

PRESCRIBING INFORMATION

**ADVAIR DISKUS<sup>®</sup> 100/50**

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

**ADVAIR DISKUS<sup>®</sup> 250/50**

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

**ADVAIR DISKUS<sup>®</sup> 500/50**

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

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

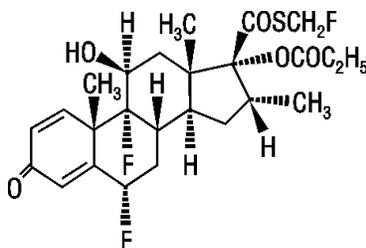
**For Oral Inhalation Only**

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

**DESCRIPTION**

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

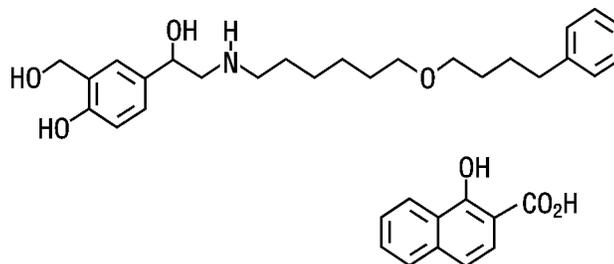
One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having the chemical name *S*-(fluoromethyl) 6 $\alpha$ ,9-difluoro-11 $\beta$ ,17-dihydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and 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 dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

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

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



38  
39

40 Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8, and the  
41 empirical formula is C<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>•C<sub>11</sub>H<sub>8</sub>O<sub>3</sub>. It is freely soluble in methanol; slightly soluble in  
42 ethanol, chloroform, and isopropanol; and sparingly soluble in water.

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

52 Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg  
53 of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS  
54 100/50, 250/50, and 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds.  
55 In adult patients (N = 9) with obstructive lung disease and severely compromised lung function  
56 (mean forced expiratory volume in 1 second [FEV<sub>1</sub>] 20% to 30% of predicted), mean peak  
57 inspiratory flow (PIF) through a DISKUS<sup>®</sup> device was 80.0 L/min (range, 46.1 to 115.3 L/min).

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

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

## 63 CLINICAL PHARMACOLOGY

64 **Mechanism of Action: ADVAIR DISKUS:** ADVAIR DISKUS is designed to produce a  
65 greater improvement in pulmonary function and symptom control than either fluticasone  
66 propionate or salmeterol used alone at their recommended dosages. Since ADVAIR DISKUS  
67 contains both fluticasone propionate and salmeterol, the mechanisms of action described below

68 for the individual components apply to ADVAIR DISKUS. These drugs represent 2 classes of  
69 medications (a synthetic corticosteroid and a long-acting beta-adrenergic receptor agonist) that  
70 have different effects on clinical, physiological, and inflammatory indices of asthma.

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

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

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

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

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

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

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

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

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

128 **Special Populations:** Formal pharmacokinetic studies using ADVAIR DISKUS were  
129 not conducted to examine gender differences or in special populations, such as elderly patients or  
130 patients with hepatic or renal impairment.

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

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

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

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

148 The percentage of fluticasone propionate bound to human plasma proteins averages 91%.  
149 Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly  
150 bound to human transcortin.

151 **Metabolism:** The total clearance of fluticasone propionate is high (average,  
152 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only  
153 circulating metabolite detected in man is the 17 $\beta$ -carboxylic acid derivative of fluticasone  
154 propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had  
155 less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of  
156 human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other  
157 metabolites detected in vitro using cultured human hepatoma cells have not been detected in  
158 man.

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

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

167 **Gender:** Full pharmacokinetic profiles were obtained from 9 female and 16 male  
168 patients given fluticasone propionate inhalation powder 500 mcg twice daily using the DISKUS.  
169 No overall differences in fluticasone propionate pharmacokinetics were observed.

170 **Other:** Formal pharmacokinetic studies using fluticasone propionate were not carried  
171 out in other special populations.

172 **Drug Interactions:** In a multiple-dose drug interaction study, coadministration of  
173 fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not  
174 affect fluticasone propionate pharmacokinetics. In another drug interaction study,  
175 coadministration of fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily)  
176 resulted in increased fluticasone propionate concentrations and reduced plasma cortisol area  
177 under the plasma concentration versus time curve (AUC), but had no effect on urinary excretion  
178 of cortisol. Since fluticasone propionate is a substrate of cytochrome P450 3A4, caution should  
179 be exercised when cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole) are  
180 coadministered with fluticasone propionate as this could result in increased plasma  
181 concentrations of fluticasone propionate.

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

186 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low  
187 or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder

188 twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol  
189 inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7  
190 patients with asthma; plasma concentrations were very low, with mean peak concentrations of  
191 167 pg/mL at 20 minutes and no accumulation with repeated doses.

192 **Distribution:** Binding of salmeterol to human plasma proteins averages 96% in vitro over  
193 the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher  
194 concentrations than those achieved following therapeutic doses of salmeterol.

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

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

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

204 **Special Populations:** Formal pharmacokinetic studies of salmeterol base have not been  
205 conducted in special populations. Since salmeterol is predominantly cleared by hepatic  
206 metabolism, impairment of liver function may lead to accumulation of salmeterol in plasma.  
207 Therefore, patients with hepatic disease should be closely monitored.

208 **Pharmacodynamics: ADVAIR DISKUS:** Since systemic pharmacodynamic effects of  
209 salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce  
210 measurable effects. Four studies were conducted in healthy subjects: (1) a single-dose crossover  
211 study using 2 inhalations of ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg  
212 and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg  
213 given alone, (2) a cumulative dose study using 50 to 400 mcg of salmeterol powder given alone  
214 or as ADVAIR DISKUS 500/50, (3) a repeat-dose study for 11 days using 2 inhalations twice  
215 daily of ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, or salmeterol  
216 powder 50 mcg, and (4) a single-dose study using 5 inhalations of ADVAIR DISKUS 100/50,  
217 fluticasone propionate powder 100 mcg alone, or placebo. In these studies no significant  
218 differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood  
219 pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as ADVAIR  
220 DISKUS, concurrently with fluticasone propionate from separate inhalers, or as salmeterol alone.  
221 The systemic pharmacodynamic effects of salmeterol were not altered by the presence of  
222 fluticasone propionate in ADVAIR DISKUS. The potential effect of salmeterol on the effects of  
223 fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis was also evaluated in  
224 these studies. No significant differences across treatments were observed in 24-hour urinary  
225 cortisol excretion and, where measured, 24-hour plasma cortisol AUC. The systemic  
226 pharmacodynamic effects of fluticasone propionate were not altered by the presence of  
227 salmeterol in ADVAIR DISKUS in healthy subjects.

228 In clinical studies with ADVAIR DISKUS in patients with asthma, no significant differences  
229 were observed in the systemic pharmacodynamic effects of salmeterol (pulse rate, blood  
230 pressure, QTc interval, potassium, and glucose) whether the salmeterol was given alone or as  
231 ADVAIR DISKUS. In 72 adolescent and adult patients with asthma given either ADVAIR  
232 DISKUS 100/50 or ADVAIR DISKUS 250/50, continuous 24-hour electrocardiographic  
233 monitoring was performed after the first dose and after 12 weeks of therapy, and no clinically  
234 significant dysrhythmias were noted.

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

240 In a 12-week study in patients with asthma, ADVAIR DISKUS 250/50 twice daily was  
241 compared with fluticasone propionate powder 250 mcg alone, salmeterol powder 50 mcg alone,  
242 and placebo. For most patients, the ability to increase cortisol production in response to stress, as  
243 assessed by 30-minute cosyntropin stimulation, remained intact with ADVAIR DISKUS. One  
244 patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal response (peak serum  
245 cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who received placebo,  
246 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients who received  
247 salmeterol.

248 **Fluticasone Propionate:** In clinical trials with fluticasone propionate inhalation powder  
249 using doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin  
250 tests (peak serum cortisol <18 mcg/dL) were noted both in patients receiving fluticasone  
251 propionate and in patients receiving placebo. The incidence of abnormal tests at 500 mcg twice  
252 daily was greater than placebo. In a 2-year study carried out in 64 patients with mild, persistent  
253 asthma (mean FEV<sub>1</sub> 91% of predicted) randomized to fluticasone propionate 500 mcg twice  
254 daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6-hour  
255 cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of  
256 <35 mcg/dL, 1 patient receiving fluticasone propionate (4%) had an abnormal response at  
257 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone  
258 propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal  
259 response at 1 or 2 years.

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

265 The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied  
266 in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as  
267 inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as

268 albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and adult  
269 patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent continuous  
270 electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month  
271 of therapy, and no clinically significant dysrhythmias were noted.

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

## 276 **CLINICAL TRIALS**

277 In clinical trials comparing ADVAIR DISKUS with the individual components,  
278 improvements in most efficacy endpoints were greater with ADVAIR DISKUS than with the use  
279 of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar  
280 results between ADVAIR DISKUS and the concurrent use of fluticasone propionate plus  
281 salmeterol at corresponding doses from separate inhalers.

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

288 **Study 1: Clinical Trial With ADVAIR DISKUS 100/50:** This placebo-controlled,  
289 12-week, US study compared ADVAIR DISKUS 100/50 with its individual components,  
290 fluticasone propionate 100 mcg and salmeterol 50 mcg. The study was stratified according to  
291 baseline asthma maintenance therapy; patients were using either inhaled corticosteroids  
292 (N = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg;  
293 fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg)  
294 or salmeterol (N = 106). Baseline FEV<sub>1</sub> measurements were similar across treatments: ADVAIR  
295 DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and  
296 placebo, 2.15 L.

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

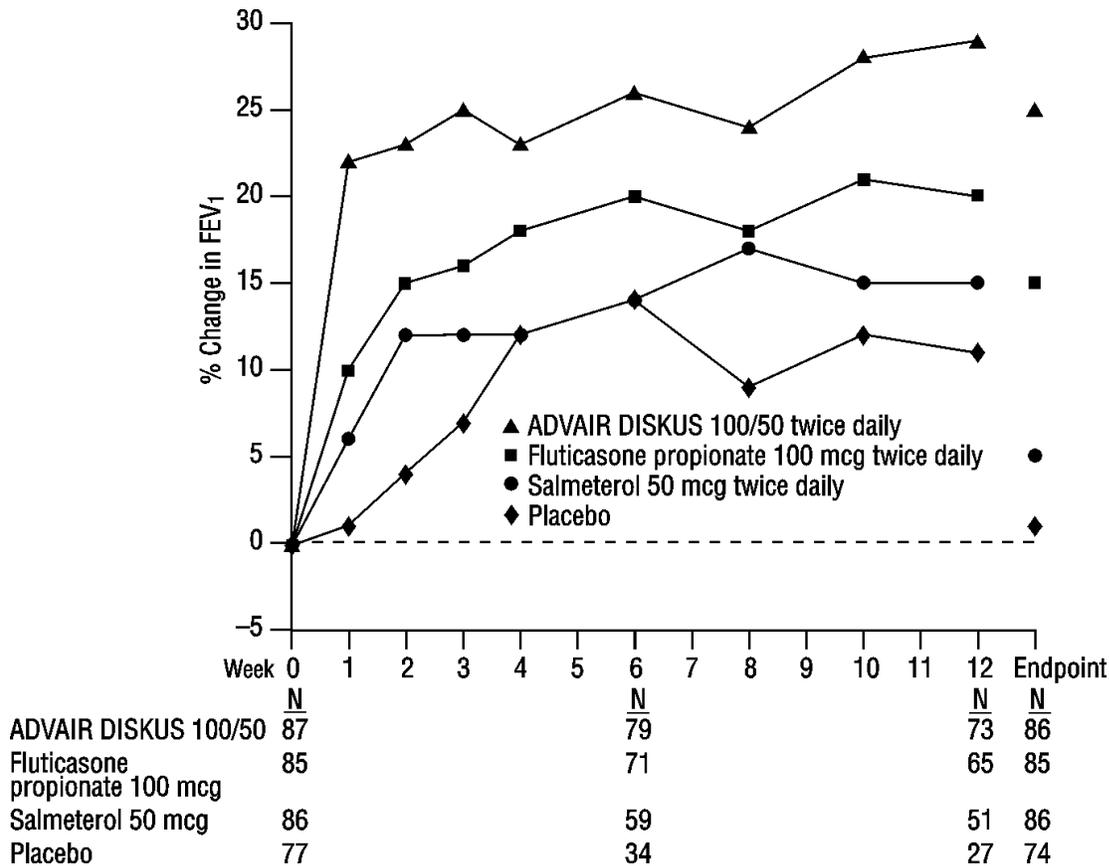
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306 **Table 1. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously**  
307 **Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**

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

308  
309 The FEV<sub>1</sub> results are displayed in Figure 1. Because this trial used predetermined criteria for  
310 worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV<sub>1</sub>  
311 results at Endpoint (last available FEV<sub>1</sub> result) are also provided. Patients receiving ADVAIR  
312 DISKUS 100/50 had significantly greater improvements in FEV<sub>1</sub> (0.51 L, 25%) compared with  
313 fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L,  
314 1%). These improvements in FEV<sub>1</sub> with ADVAIR DISKUS were achieved regardless of baseline  
315 asthma maintenance therapy (inhaled corticosteroids or salmeterol).

316  
317 **Figure 1. Mean Percent Change From Baseline in FEV<sub>1</sub> in Patients Previously**  
318 **Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**



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322

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

325

326 **Table 2. Peak Expiratory Flow Results for Patients Previously Treated With Either Inhaled**  
327 **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

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

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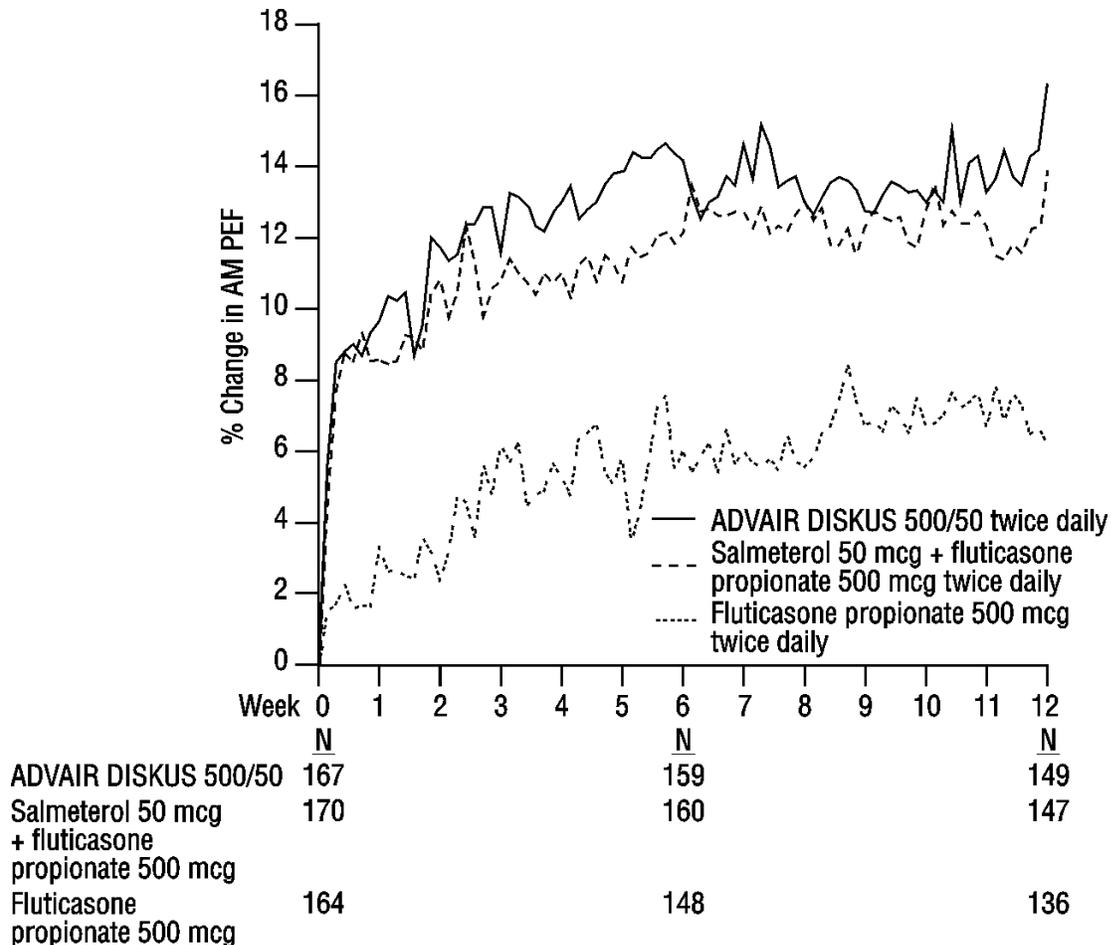
330 The subjective impact of asthma on patients' perception of health was evaluated through use  
331 of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point  
332 scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR DISKUS  
333 100/50 had clinically meaningful improvements in overall asthma-specific quality of life as  
334 defined by a difference between groups of  $\geq 0.5$  points in change from baseline AQLQ scores  
335 (difference in AQLQ score of 1.25 compared to placebo).

336 **Study 2: Clinical Trial With ADVAIR DISKUS 250/50:** This placebo-controlled,  
337 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components,  
338 fluticasone propionate 250 mcg and salmeterol 50 mcg in 349 patients using inhaled  
339 corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to  
340 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100  
341 to 1,600 mcg). Baseline FEV<sub>1</sub> measurements were similar across treatments: ADVAIR DISKUS  
342 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

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

353        **Study 3: Clinical Trial With ADVAIR DISKUS 500/50:** This 28-week, non-US study  
354 compared ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and concurrent  
355 therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from separate  
356 inhalers) twice daily in 503 patients using inhaled corticosteroids (daily doses of beclomethasone  
357 dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to  
358 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750 to 1,000 mcg  
359 inhalation powder]). The primary efficacy parameter, morning PEF, was collected daily for the  
360 first 12 weeks of the study. The primary purpose of weeks 13 to 28 was to collect safety data.  
361        Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50,  
362 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. As  
363 shown in Figure 2, morning PEF improved significantly with ADVAIR DISKUS 500/50  
364 compared with fluticasone propionate 500 mcg over the 12-week treatment period.  
365 Improvements in morning PEF observed with ADVAIR DISKUS 500/50 were similar to  
366 improvements observed with concurrent therapy.  
367

368 **Figure 2. Mean Percent Change From Baseline in Morning Peak Expiratory**  
 369 **Flow in Patients Previously Treated With Inhaled Corticosteroids (Study 3)**  
 370  
 371



372  
 373

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

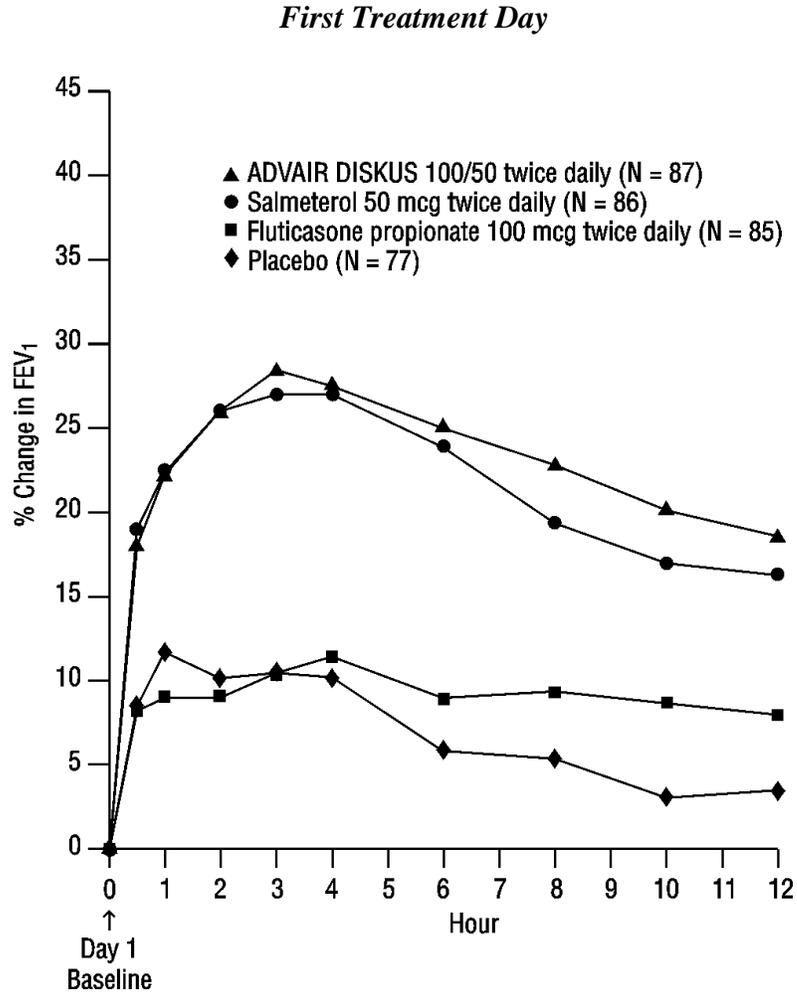
380 Following the initial dose, predose FEV<sub>1</sub> relative to day 1 baseline improved markedly over  
 381 the first week of treatment and continued to improve over the 12 weeks of treatment in both  
 382 studies.

383 No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR  
 384 DISKUS 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV<sub>1</sub> following  
 385 12 weeks of therapy.

386

387 **Figure 3. Percent Change in Serial 12-hour FEV<sub>1</sub>**  
388 **in Patients Previously Using Either Inhaled**  
389 **Corticosteroids or Salmeterol (Study 1)**

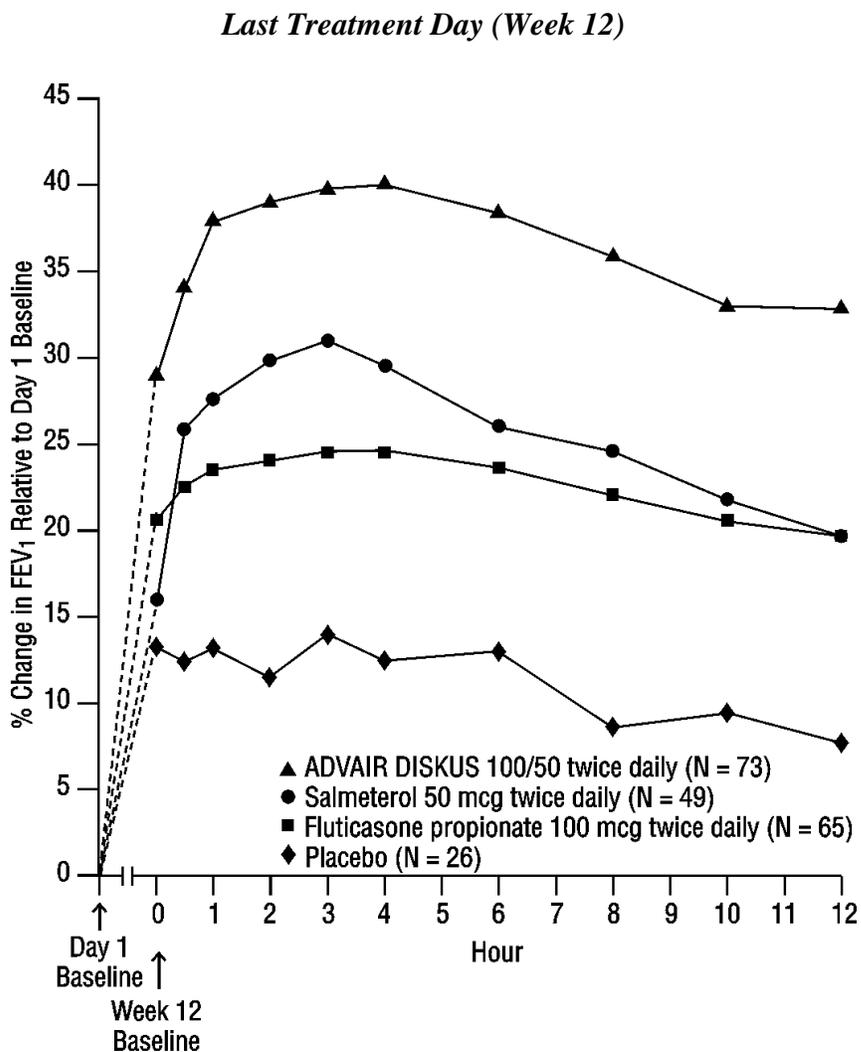
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395 **Figure 4. Percent Change in Serial 12-hour FEV<sub>1</sub>**  
396 **in Patients Previously Using Either Inhaled Corticosteroids**  
397 **or Salmeterol (Study 1)**

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401  
402

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

#### 406 **INDICATIONS AND USAGE**

407 ADVAIR DISKUS is indicated for the long-term, twice-daily, maintenance treatment of  
408 asthma in patients 12 years of age and older.

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

410 **CONTRAINDICATIONS**

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

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

416 **WARNINGS**

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

427 A planned interim analysis was conducted when approximately half of the intended number of  
428 patients had been enrolled (N = 26,353). The analysis showed no significant difference for the  
429 primary endpoint for the total population. However, a higher number of asthma-related deaths or  
430 life-threatening experiences (36 vs. 23) and a higher number of asthma-related deaths (13 vs. 4)  
431 occurred in the patients treated with SEREVENT Inhalation Aerosol. Post hoc subgroup analyses  
432 revealed no significant increase in respiratory- or asthma-related episodes, including deaths, in  
433 Caucasian patients. In African-Americans, the study showed a small, though statistically  
434 significantly greater, number of primary events (20 vs. 7), asthma-related deaths or  
435 life-threatening experiences (19 vs. 4), and asthma-related deaths (8 vs. 1) in patients taking  
436 SEREVENT Inhalation Aerosol compared to those taking placebo. Even though SMART did not  
437 reach predetermined stopping criteria for the total population, the study was stopped due to the  
438 findings in African-American patients and difficulties in enrollment. The data from the SMART  
439 study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as  
440 fluticasone propionate, a component of ADVAIR DISKUS, provides protection from this risk.  
441 Therefore, it is not known whether the findings seen with SEREVENT Inhalation Aerosol would  
442 apply to ADVAIR DISKUS.

443 Findings similar to the SMART study findings were reported in a prior 16-week clinical study  
444 performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the  
445 SNS study, the incidence of asthma-related death was numerically, though not statistically,  
446 greater in patients with asthma treated with salmeterol (42 mcg twice daily) versus albuterol  
447 (180 mcg 4 times daily) added to usual asthma therapy.

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

450 **1. ADVAIR DISKUS should not be used for transferring patients from systemic**  
451 **corticosteroid therapy.** Particular care is needed for patients who have been transferred from  
452 systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal  
453 insufficiency have occurred in patients with asthma during and after transfer from systemic  
454 corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from  
455 systemic corticosteroids, a number of months are required for recovery of HPA function.

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

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

470 **2. ADVAIR DISKUS SHOULD NOT BE INITIATED IN PATIENTS DURING RAPIDLY**  
471 **DETERIORATING OR POTENTIALLY LIFE-THREATENING EPISODES OF**  
472 **ASTHMA. Serious acute respiratory events, including fatalities, have been reported both in**  
473 **the United States and worldwide when salmeterol, a component of ADVAIR DISKUS, has**  
474 **been initiated in patients with significantly worsening or acutely deteriorating asthma. In**  
475 most cases, these have occurred in patients with severe asthma (e.g., patients with a history of  
476 corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent  
477 hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients  
478 in whom asthma has been acutely deteriorating (e.g., unresponsive to usual medications;  
479 increasing need for inhaled, short-acting beta<sub>2</sub>-agonists; increasing need for systemic  
480 corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or  
481 progressive deterioration in pulmonary function). However, they have occurred in a few patients  
482 with less severe asthma as well. It was not possible from these reports to determine whether  
483 salmeterol contributed to these events or simply failed to relieve the deteriorating asthma.

484 **3. Do Not Use ADVAIR DISKUS to Treat Acute Symptoms:** An inhaled, short-acting  
485 beta<sub>2</sub>-agonist, not ADVAIR DISKUS, should be used to relieve acute asthma symptoms. When  
486 prescribing ADVAIR DISKUS, the physician must also provide the patient with an inhaled,

487 short-acting beta<sub>2</sub>-agonist (e.g., albuterol) for treatment of symptoms that occur acutely, despite  
488 regular twice-daily (morning and evening) use of ADVAIR DISKUS.

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

494 4. Watch for Increasing Use of Inhaled, Short-Acting Beta<sub>2</sub>-Agonists, Which Is a Marker of  
495 Deteriorating Asthma: Asthma may deteriorate acutely over a period of hours or chronically over  
496 several days or longer. If the patient's inhaled, short-acting beta<sub>2</sub>-agonist becomes less effective,  
497 the patient needs more inhalations than usual, or the patient develops a significant decrease in  
498 PEF, these may be a marker of destabilization of asthma. In this setting, the patient requires  
499 immediate reevaluation with reassessment of the treatment regimen, giving special consideration  
500 to the possible need for replacing the current strength of ADVAIR DISKUS with a higher  
501 strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients  
502 should not use more than 1 inhalation twice daily (morning and evening) of ADVAIR DISKUS.

503 5. Do Not Use an Inhaled, Long-Acting Beta<sub>2</sub>-Agonist in Conjunction With ADVAIR DISKUS:  
504 Patients who are receiving ADVAIR DISKUS twice daily should not use salmeterol or other  
505 inhaled, long-acting beta<sub>2</sub>-agonists for prevention of exercise-induced bronchospasm (EIB) or  
506 the maintenance treatment of asthma. Additional benefit would not be gained from using  
507 supplemental salmeterol for prevention of EIB since ADVAIR DISKUS already contains  
508 salmeterol.

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

514 7. Paradoxical Bronchospasm: As with other inhaled asthma medications, ADVAIR DISKUS  
515 can produce paradoxical bronchospasm, which may be life threatening. If paradoxical  
516 bronchospasm occurs following dosing with ADVAIR DISKUS, it should be treated  
517 immediately with an inhaled, short-acting bronchodilator, ADVAIR DISKUS should be  
518 discontinued immediately, and alternative therapy should be instituted.

519 8. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after  
520 administration of ADVAIR DISKUS, as demonstrated by cases of urticaria, angioedema, rash,  
521 and bronchospasm.

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

525 10. Cardiovascular Disorders: ADVAIR DISKUS, like all products containing sympathomimetic  
526 amines, should be used with caution in patients with cardiovascular disorders, especially

527 coronary insufficiency, cardiac arrhythmias, and hypertension. Salmeterol, a component of  
528 ADVAIR DISKUS, can produce a clinically significant cardiovascular effect in some patients as  
529 measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon  
530 after administration of salmeterol at recommended doses, if they occur, the drug may need to be  
531 discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG)  
532 changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment  
533 depression. The clinical significance of these findings is unknown.

534 11. Discontinuation of Systemic Corticosteroids: Transfer of patients from systemic  
535 corticosteroid therapy to ADVAIR DISKUS may unmask conditions previously suppressed by  
536 the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, and arthritis.

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

## 549 **PRECAUTIONS**

550 **General:** 1. Cardiovascular Effects: No effect on the cardiovascular system is usually seen after  
551 the administration of inhaled ADVAIR DISKUS at recommended doses. The cardiovascular and  
552 central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood  
553 pressure, heart rate, excitement) can occur after use of salmeterol, a component of ADVAIR  
554 DISKUS, and may require discontinuation of ADVAIR DISKUS. ADVAIR DISKUS, like all  
555 medications containing sympathomimetic amines, should be used with caution in patients with  
556 cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and  
557 hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are  
558 unusually responsive to sympathomimetic amines.

559 As has been described with other beta-adrenergic agonist bronchodilators, clinically  
560 significant changes in electrocardiograms (ECGs) have been seen infrequently in individual  
561 patients in controlled clinical studies with ADVAIR DISKUS and salmeterol. Clinically  
562 significant changes in systolic and/or diastolic blood pressure and pulse rate have been seen  
563 infrequently in individual patients in controlled clinical studies with salmeterol, a component of  
564 ADVAIR DISKUS.

565 2. Metabolic and Other Effects: Doses of the related beta<sub>2</sub>-adrenoceptor agonist albuterol, when  
566 administered intravenously, have been reported to aggravate preexisting diabetes mellitus and  
567 ketoacidosis. Beta-adrenergic agonist medications may produce significant hypokalemia in some  
568 patients, possibly through intracellular shunting, which has the potential to produce adverse  
569 cardiovascular effects. The decrease in serum potassium is usually transient, not requiring  
570 supplementation.

571 Clinically significant changes in blood glucose and/or serum potassium were seen rarely  
572 during clinical studies with ADVAIR DISKUS at recommended doses.

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

576 Fluticasone propionate, a component of ADVAIR DISKUS, will often permit control of  
577 asthma symptoms with less suppression of HPA function than therapeutically equivalent oral  
578 doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be  
579 systemically active at higher doses, the beneficial effects of ADVAIR DISKUS in minimizing  
580 HPA dysfunction may be expected only when recommended dosages are not exceeded and  
581 individual patients are titrated to the lowest effective dose. A relationship between plasma levels  
582 of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown  
583 after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual  
584 sensitivity to effects on cortisol production exists, physicians should consider this information  
585 when prescribing ADVAIR DISKUS.

586 Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated  
587 with these drugs should be observed carefully for any evidence of systemic corticosteroid effects.  
588 Particular care should be taken in observing patients postoperatively or during periods of stress  
589 for evidence of inadequate adrenal response.

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

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

599 The long-term effects of ADVAIR DISKUS in human subjects are not fully known. In  
600 particular, the effects resulting from chronic use of fluticasone propionate on developmental or  
601 immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients  
602 have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or  
603 longer. In clinical studies with patients treated for 2 years with inhaled fluticasone propionate, no

604 apparent differences in the type or severity of adverse reactions were observed after long- versus  
605 short-term treatment.

606 Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported  
607 following the inhaled administration of corticosteroids, including fluticasone propionate, a  
608 component of ADVAIR DISKUS.

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

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

617 3. **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a  
618 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some  
619 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a  
620 condition that is often treated with systemic corticosteroid therapy. These events usually, but not  
621 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy  
622 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions  
623 have also been reported with other inhaled corticosteroids in this clinical setting. Physicians  
624 should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac  
625 complications, and/or neuropathy presenting in their patients. A causal relationship between  
626 fluticasone propionate and these underlying conditions has not been established (see ADVERSE  
627 REACTIONS).

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

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

- 634 1. Patients should use ADVAIR DISKUS at regular intervals as directed. Results of clinical  
635 trials indicate significant improvement may occur within the first 30 minutes of taking the  
636 first dose; however, the full benefit may not be achieved until treatment has been  
637 administered for 1 week or longer. The patient should not exceed the prescribed dosage and  
638 should contact the physician if symptoms do not improve or if the condition worsens.
- 639 2. Patients should not stop therapy with ADVAIR DISKUS without physician/provider  
640 guidance since symptoms may recur after discontinuation.
- 641 3. Most patients are able to taste or feel a dose delivered from ADVAIR DISKUS. However,  
642 whether or not patients are able to sense delivery of a dose, you should instruct them not to

- 643 exceed the recommended dose of 1 inhalation each morning and evening, approximately 12  
644 hours apart. You should instruct them to contact you or the pharmacist if they have questions.
- 645 4. The bronchodilation from a single dose of ADVAIR DISKUS may last up to 12 hours or  
646 longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not  
647 be exceeded. Patients who are receiving ADVAIR DISKUS twice daily should not use  
648 salmeterol or other inhaled, long-acting beta<sub>2</sub>-agonists for prevention of EIB or maintenance  
649 treatment of asthma.
- 650 5. ADVAIR DISKUS is not meant to relieve acute asthma symptoms and extra doses should  
651 not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting  
652 beta<sub>2</sub>-agonist such as albuterol (the physician should provide the patient with such  
653 medication and instruct the patient in how it should be used).
- 654 6. The physician should be notified immediately if any of the following situations occur, which  
655 may be a sign of seriously worsening asthma:
- 656 • decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonists;
  - 657 • need for more inhalations than usual of inhaled, short-acting beta<sub>2</sub>-agonists;
  - 658 • significant decrease in peak flow as outlined by the physician.
- 659 7. Patients should be cautioned regarding common adverse cardiovascular effects, such as  
660 palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 661 8. When patients are prescribed ADVAIR DISKUS, other inhaled drugs and asthma  
662 medications should be used only as directed by the physician.
- 663 9. ADVAIR DISKUS should not be used with a spacer device.
- 664 10. Patients who are pregnant or nursing should contact the physician about the use of ADVAIR  
665 DISKUS.
- 666 11. Effective and safe use of ADVAIR DISKUS includes an understanding of the way that it  
667 should be used:
- 668 • Never exhale into the DISKUS.
  - 669 • Never attempt to take the DISKUS apart.
  - 670 • Always activate and use the DISKUS in a level, horizontal position.
  - 671 • After inhalation, rinse the mouth with water without swallowing.
  - 672 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
  - 673 • Always keep the DISKUS in a dry place.
  - 674 • Discard **1 month** after removal from the moisture-protective foil overwrap pouch or after  
675 every blister has been used (when the dose indicator reads “0”), whichever comes first.
- 676 12. Patients should be warned to avoid exposure to chickenpox or measles and, if they are  
677 exposed, to consult their physicians without delay.
- 678 13. For the proper use of ADVAIR DISKUS and to attain maximum improvement, the patient  
679 should read and follow carefully the Patient's Instructions for Use accompanying the  
680 product.
- 681 **Drug Interactions:** ADVAIR DISKUS has been used concomitantly with other drugs,  
682 including short-acting beta<sub>2</sub>-agonists, methylxanthines, and intranasal corticosteroids, commonly

683 used in patients with asthma, without adverse drug reactions. No formal drug interaction studies  
684 have been performed with ADVAIR DISKUS.

685 **Short-Acting Beta<sub>2</sub>-Agonists:** In clinical trials, the mean daily need for additional  
686 beta<sub>2</sub>-agonist use in 166 patients using ADVAIR DISKUS was approximately  
687 1.3 inhalations/day, and ranged from 0 to 9 inhalations/day. Five percent (5%) of the patients  
688 using ADVAIR DISKUS in these trials averaged 6 or more inhalations per day over the course  
689 of the 12-week trials. No observed increase in frequency of cardiovascular events was noted  
690 among patients who averaged 6 or more inhalations per day.

691 **Methylxanthines:** The concurrent use of intravenously or orally administered  
692 methylxanthines (e.g., aminophylline, theophylline) by patients receiving ADVAIR DISKUS has  
693 not been completely evaluated. In clinical trials, 39 patients receiving ADVAIR DISKUS  
694 100/50, 250/50, or 500/50 twice daily concurrently with a theophylline product had adverse  
695 event rates similar to those in 304 patients receiving ADVAIR DISKUS without theophylline.  
696 Similar results were observed in patients receiving salmeterol 50 mcg plus fluticasone propionate  
697 500 mcg twice daily concurrently with a theophylline product (N = 39) or without theophylline  
698 (N = 132).

699 **Fluticasone Propionate Nasal Spray:** In patients taking ADVAIR DISKUS in clinical  
700 trials, no difference in the profile of adverse events or HPA axis effects was noted between  
701 patients taking FLONASE<sup>®</sup> (fluticasone propionate) Nasal Spray, 50 mcg concurrently (N = 46)  
702 and those who were not (N = 130).

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

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

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

720 **Ketoconazole and Other Inhibitors of Cytochrome P450:** In a placebo-controlled,  
721 crossover study in 8 healthy volunteers, coadministration of a single dose of fluticasone  
722 propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in

723 increased mean fluticasone propionate concentrations, a reduction in plasma cortisol AUC, and  
724 no effect on urinary excretion of cortisol. This interaction may be due to an inhibition of  
725 cytochrome P450 3A4 by ketoconazole, which is also the route of metabolism of fluticasone  
726 propionate. Care should be exercised when ADVAIR DISKUS is coadministered with long-term  
727 ketoconazole and other known cytochrome P450 3A4 inhibitors.

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

729 Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to  
730 1,000 mcg/kg (approximately 4 times the maximum recommended daily inhalation dose in adults  
731 on a mcg/m<sup>2</sup> basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than the  
732 maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) for 104 weeks.

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

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

740 **Salmeterol:** In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of  
741 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose  
742 in adults based on comparison of the plasma area under the curves [AUCs]) caused a  
743 dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular  
744 hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of  
745 leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg  
746 (approximately 3 times the maximum recommended daily inhalation doses in adults based on  
747 comparison of the AUCs).

748 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol  
749 caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at  
750 doses of 0.68 mg/kg and above (approximately 60 times the maximum recommended daily  
751 inhalation dose in adults on a mg/m<sup>2</sup> basis). No tumors were seen at 0.21 mg/kg (approximately  
752 20 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). These  
753 findings in rodents are similar to those reported previously for other beta-adrenergic agonist  
754 drugs. The relevance of these findings to human use is unknown.

755 Salmeterol produced no detectable or reproducible increases in microbial and mammalian  
756 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo  
757 in a rat micronucleus test. No effects on fertility were identified in male and female rats treated  
758 with salmeterol at oral doses up to 2 mg/kg (approximately 180 times the maximum  
759 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis).

760 **Pregnancy: Teratogenic Effects: ADVAIR DISKUS:** Pregnancy Category C. From the  
761 reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using  
762 combinations of fluticasone propionate and salmeterol compared to toxicity data from the

763 components administered separately. In mice combining 150 mcg/kg subcutaneously of  
764 fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a  
765 mcg/m<sup>2</sup> basis) with 10 mg/kg orally of salmeterol (approximately 450 times the maximum  
766 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis) was teratogenic. Cleft palate,  
767 fetal death, increased implantation loss and delayed ossification were seen. These observations  
768 are characteristic of glucocorticoids. No developmental toxicity was observed at combination  
769 doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum  
770 recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) and up to 1.4 mg/kg orally of  
771 salmeterol (approximately 65 times the maximum recommended daily inhalation dose in adults  
772 on a mg/m<sup>2</sup> basis). In rats, no teratogenicity was observed at combination doses up to 30 mcg/kg  
773 subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation  
774 dose in adults on a mcg/m<sup>2</sup> basis) and up to 1 mg/kg of salmeterol (approximately 90 times the  
775 maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Combining  
776 100 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended  
777 daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) with 10 mg/kg orally of salmeterol  
778 (approximately 900 times the maximum recommended daily inhalation dose in adults on a  
779 mg/m<sup>2</sup> basis) produced maternal toxicity, decreased placental weight, decreased fetal weight,  
780 umbilical hernia, delayed ossification, and changes in the occipital bone. There are no adequate  
781 and well-controlled studies with ADVAIR DISKUS in pregnant women. ADVAIR DISKUS  
782 should be used during pregnancy only if the potential benefit justifies the potential risk to the  
783 fetus.

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

789 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of  
790 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
791 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg  
792 (approximately 5 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
793 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this  
794 study, consistent with the established low bioavailability following oral administration (see  
795 CLINICAL PHARMACOLOGY).

796 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose  
797 of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a  
798 mcg/m<sup>2</sup> basis) administration of a subcutaneous or an oral dose of 100 mcg/kg to rats  
799 (approximately equivalent to the maximum recommended daily inhalation dose in adults on a  
800 mcg/m<sup>2</sup> basis) and an oral dose of 300 mcg/kg administered to rabbits (approximately 5 times the  
801 maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis).

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

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

810 **Salmeterol:** Pregnancy Category C. No teratogenic effects occurred in rats at oral doses  
811 up to 2 mg/kg (approximately 180 times the maximum recommended daily inhalation dose in  
812 adults on a mg/m<sup>2</sup> basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and  
813 above (approximately 50 times the maximum recommended daily inhalation dose in adults based  
814 on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting  
815 from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate,  
816 sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones.  
817 No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the  
818 maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

819 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal  
820 bones was seen at an oral dose of 10 mg/kg (approximately 1,800 times the maximum  
821 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Extensive use of other  
822 beta-agonists has provided no evidence that these class effects in animals are relevant to their use  
823 in humans. There are no adequate and well-controlled studies with salmeterol in pregnant  
824 women. Salmeterol should be used during pregnancy only if the potential benefit justifies the  
825 potential risk to the fetus.

826 Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice  
827 and rats (approximately 450 and 900 times, respectively, the maximum recommended daily  
828 inhalation dose in adults on a mg/m<sup>2</sup> basis).

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

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

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

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

846 **Pediatric Use:** The safety and effectiveness of ADVAIR DISKUS in children under 12 years  
847 of age have not been established. In one 12-week study, 257 patients 4 to 11 years inadequately  
848 controlled using inhaled corticosteroids were randomized to ADVAIR DISKUS 100/50 or  
849 concurrent therapy with fluticasone propionate inhalation powder 100 mcg plus salmeterol  
850 inhalation powder 50 mcg twice daily. The pattern of adverse events reported in patients 4 to  
851 11 years of age was similar to that seen in patients 12 years of age and older treated with  
852 ADVAIR DISKUS.

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

861 Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS,  
862 may cause a reduction in growth velocity in children and adolescents (see PRECAUTIONS).  
863 The growth of pediatric patients receiving orally inhaled corticosteroids, including ADVAIR  
864 DISKUS, should be monitored. If a child or adolescent on any corticosteroid appears to have  
865 growth suppression, the possibility that he/she is particularly sensitive to this effect of  
866 corticosteroids should be considered. The potential growth effects of prolonged treatment should  
867 be weighed against the clinical benefits obtained. To minimize the systemic effects of orally  
868 inhaled corticosteroids, including ADVAIR DISKUS, each patient should be titrated to the  
869 lowest strength that effectively controls his/her asthma (see DOSAGE AND  
870 ADMINISTRATION).

871 **Geriatric Use:** Of the total number of patients in clinical studies of ADVAIR DISKUS, 44  
872 were 65 years of age or older and 3 were 75 years of age or older. No overall differences in  
873 safety were observed between these patients and younger patients, and other reported clinical  
874 experience, including studies of the individual components, has not identified differences in  
875 responses between the elderly and younger patients, but greater sensitivity of some older  
876 individuals cannot be ruled out. As with other products containing beta<sub>2</sub>-agonists, special caution  
877 should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant  
878 cardiovascular disease that could be adversely affected by beta<sub>2</sub>-agonists. Based on available  
879 data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR  
880 DISKUS in geriatric patients is warranted.

881 **ADVERSE REACTIONS**

882 The incidence of common adverse events in Table 3 is based upon 2 placebo-controlled,  
883 12-week, US clinical studies (Studies 1 and 2). A total of 705 adolescent and adult patients (349  
884 females and 356 males) previously treated with salmeterol or inhaled corticosteroids were treated  
885 twice daily with ADVAIR DISKUS (100/50- or 250/50-mcg doses), fluticasone propionate  
886 inhalation powder (100- or 250-mcg doses), salmeterol inhalation powder 50 mcg, or placebo.  
887

888 **Table 3. Overall Adverse Events With  $\geq 3\%$  Incidence With ADVAIR DISKUS**

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

889  
890 Table 3 includes all events (whether considered drug-related or nondrug-related by the  
891 investigator) that occurred at a rate of 3% or greater in either of the groups receiving ADVAIR  
892 DISKUS and were more common than in the placebo group. In considering these data,  
893 differences in average duration of exposure should be taken into account.

894 These adverse reactions were mostly mild to moderate in severity. Rare cases of immediate  
895 and delayed hypersensitivity reactions, including rash and other rare events of angioedema and  
896 bronchospasm, have been reported.

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

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

900 **Cardiovascular:** Palpitations.

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

903 **Ear, Nose, and Throat:** Rhinorrhea/post nasal drip; ear, nose and throat infections; ear  
904 signs and symptoms; nasal signs and symptoms; nasal sinus disorders; rhinitis; sneezing; nasal  
905 irritation; blood in nasal mucosa.

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

907 **Gastrointestinal:** Dental discomfort and pain, gastrointestinal signs and symptoms,  
908 gastrointestinal infections, gastroenteritis, gastrointestinal disorders, oral ulcerations, oral  
909 erythema and rashes, constipation, appendicitis, oral discomfort and pain.

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

911 **Lower Respiratory:** Lower respiratory signs and symptoms, pneumonia, lower respiratory  
912 infections.

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

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

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

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

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

925 **Observed During Clinical Practice:** In addition to adverse events reported from clinical  
926 trials, the following events have been identified during postapproval use of ADVAIR DISKUS,  
927 fluticasone propionate, and/or salmeterol. Because they are reported voluntarily from a  
928 population of unknown size, estimates of frequency cannot be made. These events have been  
929 chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection  
930 to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol or a combination of these  
931 factors.

932 In extensive US and worldwide postmarketing experience with salmeterol, a component of  
933 ADVAIR DISKUS, serious exacerbations of asthma, including some that have been fatal, have

934 been reported. In most cases, these have occurred in patients with severe asthma and/or in some  
935 patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also  
936 occurred in a few patients with less severe asthma. It was not possible from these reports to  
937 determine whether salmeterol contributed to these events or simply failed to relieve the  
938 deteriorating asthma.

939 **Cardiovascular:** Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular  
940 tachycardia), ventricular tachycardia.

941 **Ear, Nose, and Throat:** Aphonia, earache, facial and oropharyngeal edema, paranasal sinus  
942 pain, throat soreness and irritation.

943 **Endocrine and Metabolic:** Cushing syndrome, Cushingoid features, growth velocity  
944 reduction in children/adolescents, hypercorticism, hyperglycemia, weight gain.

945 **Gastrointestinal:** Abdominal pain, dyspepsia, xerostomia.

946 **Musculoskeletal:** Back pain, cramps, muscle spasm, myositis.

947 **Neurology:** Paresthesia, restlessness.

948 **Non-Site Specific:** Immediate and delayed hypersensitivity reaction (including very rare  
949 anaphylactic reaction), pallor. Very rare anaphylactic reaction in patients with severe milk  
950 protein allergy.

951 **Psychiatry:** Agitation, aggression, depression.

952 **Respiratory:** Chest congestion, chest tightness, dyspnea, immediate bronchospasm,  
953 influenza, paradoxical bronchospasm, tracheitis, wheezing, reports of upper respiratory  
954 symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

955 **Skin:** Contact dermatitis, contusions, ecchymoses, photodermatitis.

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

958 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a  
959 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some  
960 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a  
961 condition that is often treated with systemic corticosteroid therapy. These events usually, but not  
962 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy  
963 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions  
964 have also been reported with other inhaled corticosteroids in this clinical setting. While  
965 ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid  
966 therapy, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary  
967 symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal  
968 relationship between fluticasone propionate and these underlying conditions has not been  
969 established (see PRECAUTIONS: Eosinophilic Conditions).

## 970 OVERDOSAGE

971 **ADVAIR DISKUS:** No deaths occurred in rats given combinations of salmeterol and  
972 fluticasone propionate at acute inhalation doses of 3.6 and 1.9 mg/kg, respectively

973 (approximately 320 and 15 times the maximum recommended daily inhalation dose in adults on  
974 a mg/m<sup>2</sup> basis).

975 **Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in  
976 signs/symptoms of hypercorticism (see PRECAUTIONS). Inhalation by healthy volunteers of a  
977 single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or  
978 3,520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone  
979 propionate given by inhalation aerosol at doses of 1,320 mcg twice daily for 7 to 15 days to  
980 healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for  
981 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients  
982 were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were  
983 similar in active and placebo treatment groups. The oral and subcutaneous median lethal doses in  
984 mice and rats were >1,000 mg/kg (>4,300 and >8,700 times, respectively, the maximum  
985 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis).

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

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

998 Treatment consists of discontinuation of salmeterol together with appropriate symptomatic  
999 therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing  
1000 in mind that such medication can produce bronchospasm. There is insufficient evidence to  
1001 determine if dialysis is beneficial for overdosage of salmeterol. Cardiac monitoring is  
1002 recommended in cases of overdosage.

1003 No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg  
1004 (approximately 250 times the maximum recommended daily inhalation dose in adults on a  
1005 mg/m<sup>2</sup> basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 200 times the  
1006 maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). By the oral route, no  
1007 deaths occurred in mice at 150 mg/kg (approximately 6,500 times the maximum recommended  
1008 daily inhalation dose in adults on a mg/m<sup>2</sup> basis) and in rats at 1,000 mg/kg (approximately  
1009 86,000 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis).

1010 **DOSAGE AND ADMINISTRATION**

1011 ADVAIR DISKUS is available in 3 strengths, ADVAIR DISKUS 100/50, ADVAIR DISKUS  
1012 250/50, and ADVAIR DISKUS 500/50, containing 100, 250, and 500 mcg of fluticasone  
1013 propionate, respectively, and 50 mcg of salmeterol per inhalation. ADVAIR DISKUS should be  
1014 administered by the orally inhaled route only (see Patient’s Instructions for Use).

1015 For patients 12 years of age and older, the dosage is 1 inhalation twice daily (morning and  
1016 evening, approximately 12 hours apart).

1017 The recommended starting dosages for ADVAIR DISKUS are based upon patients’ current  
1018 asthma therapy.

- 1019 • For patients who are not currently on an inhaled corticosteroid, whose disease severity  
1020 warrants treatment with 2 maintenance therapies, including patients on non-corticosteroid  
1021 maintenance therapy, the recommended starting dosage is ADVAIR DISKUS 100/50 twice  
1022 daily.
- 1023 • For patients on an inhaled corticosteroid, Table 4 provides the recommended starting dosage.  
1024 The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

1025 **For all patients it is desirable to titrate to the lowest effective strength after adequate**  
1026 **asthma stability is achieved.**

1027

1028 **Table 4. Recommended Dosages of ADVAIR DISKUS for Patients Taking Inhaled**  
1029 **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

1030 \* ADVAIR DISKUS should not be used for transferring patients from systemic corticosteroid  
1031 therapy.

1032

1033       ADVAIR DISKUS should be administered twice daily every day. More frequent  
1034 administration (more than twice daily) or a higher number of inhalations (more than 1 inhalation  
1035 twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some  
1036 patients are more likely to experience adverse effects with higher doses of salmeterol. The safety  
1037 and efficacy of ADVAIR DISKUS when administered in excess of recommended doses have not  
1038 been established.

1039       If symptoms arise in the period between doses, an inhaled, short-acting beta<sub>2</sub>-agonist should  
1040 be taken for immediate relief.

1041       Patients who are receiving ADVAIR DISKUS twice daily should not use salmeterol for  
1042 prevention of EIB, or for any other reason.

1043       Improvement in asthma control following inhaled administration of ADVAIR DISKUS can  
1044 occur within 30 minutes of beginning treatment, although maximum benefit may not be  
1045 achieved for 1 week or longer after starting treatment. Individual patients will experience a  
1046 variable time to onset and degree of symptom relief.

1047       For patients who do not respond adequately to the starting dosage after 2 weeks of therapy,  
1048 replacing the current strength of ADVAIR DISKUS with a higher strength may provide  
1049 additional asthma control.

1050       If a previously effective dosage regimen of ADVAIR DISKUS fails to provide adequate  
1051 control of asthma, the therapeutic regimen should be reevaluated and additional therapeutic  
1052 options, e.g., replacing the current strength of ADVAIR DISKUS with a higher strength, adding  
1053 additional inhaled corticosteroid, or initiating oral corticosteroids, should be considered.

1054       **Geriatric Use:** In studies where geriatric patients (65 years of age or older, see  
1055 PRECAUTIONS: Geriatric Use) have been treated with ADVAIR DISKUS, efficacy and safety  
1056 did not differ from that in younger patients. Based on available data for ADVAIR DISKUS and  
1057 its active components, no dosage adjustment is recommended.

1058       **Directions for Use:** Illustrated Patient's Instructions for Use accompany each package of  
1059 ADVAIR DISKUS.

## 1060       **HOW SUPPLIED**

1061       ADVAIR DISKUS 100/50 is supplied as a disposable, purple device containing 60 blisters.  
1062 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective  
1063 foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional  
1064 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS  
1065 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch  
1066 (NDC 0173-0695-02).

1067       ADVAIR DISKUS 250/50 is supplied as a disposable, purple device containing 60 blisters.  
1068 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective  
1069 foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional  
1070 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS

1071 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch  
1072 (NDC 0173-0696-02).

1073       ADVAIR DISKUS 500/50 is supplied as a disposable, purple device containing 60 blisters.  
1074 The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective  
1075 foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional  
1076 pack of 1 purple, disposable DISKUS inhalation device containing 28 blisters. The DISKUS  
1077 inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch  
1078 (NDC 0173-0697-02).

1079       **Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place**  
1080 **away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation**  
1081 **device is not reusable. The device should be discarded 1 month after removal from the**  
1082 **moisture-protective foil overwrap pouch or after every blister has been used (when the**  
1083 **dose indicator reads “0”), whichever comes first. Do not attempt to take the device apart.**  
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