy: Teratogenic Effects: ADVAIR DISKUS:** Pregnancy Category C. From the  
1019 reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using  
1020 combinations of fluticasone propionate and salmeterol compared to toxicity data from the  
1021 components administered separately. In mice combining 150 mcg/kg subcutaneously of  
1022 fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a  
1023 mcg/m<sup>2</sup> basis) with 10 mg/kg orally of salmeterol (approximately 410 times the maximum  
1024 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis) was teratogenic. Cleft palate,  
1025 fetal death, increased implantation loss and delayed ossification were seen. These observations  
1026 are characteristic of glucocorticoids. No developmental toxicity was observed at combination  
1027 doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum  
1028 recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) and up to 1.4 mg/kg orally of  
1029 salmeterol (approximately 55 times the maximum recommended daily inhalation dose in adults  
1030 on a mg/m<sup>2</sup> basis). In rats, no teratogenicity was observed at combination doses up to 30 mcg/kg  
1031 subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation  
1032 dose in adults on a mcg/m<sup>2</sup> basis) and up to 1 mg/kg of salmeterol (approximately 80 times the  
1033 maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Combining  
1034 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the maximum recommended  
1035 daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) with 10 mg/kg orally of salmeterol  
1036 (approximately 810 times the maximum recommended daily inhalation dose in adults on a  
1037 mg/m<sup>2</sup> basis) produced maternal toxicity, decreased placental weight, decreased fetal weight,  
1038 umbilical hernia, delayed ossification, and changes in the occipital bone. There are no adequate  
1039 and well-controlled studies with ADVAIR DISKUS in pregnant women. ADVAIR DISKUS

1040 should be used during pregnancy only if the potential benefit justifies the potential risk to the  
1041 fetus.

1042 **Fluticasone Propionate:** Pregnancy Category C. Subcutaneous studies in the mouse  
1043 and rat at 45 and 100 mcg/kg (less than or equivalent to the maximum recommended daily  
1044 inhalation dose in adults on a mcg/m<sup>2</sup> basis), respectively, revealed fetal toxicity characteristic of  
1045 potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft  
1046 palate, and retarded cranial ossification.

1047 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of  
1048 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
1049 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg  
1050 (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
1051 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this  
1052 study, consistent with the established low bioavailability following oral administration (see  
1053 CLINICAL PHARMACOLOGY).

1054 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose  
1055 of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a  
1056 mcg/m<sup>2</sup> basis), administration of a subcutaneous or an oral dose of 100 mcg/kg to rats  
1057 (approximately equivalent to the maximum recommended daily inhalation dose in adults on a  
1058 mcg/m<sup>2</sup> basis), and administration of an oral dose of 300 mcg/kg to rabbits (approximately 5  
1059 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis).

1060 There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate  
1061 should be used during pregnancy only if the potential benefit justifies the potential risk to the  
1062 fetus.

1063 Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to  
1064 physiologic, doses suggests that rodents are more prone to teratogenic effects from  
1065 corticosteroids than humans. In addition, because there is a natural increase in corticosteroid  
1066 production during pregnancy, most women will require a lower exogenous corticosteroid dose  
1067 and many will not need corticosteroid treatment during pregnancy.

1068 **Salmeterol:** Pregnancy Category C. No teratogenic effects occurred in rats at oral doses  
1069 up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in  
1070 adults on a mg/m<sup>2</sup> basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and  
1071 above (approximately 50 times the maximum recommended daily inhalation dose in adults based  
1072 on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting  
1073 from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate,  
1074 sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones.  
1075 No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the  
1076 maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

1077 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal  
1078 bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the maximum  
1079 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Extensive use of other



1080 beta-agonists has provided no evidence that these class effects in animals are relevant to their use  
1081 in humans. There are no adequate and well-controlled studies with salmeterol in pregnant  
1082 women. Salmeterol should be used during pregnancy only if the potential benefit justifies the  
1083 potential risk to the fetus.

1084 Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice  
1085 and rats (approximately 410 and 810 times, respectively, the maximum recommended daily  
1086 inhalation dose in adults on a mg/m<sup>2</sup> basis).

1087 **Use in Labor and Delivery:** There are no well-controlled human studies that have  
1088 investigated effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the  
1089 potential for beta-agonist interference with uterine contractility, use of ADVAIR DISKUS during  
1090 labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

1091 **Nursing Mothers:** Plasma levels of salmeterol, a component of ADVAIR DISKUS, after  
1092 inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There  
1093 are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known  
1094 whether fluticasone propionate, a component of ADVAIR DISKUS, is excreted in human breast  
1095 milk. However, other corticosteroids have been detected in human milk. Subcutaneous  
1096 administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the  
1097 maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) resulted in  
1098 measurable radioactivity in milk.

1099 Since there are no data from controlled trials on the use of ADVAIR DISKUS by nursing  
1100 mothers, a decision should be made whether to discontinue nursing or to discontinue ADVAIR  
1101 DISKUS, taking into account the importance of ADVAIR DISKUS to the mother.

1102 Caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.

1103 **Pediatric Use:** Use of ADVAIR DISKUS 100/50 in patients 4 to 11 years of age is supported  
1104 by extrapolation of efficacy data from older patients and by safety and efficacy data from a study  
1105 of ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years (see CLINICAL  
1106 TRIALS: Asthma: *Pediatric Patients* and ADVERSE REACTIONS: Asthma: *Pediatric*  
1107 *Patients*). The safety and effectiveness of ADVAIR DISKUS in children with asthma under  
1108 4 years of age have not been established.

1109 Controlled clinical studies have shown that orally inhaled corticosteroids may cause a  
1110 reduction in growth velocity in pediatric patients. This effect has been observed in the absence of  
1111 laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive  
1112 indicator of systemic corticosteroid exposure in pediatric patients than some commonly used  
1113 tests of HPA axis function. The long-term effects of this reduction in growth velocity associated  
1114 with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The  
1115 potential for “catch-up” growth following discontinuation of treatment with orally inhaled  
1116 corticosteroids has not been adequately studied.

1117 Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS,  
1118 may cause a reduction in growth velocity in children and adolescents (see PRECAUTIONS:  
1119 General: *Metabolic and Other Effects*). The growth of pediatric patients receiving orally inhaled

1120 corticosteroids, including ADVAIR DISKUS, should be monitored. If a child or adolescent on  
1121 any corticosteroid appears to have growth suppression, the possibility that he/she is particularly  
1122 sensitive to this effect of corticosteroids should be considered. The potential growth effects of  
1123 prolonged treatment should be weighed against the clinical benefits obtained. To minimize the  
1124 systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, each patient  
1125 should be titrated to the lowest strength that effectively controls his/her asthma (see DOSAGE  
1126 AND ADMINISTRATION: Asthma).

1127 **Geriatric Use:** Of the total number of patients in clinical studies of ADVAIR DISKUS for  
1128 asthma, 44 were 65 years of age or older and 3 were 75 years of age or older. Of the total  
1129 number of patients in a clinical study of ADVAIR DISKUS 250/50 for COPD, 85 were 65 years  
1130 of age or older and 31 were 75 years of age or older. For both diseases, no overall differences in  
1131 safety were observed between these patients and younger patients, and other reported clinical  
1132 experience, including studies of the individual components, has not identified differences in  
1133 responses between the elderly and younger patients, but greater sensitivity of some older  
1134 individuals cannot be ruled out. As with other products containing beta<sub>2</sub>-agonists, special caution  
1135 should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant  
1136 cardiovascular disease that could be adversely affected by beta<sub>2</sub>-agonists. Based on available  
1137 data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR  
1138 DISKUS in geriatric patients is warranted.

### 1139 **ADVERSE REACTIONS**

1140 **Asthma: *Adult and Adolescent Patients 12 Years of Age and Older:*** The incidence of  
1141 common adverse events in Table 3 is based upon 2 placebo-controlled, 12-week, US clinical  
1142 studies (Studies 1 and 2). A total of 705 adolescent and adult patients (349 females and 356  
1143 males) previously treated with salmeterol or inhaled corticosteroids were treated twice daily with  
1144 ADVAIR DISKUS (100/50- or 250/50-mcg doses), fluticasone propionate inhalation powder  
1145 (100- or 250-mcg doses), salmeterol inhalation powder 50 mcg, or placebo.

1146

1147 **Table 3. Overall Adverse Events With  $\geq 3\%$  Incidence in US Controlled Clinical Trials**  
 1148 **With ADVAIR DISKUS in Patients With Asthma**

Adverse Event	ADVAIR DISKUS 100/50 (N = 92) %	ADVAIR DISKUS 250/50 (N = 84) %	Fluticasone Propionate 100 mcg (N = 90) %	Fluticasone Propionate 250 mcg (N = 84) %	Salmeterol 50 mcg (N = 180) %	Placebo (N = 175) %
Ear, nose, & 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

1149  
 1150 Table 3 includes all events (whether considered drug-related or nondrug-related by the  
 1151 investigator) that occurred at a rate of 3% or greater in either of the groups receiving ADVAIR  
 1152 DISKUS and were more common than in the placebo group. In considering these data,  
 1153 differences in average duration of exposure should be taken into account. Rare cases of

1154 immediate and delayed hypersensitivity reactions, including rash and other rare events of  
1155 angioedema and bronchospasm, have been reported.

1156 These adverse reactions were mostly mild to moderate in severity.

1157 Other adverse events that occurred in the groups receiving ADVAIR DISKUS in these studies  
1158 with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1159 **Blood and Lymphatic:** Lymphatic signs and symptoms.

1160 **Cardiovascular:** Palpitations.

1161 **Drug Interaction, Overdose, and Trauma:** Muscle injuries, fractures, wounds and  
1162 lacerations, contusions and hematomas, burns.

1163 **Ear, Nose, and Throat:** Rhinorrhea/postnasal drip; ear, nose and throat infections; ear  
1164 signs and symptoms; nasal signs and symptoms; nasal sinus disorders; rhinitis; sneezing; nasal  
1165 irritation; blood in nasal mucosa.

1166 **Eye:** Keratitis and conjunctivitis, viral eye infections, eye redness.

1167 **Gastrointestinal:** Dental discomfort and pain, gastrointestinal signs and symptoms,  
1168 gastrointestinal infections, gastroenteritis, gastrointestinal disorders, oral ulcerations, oral  
1169 erythema and rashes, constipation, appendicitis, oral discomfort and pain.

1170 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1171 **Lower Respiratory:** Lower respiratory signs and symptoms, pneumonia, lower respiratory  
1172 infections.

1173 **Musculoskeletal:** Arthralgia and articular rheumatism; muscle stiffness, tightness, and  
1174 rigidity; bone and cartilage disorders.

1175 **Neurology:** Sleep disorders, tremors, hypnagogic effects, compressed nerve syndromes.

1176 **Non-Site Specific:** Allergies and allergic reactions, congestion, viral infections, pain, chest  
1177 symptoms, fluid retention, bacterial infections, wheeze and hives, unusual taste.

1178 **Skin:** Viral skin infections, urticaria, skin flakiness and acquired ichthyosis, disorders of  
1179 sweat and sebum, sweating.

1180 The incidence of common adverse events reported in Study 3, a 28-week, non-US clinical  
1181 study of 503 patients previously treated with inhaled corticosteroids who were treated twice daily  
1182 with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and  
1183 salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation  
1184 powder 500 mcg was similar to the incidences reported in Table 3.

1185 **Pediatric Patients: Pediatric Study:** ADVAIR DISKUS 100/50 was well tolerated in  
1186 clinical trials conducted in children with asthma aged 4 to 11 years. The incidence of common  
1187 adverse events in Table 4 is based upon a 12-week US study in 203 patients with asthma aged 4  
1188 to 11 years (74 females and 129 males) who were receiving inhaled corticosteroids at study entry  
1189 and were randomized to either ADVAIR DISKUS 100/50 or fluticasone propionate inhalation  
1190 powder 100 mcg twice daily.

1191

1192 **Table 4. Overall Adverse Events With  $\geq 3\%$  Incidence With ADVAIR DISKUS 100/50**  
 1193 **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

1194  
 1195 Table 4 includes all events (whether considered drug-related or nondrug-related by the  
 1196 investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS  
 1197 100/50.

1198 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The  
 1199 incidence of common adverse events in Table 5 is based upon 1 placebo-controlled, 24-week, US  
 1200 clinical trial in patients with COPD associated with chronic bronchitis. A total of 723 adult  
 1201 patients (266 females and 457 males) were treated twice daily with ADVAIR DISKUS 250/50,  
 1202 fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder 50 mcg, or  
 1203 placebo.  
 1204

1205 **Table 5. Overall Adverse Events With  $\geq 3\%$  Incidence With ADVAIR DISKUS 250/50**  
 1206 **in Patients With Chronic Obstructive Pulmonary Disease Associated With Chronic**  
 1207 **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

1208  
 1209 Table 5 includes all events (whether considered drug-related or nondrug-related by the  
 1210 investigator) that occurred at a rate of 3% or greater in the group receiving ADVAIR DISKUS  
 1211 250/50 and were more common than in the placebo group.

1212 These adverse reactions were mostly mild to moderate in severity.

1213 Other adverse events that occurred in the groups receiving ADVAIR DISKUS 250/50 with an  
 1214 incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

1215 **Cardiovascular:** Syncope.

1216 **Drug Interaction, Overdose, and Trauma:** Postoperative complications.

1217 **Ear, Nose, and Throat:** Ear, nose, and throat infections; ear signs and symptoms;  
 1218 laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection.

1219 **Endocrine and Metabolic:** Hypothyroidism.

1220 **Eye:** Dry eyes, eye infections.

1221 **Gastrointestinal:** Constipation, gastrointestinal signs and symptoms, oral lesions.

1222 **Hepatobiliary Tract and Pancreas:** Abnormal liver function tests.

1223 **Lower Respiratory:** Breathing disorders, lower respiratory signs and symptoms.  
1224 **Non-Site Specific:** Bacterial infections, candidiasis unspecified site, edema and swelling,  
1225 nonspecific conditions, viral infections.  
1226 **Psychiatry:** Situational disorders.  
1227 **Observed During Clinical Practice:** In addition to adverse events reported from clinical  
1228 trials, the following events have been identified during worldwide use of any formulation of  
1229 ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are  
1230 reported voluntarily from a population of unknown size, estimates of frequency cannot be made.  
1231 These events have been chosen for inclusion due to either their seriousness, frequency of  
1232 reporting, or causal connection to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol  
1233 or a combination of these factors.  
1234 In extensive US and worldwide postmarketing experience with salmeterol, a component of  
1235 ADVAIR DISKUS, serious exacerbations of asthma, including some that have been fatal, have  
1236 been reported. In most cases, these have occurred in patients with severe asthma and/or in some  
1237 patients in whom asthma has been acutely deteriorating (see WARNINGS no. 2), but they have  
1238 also occurred in a few patients with less severe asthma. It was not possible from these reports to  
1239 determine whether salmeterol contributed to these events or simply failed to relieve the  
1240 deteriorating asthma.  
1241 **Cardiovascular:** Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular  
1242 tachycardia), ventricular tachycardia.  
1243 **Ear, Nose, and Throat:** Aphonia, earache, facial and oropharyngeal edema, paranasal sinus  
1244 pain, throat soreness.  
1245 **Endocrine and Metabolic:** Cushing syndrome, Cushingoid features, growth velocity  
1246 reduction in children/adolescents, hypercorticism, hyperglycemia, weight gain, osteoporosis.  
1247 **Eye:** Cataracts, glaucoma.  
1248 **Gastrointestinal:** Abdominal pain, dyspepsia, xerostomia.  
1249 **Musculoskeletal:** Back pain, cramps, muscle spasm, myositis.  
1250 **Neurology:** Paresthesia, restlessness.  
1251 **Non-Site Specific:** Immediate and delayed hypersensitivity reaction (including very rare  
1252 anaphylactic reaction), pallor. Very rare anaphylactic reaction in patients with severe milk  
1253 protein allergy.  
1254 **Psychiatry:** Agitation, aggression, depression.  
1255 **Respiratory:** Chest congestion; chest tightness; dyspnea; immediate bronchospasm;  
1256 influenza; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory  
1257 symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.  
1258 **Skin:** Contact dermatitis, contusions, ecchymoses, photodermatitis.  
1259 **Urogenital:** Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal  
1260 candidiasis, vaginitis, vulvovaginitis.  
1261 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a  
1262 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some

1263 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a  
1264 condition that is often treated with systemic corticosteroid therapy. These events usually, but not  
1265 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy  
1266 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions  
1267 have also been reported with other inhaled corticosteroids in this clinical setting. While  
1268 ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid  
1269 therapy, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary  
1270 symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal  
1271 relationship between fluticasone propionate and these underlying conditions has not been  
1272 established (see PRECAUTIONS: General: *Eosinophilic Conditions*).

### 1273 **OVERDOSAGE**

1274 **ADVAIR DISKUS:** No deaths occurred in rats given an inhaled single-dose combination of  
1275 salmeterol 3.6 mg/kg (approximately 290 and 140 times, respectively, the maximum  
1276 recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis) and 1.9 mg/kg of  
1277 fluticasone propionate (approximately 15 and 35 times, respectively, the maximum  
1278 recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis).

1279 **Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in  
1280 signs/symptoms of hypercorticism (see PRECAUTIONS: General: *Metabolic and Other*  
1281 *Effects*). Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate  
1282 inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate inhalation  
1283 aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of  
1284 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated.  
1285 Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to  
1286 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or  
1287 moderate severity, and incidences were similar in active and placebo treatment groups. In mice,  
1288 the oral median lethal dose was >1,000 mg/kg (>4,100 and >9,600 times, respectively, the  
1289 maximum recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis). In rats  
1290 the subcutaneous median lethal dose was >1,000 mg/kg (>8,100 and >19,200 times,  
1291 respectively, the maximum recommended daily inhalation dose in adults and children on a  
1292 mg/m<sup>2</sup> basis).

1293 **Salmeterol:** The expected signs and symptoms with overdosage of salmeterol are those of  
1294 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and  
1295 symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or  
1296 hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache,  
1297 tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and  
1298 insomnia. Overdosage with salmeterol may be expected to result in exaggeration of the  
1299 pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia  
1300 and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead



1301 to clinically significant prolongation of the QTc interval, which can produce ventricular  
1302 arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.  
1303 As with all sympathomimetic medications, cardiac arrest and even death may be associated  
1304 with abuse of salmeterol.

1305 Treatment consists of discontinuation of salmeterol together with appropriate symptomatic  
1306 therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing  
1307 in mind that such medication can produce bronchospasm. There is insufficient evidence to  
1308 determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is  
1309 recommended in cases of overdosage.

1310 No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg  
1311 (approximately 240 times and 110 times, respectively, the maximum recommended daily  
1312 inhalation dose in adults and children on a mg/m<sup>2</sup> basis) and in dogs at an inhalation dose of  
1313 0.7 mg/kg (approximately 190 and 90 times, respectively, the maximum recommended daily  
1314 inhalation dose in adults and children on a mg/m<sup>2</sup> basis). By the oral route, no deaths occurred in  
1315 mice at 150 mg/kg (approximately 6,100 and 2,900 times, respectively, the maximum  
1316 recommended daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis) and in rats at  
1317 1,000 mg/kg (approximately 81,000 and 38,000 times, respectively, the maximum recommended  
1318 daily inhalation dose in adults and children on a mg/m<sup>2</sup> basis).

## 1319 **DOSAGE AND ADMINISTRATION**

1320 ADVAIR DISKUS should be administered by the orally inhaled route only (see Patient's  
1321 Instructions For Use). After inhalation, the patient should rinse the mouth with water without  
1322 swallowing. ADVAIR DISKUS should not be used for transferring patients from systemic  
1323 corticosteroid therapy.

1324 **Asthma:** ADVAIR DISKUS is available in 3 strengths, ADVAIR DISKUS 100/50, ADVAIR  
1325 DISKUS 250/50, and ADVAIR DISKUS 500/50, containing 100, 250, and 500 mcg of  
1326 fluticasone propionate, respectively, and 50 mcg of salmeterol per inhalation.

1327 ADVAIR DISKUS should be administered twice daily every day. More frequent  
1328 administration (more than twice daily) or a higher number of inhalations (more than 1 inhalation  
1329 twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some  
1330 patients are more likely to experience adverse effects with higher doses of salmeterol. The safety  
1331 and efficacy of ADVAIR DISKUS when administered in excess of recommended doses have not  
1332 been established.

1333 If symptoms arise in the period between doses, an inhaled, short-acting beta<sub>2</sub>-agonist should  
1334 be taken for immediate relief.

1335 Patients who are receiving ADVAIR DISKUS twice daily should not use additional  
1336 salmeterol or other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for prevention of EIB,  
1337 or for any other reason.

1338 **Adult and Adolescent Patients 12 Years of Age and Older:** For patients 12 years of  
 1339 age and older, the dosage is 1 inhalation twice daily (morning and evening, approximately  
 1340 12 hours apart).

1341 The recommended starting dosages for ADVAIR DISKUS for patients 12 years of age and  
 1342 older are based upon patients' current asthma therapy.

- 1343 • For patients who are not currently on an inhaled corticosteroid, whose disease severity  
 1344 warrants treatment with 2 maintenance therapies, including patients on non-corticosteroid  
 1345 maintenance therapy, the recommended starting dosage is ADVAIR DISKUS 100/50 twice  
 1346 daily.
- 1347 • For patients on an inhaled corticosteroid, Table 6 provides the recommended starting dosage.  
 1348 The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

1349 **For all patients it is desirable to titrate to the lowest effective strength after adequate**  
 1350 **asthma stability is achieved.**

1351

1352 **Table 6. Recommended Dosages of ADVAIR DISKUS for Patients With Asthma Aged 12**  
 1353 **Years and Older Taking Inhaled Corticosteroids**

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

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

1354

1355 Improvement in asthma control following inhaled administration of ADVAIR DISKUS can  
 1356 occur within 30 minutes of beginning treatment, although maximum benefit may not be

1357 achieved for 1 week or longer after starting treatment. Individual patients will experience a  
1358 variable time to onset and degree of symptom relief.

1359 For patients who do not respond adequately to the starting dosage after 2 weeks of therapy,  
1360 replacing the current strength of ADVAIR DISKUS with a higher strength may provide  
1361 additional improvement in asthma control.

1362 If a previously effective dosage regimen of ADVAIR DISKUS fails to provide adequate  
1363 improvement in asthma control, the therapeutic regimen should be reevaluated and additional  
1364 therapeutic options, e.g., replacing the current strength of ADVAIR DISKUS with a higher  
1365 strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be  
1366 considered.

1367 **Pediatric Patients:** For patients aged 4 to 11 years who are symptomatic on an inhaled  
1368 corticosteroid the dosage is 1 inhalation of ADVAIR DISKUS 100/50 twice daily (morning and  
1369 evening, approximately 12 hours apart).

1370 **Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis:** The  
1371 dosage for adults is 1 inhalation (250/50 mcg) twice daily (morning and evening, approximately  
1372 12 hours apart).

1373 ADVAIR DISKUS 250/50 mcg twice daily is the only approved dosage for the treatment of  
1374 COPD associated with chronic bronchitis. Higher doses, including ADVAIR DISKUS 500/50,  
1375 are not recommended, as no additional improvement in lung function was observed in clinical  
1376 trials and higher doses of corticosteroids increase the risk of systemic effects.

1377 If shortness of breath occurs in the period between doses, an inhaled, short-acting  
1378 beta<sub>2</sub>-agonist should be taken for immediate relief.

1379 Patients who are receiving ADVAIR DISKUS twice daily should not use additional  
1380 salmeterol or other inhaled, long-acting beta<sub>2</sub>-agonists (e.g., formoterol) for the maintenance  
1381 treatment of COPD or for any other reason.

1382 **Geriatric Use:** In studies where geriatric patients (65 years of age or older, see  
1383 PRECAUTIONS: Geriatric Use) have been treated with ADVAIR DISKUS, efficacy and safety  
1384 did not differ from that in younger patients. Based on available data for ADVAIR DISKUS and  
1385 its active components, no dosage adjustment is recommended.

1386 **Directions for Use:** Illustrated Patient's Instructions for Use accompany each package of  
1387 ADVAIR DISKUS.

## 1388 HOW SUPPLIED

1389 ADVAIR DISKUS 100/50 is supplied as a disposable, purple device containing 60 blisters.  
1390 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective  
1391 foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional  
1392 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS  
1393 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch  
1394 (NDC 0173-0695-02).

1395 ADVAIR DISKUS 250/50 is supplied as a disposable, purple device containing 60 blisters.  
1396 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective  
1397 foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional  
1398 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS  
1399 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch  
1400 (NDC 0173-0696-02).

1401 ADVAIR DISKUS 500/50 is supplied as a disposable, purple device containing 60 blisters.  
1402 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective  
1403 foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional  
1404 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS  
1405 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch  
1406 (NDC 0173-0697-02).

1407 **Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F), in a dry place**  
1408 **away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation**  
1409 **device is not reusable. The device should be discarded 1 month after removal from the**  
1410 **moisture-protective foil overwrap pouch or after all blisters have been used (when the dose**  
1411 **indicator reads “0”), whichever comes first. Do not attempt to take the device apart.**  
1412  
1413



GlaxoSmithKline

1414  
1415 GlaxoSmithKline  
1416 Research Triangle Park, NC 27709  
1417

1418 ©2004, GlaxoSmithKline. All rights reserved.  
1419

1420 April 2004

RL-2085