

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** 21-077

**FINAL PRINTED LABELING**

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## PRODUCT INFORMATION

**ADVAIR™ DISKUS® 100/50**

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

**ADVAIR™ DISKUS® 250/50**

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

**ADVAIR™ DISKUS® 500/50**

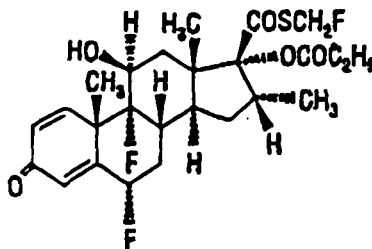
(fluticasone propionate 500 mcg and salmeterol\* 50 mcg inhalation powder)

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

**FOR ORAL INHALATION ONLY**

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

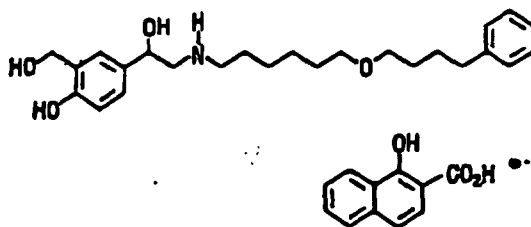
One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having the chemical name S-(fluoromethyl)6 $\alpha$ ,9-difluoro-11 $\beta$ ,17-dihydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioate, 17-propionate and the following chemical structure:



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

ADVAIR™ DISKUS® 100/50  
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 ADVAIR™ DISKUS® 500/50  
 (fluticasone propionate 500 mcg and salmeterol® 50 mcg inhalation powder)



Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.6, and the empirical formula is  $C_{23}H_{37}NO_4 \cdot C_{11}H_6O_3$ . It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

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

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

Inhalation profiles for adolescent ( $n = 13$ , aged 12 to 17 years) and adult ( $n = 17$ , aged 18 to 50 years) patients with asthma inhaling maximally through the DISKUS device show mean PIF of 122.2 L/min (range, 81.8 to 152.1 L/min).

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

#### CLINICAL PHARMACOLOGY:

**Mechanism of Action: ADVAIR DISKUS:** ADVAIR DISKUS is designed to produce a greater improvement in pulmonary function and symptom control than either fluticasone propionate or salmeterol used alone at their recommended dosages. Since ADVAIR DISKUS contains both fluticasone propionate and salmeterol, the mechanisms of action described below for the individual components apply to ADVAIR DISKUS. These drugs represent 2 classes of medications (a synthetic corticosteroid and a long-acting beta-adrenergic receptor agonist) that have different effects on clinical, physiological, and inflammatory indices of asthma.

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**ADVAIR™ DISKUS® 500/50**  
(fluticasone propionate 500 mcg and salmeterol\* 50 mcg inhalation powder)

65 **Fluticasone Propionate:** Fluticasone propionate is a synthetic, trifluorinated corticosteroid with  
66 potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have  
67 established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity  
68 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate  
69 (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide.  
70 Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

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

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

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

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

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

100 In a single-dose crossover study, a higher than recommended dose of ADVAIR DISKUS was  
101 administered to 14 healthy subjects. Two inhalations of the following treatments were administered:

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**ADVAIR™ DISKUS® 500/50**  
(fluticasone propionate 500 mcg and salmeterol\* 50 mcg inhalation powder)

102 ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg  
103 given concurrently, and fluticasone propionate powder 500 mcg alone. Mean peak plasma  
104 concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL, respectively; those for  
105 salmeterol averaged 200 and 150 pg/mL, respectively. Indicating no significant changes in systemic  
106 exposures of fluticasone propionate and salmeterol.

107 In a repeat-dose study, the highest recommended dose of ADVAIR DISKUS was administered to  
108 45 asthmatic patients. One inhalation twice daily of the following treatments was administered:  
109 ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg  
110 given concurrently, or fluticasone propionate powder 500 mcg alone. Mean peak steady-state  
111 plasma concentrations of fluticasone propionate averaged 57, 73, and 70 pg/mL, respectively,  
112 indicating no significant changes in systemic exposure of fluticasone propionate. No plasma  
113 concentrations of salmeterol were measured in this repeat-dose study.

114 No significant changes in excretion of fluticasone propionate or salmeterol were observed. The  
115 terminal half-life of fluticasone propionate averaged 5.33 to 7.65 hours when ADVAIR DISKUS was  
116 administered, which is similar to that reported when fluticasone propionate was given concurrently  
117 with salmeterol or when fluticasone propionate was given alone (average, 5.30 to 6.91 hours). No  
118 terminal half-life of salmeterol was reported upon administration of ADVAIR DISKUS or salmeterol  
119 given concurrently with fluticasone propionate.

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

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

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

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

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

140 The percentage of fluticasone propionate bound to human plasma proteins averages 91%.  
141 Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound  
142 to human transcortin.

143 **Metabolism:** The total clearance of fluticasone propionate is high (average, 1093 mL/min),  
144 with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite  
145 detected in man is the 17 $\beta$ -carboxylic acid derivative of fluticasone propionate, which is formed  
146 through the cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately  
147 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and  
148 negligible pharmacological activity in animal studies. Other metabolites detected in vitro using  
149 cultured human hepatoma cells have not been detected in man.

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

154 **Hepatic Impairment:** Since fluticasone propionate is predominantly cleared by hepatic  
155 metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in  
156 plasma. Therefore, patients with hepatic disease should be closely monitored.

157 **Gender:** Full pharmacokinetic profiles were obtained from 9 female and 18 male patients  
158 given fluticasone propionate Inhalation powder 500 mcg twice daily using the DISKUS. No overall  
159 differences in fluticasone propionate pharmacokinetics were observed.

160 **Special Populations:** Formal pharmacokinetic studies using fluticasone propionate were not  
161 carried out in other special populations.

162 **Drug-Drug Interactions:** In a multiple-dose drug interaction study, coadministration of  
163 fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect  
164 fluticasone propionate pharmacokinetics. In another drug interaction study, coadministration of  
165 fluticasone propionate (1000 mcg) and ketoconazole (200 mg once daily) resulted in increased  
166 fluticasone propionate concentrations and reduced plasma cortisol area under the plasma  
167 concentration versus time curve (AUC), but had no effect on urinary excretion of cortisol. Since  
168 fluticasone propionate is a substrate of cytochrome P450 3A4, caution should be exercised when  
169 cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole) are coadministered with fluticasone  
170 propionate as this could result in increased plasma concentrations of fluticasone propionate.

171 **Salmeterol Xinafoate:** Salmeterol xinafoate, an ionic salt, dissociates in solution so that the  
172 salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed,

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173 metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma  
174 levels do not predict therapeutic effect.

175 **Absorption:** Because of the small therapeutic dose, systemic levels of salmeterol are low or  
176 undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder twice  
177 daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol inhalation  
178 powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7 asthmatic  
179 patients; plasma concentrations were very low, with mean peak concentrations of 187 pg/mL at  
180 20 minutes and no accumulation with repeated doses.

181 **Distribution:** Binding of salmeterol to human plasma proteins averages 96% in vitro over the  
182 concentration range of 8 to 7722 ng of salmeterol base per milliliter, much higher concentrations  
183 than those achieved following therapeutic doses of salmeterol.

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

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

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

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

197 **Pharmacodynamics: ADVAIR DISKUS:** Since systemic pharmacodynamic effects of salmeterol  
198 are not normally seen at the therapeutic dose, higher doses were used to produce measurable  
199 effects. Four studies were conducted in healthy subjects: (1) a single-dose crossover study using  
200 2 inhalations of ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol  
201 powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg given alone, (2) a  
202 cumulative dose study using 50 to 400 mcg of salmeterol powder given alone or as ADVAIR  
203 DISKUS 500/50, (3) a repeat-dose study for 11 days using 2 inhalations twice daily of ADVAIR  
204 DISKUS 250/50, fluticasone propionate powder 250 mcg, or salmeterol powder 50 mcg, and (4) a  
205 single-dose study using 5 inhalations of ADVAIR DISKUS 100/50, fluticasone propionate powder  
206 100 mcg alone, or placebo. In these studies no significant differences were observed in the  
207 pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and  
208 glucose) whether the salmeterol was given as ADVAIR DISKUS, concurrently with fluticasone  
209 propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic effects

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210 of salmeterol were not altered by the presence of fluticasone propionate in ADVAIR DISKUS. The  
211 potential effect of salmeterol on the effects of fluticasone propionate on the  
212 hypothalamic-pituitary-adrenal (HPA) axis was also evaluated in these studies. No significant  
213 differences across treatments were observed in 24-hour urinary cortisol excretion and, where  
214 measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone  
215 propionate were not altered by the presence of salmeterol in ADVAIR DISKUS in healthy subjects.

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

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

227 In a 12-week study in patients with asthma, ADVAIR DISKUS 250/50 twice daily was compared  
228 with fluticasone propionate powder 250 mcg alone, salmeterol powder 50 mcg alone, and placebo.  
229 For most patients, the ability to increase cortisol production in response to stress, as assessed by  
230 30-minute cosyntropin stimulation, remained intact with ADVAIR DISKUS. One patient (3%) who  
231 received ADVAIR DISKUS 250/50 had an abnormal response (peak serum cortisol <18 mcg/dL)  
232 after dosing, compared with 2 patients (6%) who received placebo, 2 patients (6%) who received  
233 fluticasone propionate 250 mcg, and no patients who received salmeterol.

234 **Fluticasone Propionate:** In clinical trials with fluticasone propionate inhalation powder using  
235 doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak  
236 serum cortisol <18 mcg/dL) were noted both in patients receiving fluticasone propionate and in  
237 patients receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than  
238 placebo. In a 2-year study carried out in 64 patients with mild, persistent asthma (mean FEV<sub>1</sub> 91%  
239 of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no patient  
240 receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak  
241 serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, one patient receiving  
242 fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and  
243 2 years was normal. Another patient receiving fluticasone propionate (5%) had an abnormal  
244 response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

245 **Salmeterol Xinafoate:** Inhaled salmeterol, like other beta-adrenergic agonist drugs, can in some  
246 patients produce dose-related cardiovascular effects and effects on blood glucose and/or serum



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247 potassium (see PRECAUTIONS). The cardiovascular effects (heart rate, blood pressure) associated  
248 with salmeterol occur with similar frequency, and are of similar type and severity, as those noted  
249 following albuterol administration.

250 The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied in  
251 volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as inhalation  
252 aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at  
253 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and adult patients receiving 50-mcg  
254 doses of salmeterol inhalation powder (n = 60) underwent continuous electrocardiographic  
255 monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no  
256 clinically significant dysrhythmias were noted.

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

261

262 **CLINICAL TRIALS:** In clinical trials comparing ADVAIR DISKUS with the individual components,  
263 improvements in most efficacy endpoints were greater with ADVAIR DISKUS than with the use of  
264 either fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar results  
265 between ADVAIR DISKUS and the concurrent use of fluticasone propionate plus salmeterol at  
266 corresponding doses from separate inhalers.

267 **Studies Comparing ADVAIR DISKUS to Fluticasone Propionate Alone or Salmeterol Alone:**

268 Three double-blind, parallel-group clinical trials were conducted with ADVAIR DISKUS in 1208  
269 adolescent and adult patients (≥12 years, baseline FEV<sub>1</sub> 63% to 72% of predicted normal) with  
270 asthma that was not optimally controlled on their current therapy. All treatments were inhalation  
271 powders, given as 1 inhalation from the DISKUS device twice daily, and other maintenance  
272 therapies were discontinued.

273 **Study 1: Clinical Trial With ADVAIR DISKUS 100/50:** This placebo-controlled, 12-week, US  
274 study compared ADVAIR DISKUS 100/50 with its individual components, fluticasone propionate  
275 100 mcg and salmeterol 50 mcg. The study was stratified according to baseline asthma  
276 maintenance therapy; patients were using either inhaled corticosteroids (n = 250) (daily doses of  
277 beclomethasone dipropionate 252 to 420 mcg, flunisolide 1000 mcg, fluticasone propionate  
278 inhalation aerosol 176 mcg, or triamcinolone acetonide 600 to 1000 mcg) or salmeterol (n = 106).  
279 Baseline FEV<sub>1</sub> measurements were similar across treatments: ADVAIR DISKUS 100/50, 2.17 L;  
280 fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and placebo, 2.15 L.

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

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284 Aerosol, increase in night awakenings due to asthma, emergency intervention or hospitalization due  
285 to asthma, or requirement for asthma medication not allowed by the protocol. As shown in Table 1,  
286 statistically significantly fewer patients receiving ADVAIR DISKUS 100/50 were withdrawn due to  
287 worsening asthma compared with fluticasone propionate, salmeterol, and placebo.

288

289 **Table 1: Percent of Patients Withdrawn Due to Worsening Asthma in Patients**  
290 **Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**

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

291

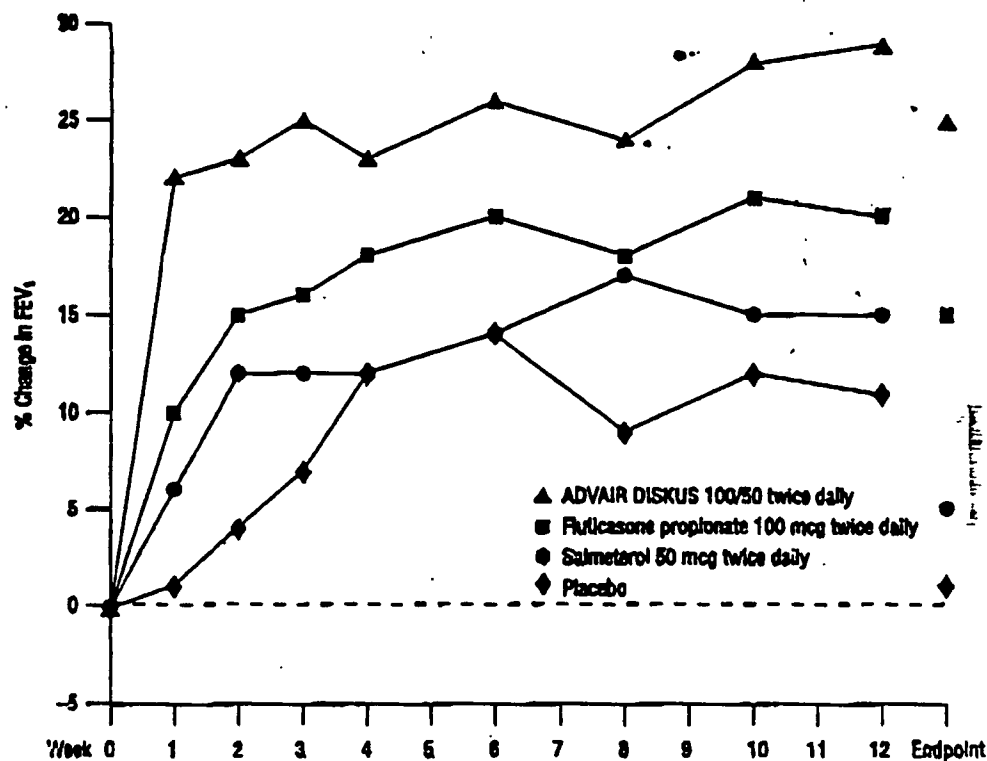
292 The FEV<sub>1</sub> results are displayed in Figure 1. Because this trial used predetermined criteria for  
293 worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV<sub>1</sub> results  
294 at Endpoint (last available FEV<sub>1</sub> result) are also provided. Patients receiving ADVAIR DISKUS  
295 100/50 had significantly greater improvements in FEV<sub>1</sub> (0.51 L, 25%) compared with fluticasone  
296 propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L, 1%). These  
297 improvements in FEV<sub>1</sub> with ADVAIR DISKUS were achieved regardless of baseline asthma  
298 maintenance therapy (inhaled corticosteroids or salmeterol).

299

**APPEARS THIS WAY  
ON ORIGINAL**

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 (fluticasone propionate 100 mcg and salmeterol<sup>®</sup> 50 mcg Inhalation powder)  
**ADVAIR<sup>®</sup> DISKUS<sup>®</sup> 250/50**  
 (fluticasone propionate 250 mcg and salmeterol<sup>®</sup> 50 mcg Inhalation powder)  
**ADVAIR<sup>®</sup> DISKUS<sup>®</sup> 500/50**  
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**Figure 1: Mean Percent Change From Baseline in FEV<sub>1</sub> In Patients  
 Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)**



	Week 0	N	Week 6	N	Week 12	N	Endpoint	N
ADVAIR DISKUS 100/50		87		79		73		86
Fluticasone propionate 100 mcg		85		71		65		85
Salmeterol 50 mcg		88		69		51		86
Placebo		77		34		27		74

The effect of ADVAIR DISKUS 100/50 on morning and evening peak expiratory flow (PEF) endpoints is shown in Table 2.

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

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

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

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

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**Study 2: Clinical Trial With ADVAIR DISKUS 250/50:** This placebo-controlled, 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components, fluticasone propionate 250 mcg and salmeterol 50 mcg in 349 patients using inhaled corticosteroids (daily doses of beclomethasone dipropionate 462 to 872 mcg, flunisolide 1250 to 2000 mcg, fluticasone propionate inhalation aerosol 440 mcg, or triamcinolone acetonide 1100 to 1600 mcg). Baseline FEV<sub>1</sub> measurements were similar across treatments: ADVAIR DISKUS 250/50, 2.23 L; fluticasone propionate 250 mcg; 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

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

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335 **Study 3: Clinical Trial With ADVAIR DISKUS 500/50:** This 28-week, non-US study compared  
336 ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and concurrent therapy  
337 (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from separate inhalers) twice  
338 daily in 503 patients using inhaled corticosteroids [daily doses of beclomethasone dipropionate  
339 1260 to 1680 mcg, budesonide 1500 to 2000 mcg, flunisolide 1500 to 2000 mcg, or fluticasone  
340 propionate inhalation aerosol 660 to 880 mcg (750 to 1000 mcg inhalation powder)]. The primary  
341 efficacy parameter, morning PEF, was collected daily for the first 12 weeks of the study. The  
342 primary purpose of weeks 13 to 28 was to collect safety data.

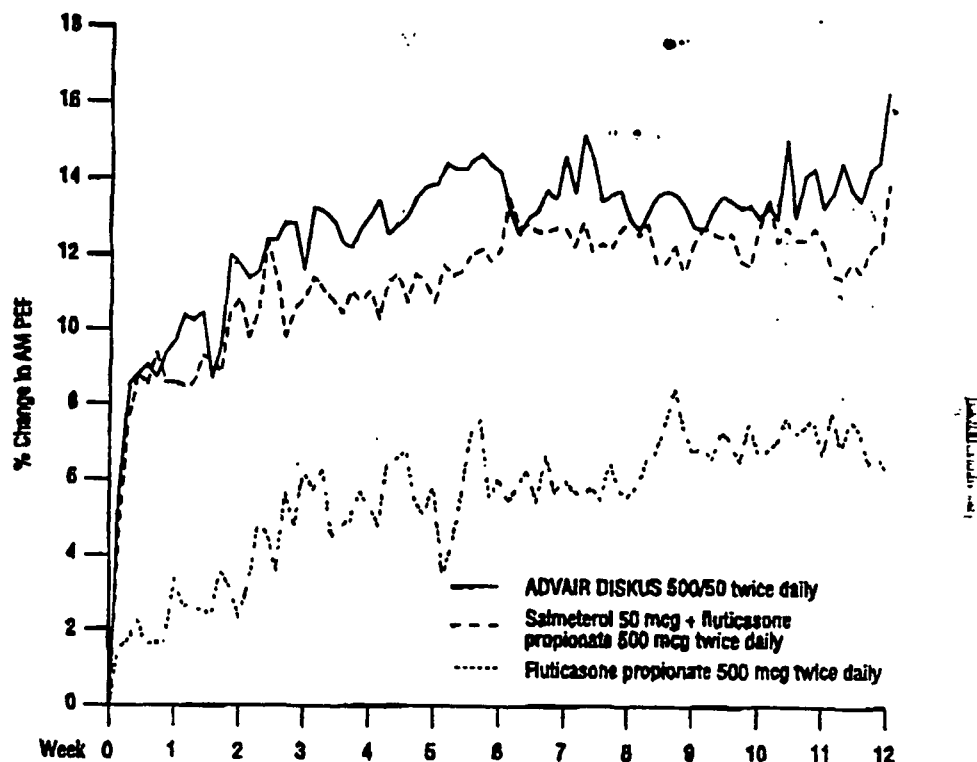
343 Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50,  
344 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. As  
345 shown in Figure 2, morning PEF improved significantly with ADVAIR DISKUS 500/50 compared  
346 with fluticasone propionate 500 mcg over the 12-week treatment period. Improvements in morning  
347 PEF observed with ADVAIR DISKUS 500/50 were similar to improvements observed with  
348 concurrent therapy.

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Figure 2: Mean Percent Change From Baseline in Morning Peak Expiratory Flow  
 in Patients Previously Treated With Inhaled Corticosteroids (Study 3)



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

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

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

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

364 No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR DISKUS  
365 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV<sub>1</sub> following 12 weeks of  
366 therapy.

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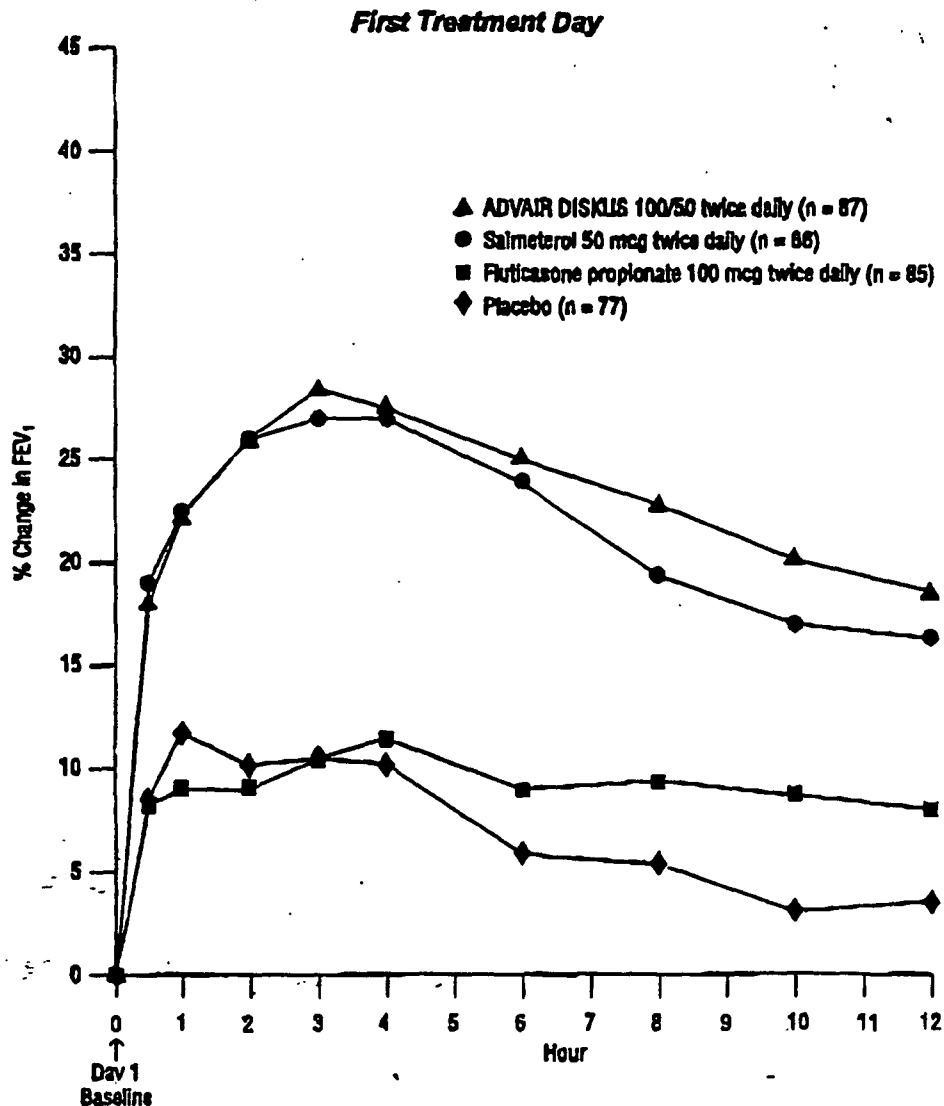
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Figure 3: Percent Change in Serial 12-hour FEV<sub>1</sub> in Patients  
Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)



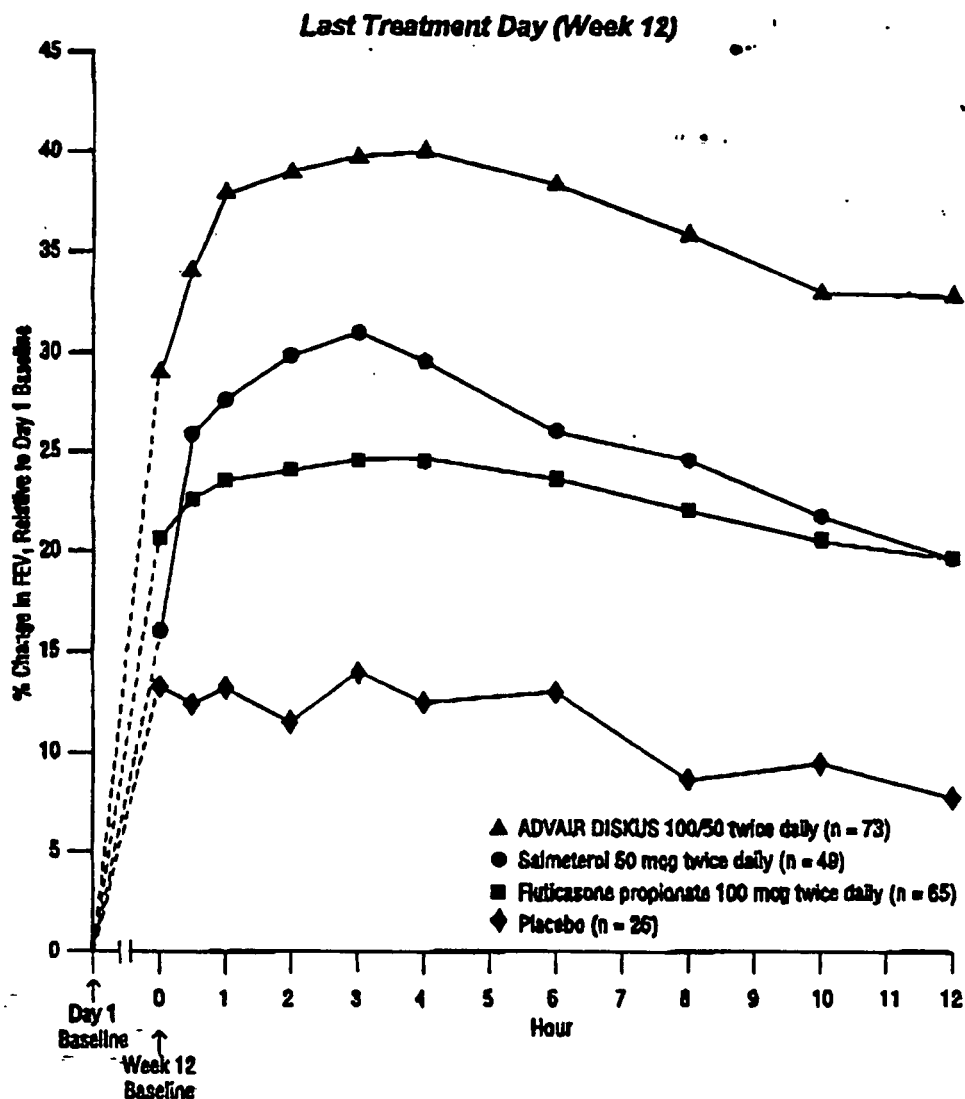
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Figure 4: Percent Change in Serial 12-hour FEV<sub>1</sub> in Patients  
Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)



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

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

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



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389 **CONTRAINDICATIONS:** ADVAIR DISKUS is contraindicated in the primary treatment of status  
390 asthmaticus or other acute episodes of asthma where intensive measures are required.

391 Hypersensitivity to any of the ingredients of these preparations contraindicates their use.

392

393 **WARNINGS:** ADVAIR DISKUS should not be used for transferring patients from systemic  
394 corticosteroid therapy.

395 Particular care is needed for patients who have been transferred from systemically active  
396 corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred  
397 in patients with asthma during and after transfer from systemic corticosteroids to less systemically  
398 available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of  
399 months are required for recovery of HPA function.

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

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

413 **1. ADVAIR DISKUS SHOULD NOT BE INITIATED IN PATIENTS DURING RAPIDLY**  
414 **DETERIORATING OR POTENTIALLY LIFE-THREATENING EPISODES OF ASTHMA.** Serious  
415 acute respiratory events, including fatalities, have been reported both in the United States  
416 and worldwide when salmeterol, a component of ADVAIR DISKUS, has been initiated in  
417 patients with significantly worsening or acutely deteriorating asthma. In most cases, these  
418 have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid  
419 dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations,  
420 or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma  
421 has been acutely deteriorating (e.g., unresponsive to usual medications; increasing need for  
422 inhaled, short-acting beta<sub>2</sub>-agonists; increasing need for systemic corticosteroids; significant  
423 increase in symptoms; recent emergency room visits; sudden or progressive deterioration in  
424 pulmonary function). However, they have occurred in a few patients with less severe asthma as

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425 well. It was not possible from these reports to determine whether salmeterol contributed to these  
426 events or simply failed to relieve the deteriorating asthma.

427 **2. Do Not Use ADVAIR DISKUS To Treat Acute Symptoms:** An inhaled, short-acting beta<sub>2</sub>-agonist,  
428 not ADVAIR DISKUS, should be used to relieve acute asthma symptoms. When prescribing  
429 ADVAIR DISKUS, the physician must also provide the patient with an inhaled, short-acting  
430 beta<sub>2</sub>-agonist (e.g., albuterol) for treatment of symptoms that occur acutely, despite regular twice  
431 daily (morning and evening) use of ADVAIR DISKUS.

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

437 **3. Watch for Increasing Use of Inhaled, Short-Acting Beta<sub>2</sub>-agonists. Which Is a Marker of**  
438 **Deteriorating Asthma.** Asthma may deteriorate acutely over a period of hours or chronically over  
439 several days or longer. If the patient's inhaled, short-acting beta<sub>2</sub>-agonist becomes less effective,  
440 the patient needs more inhalations than usual, or the patient develops a significant decrease in  
441 PEF, these may be a marker of destabilization of asthma. In this setting, the patient requires  
442 immediate reevaluation with reassessment of the treatment regimen, giving special consideration to  
443 the possible need for replacing the current strength of ADVAIR DISKUS with a higher strength,  
444 adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not  
445 use more than one inhalation twice daily (morning and evening) of ADVAIR DISKUS.

446 **4. Do Not Use an Inhaled, Long-Acting Beta<sub>2</sub>-agonist In Conjunction With ADVAIR DISKUS.**

447 Patients who are receiving ADVAIR DISKUS twice daily should not use salmeterol or other  
448 long-acting inhaled beta<sub>2</sub>-agonists for prevention of exercise-induced bronchospasm or the  
449 maintenance treatment of asthma. Additional benefit would not be gained from using supplemental  
450 salmeterol for prevention of exercise-induced bronchospasm since ADVAIR DISKUS already  
451 contains salmeterol.

452 **5. Do Not Exceed Recommended Dosage:** ADVAIR DISKUS should not be used more often or at  
453 higher doses than recommended. Fatalities have been reported in association with excessive use of  
454 inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the  
455 recommended dose) have been associated with clinically significant prolongation of the QT<sub>c</sub>  
456 interval, which has the potential for producing ventricular arrhythmias.

457 **6. Paradoxical Bronchospasm:** As with other inhaled asthma medications, ADVAIR DISKUS can  
458 produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm  
459 occurs following dosing with ADVAIR DISKUS, it should be treated immediately with a short-acting,  
460 inhaled bronchodilator. ADVAIR DISKUS should be discontinued immediately, and alternative  
461 therapy should be instituted.

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- 462 7. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after  
463 administration of ADVAIR DISKUS, as demonstrated by cases of urticaria, angioedema, rash, and  
464 bronchospasm.
- 465 8. Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as stridor  
466 and choking, have been reported in patients receiving fluticasone propionate and salmeterol,  
467 components of ADVAIR DISKUS.
- 468 9. Cardiovascular Disorders: ADVAIR DISKUS, like all products containing sympathomimetic  
469 amines, should be used with caution in patients with cardiovascular disorders, especially coronary  
470 insufficiency, cardiac arrhythmias, and hypertension. Salmeterol, a component of ADVAIR DISKUS,  
471 can produce a clinically significant cardiovascular effect in some patients as measured by pulse  
472 rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of  
473 salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition,  
474 beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening  
475 of the T wave, prolongation of the QT<sub>c</sub> interval, and ST segment depression. The clinical  
476 significance of these findings is unknown.
- 477 10. Discontinuation of Systemic Corticosteroids: Transfer of patients from systemic corticosteroid  
478 therapy to ADVAIR DISKUS may unmask conditions previously suppressed by the systemic  
479 corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, and arthritis.
- 480 11. Immunosuppression: Persons who are using drugs that suppress the immune system are more  
481 susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have  
482 a more serious or even fatal course in susceptible children or adults using corticosteroids. In such  
483 children or adults who have not had these diseases or been properly immunized, particular care  
484 should be taken to avoid exposure. How the dose, route, and duration of corticosteroid  
485 administration affect the risk of developing a disseminated infection is not known. The contribution  
486 of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If  
487 exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated.  
488 If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be  
489 indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If  
490 chickenpox develops, treatment with antiviral agents may be considered.

491

492 **PRECAUTIONS:**

- 493 **General:** 1. Cardiovascular Effects: No effect on the cardiovascular system is usually seen after the  
494 administration of inhaled ADVAIR DISKUS at recommended doses. The cardiovascular and central  
495 nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart  
496 rate, excitement) can occur after use of salmeterol, a component of ADVAIR DISKUS, and may  
497 require discontinuation of ADVAIR DISKUS. ADVAIR DISKUS, like all medications containing  
498 sympathomimetic amines, should be used with caution in patients with cardiovascular disorders.

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499 especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive  
500 disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic  
501 amines.

502 As has been described with other beta-adrenergic agonist bronchodilators, clinically significant  
503 changes in electrocardiograms have been seen infrequently in individual patients in controlled  
504 clinical studies with ADVAIR DISKUS and salmeterol. Clinically significant changes in systolic  
505 and/or diastolic blood pressure and pulse rate have been seen infrequently in individual patients in  
506 controlled clinical studies with salmeterol, a component of ADVAIR DISKUS.

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

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

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

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

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

531 It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression  
532 may appear in a small number of patients, particularly at higher doses. If such changes occur, the  
533 dose of fluticasone propionate should be reduced slowly, consistent with accepted procedures for  
534 reducing systemic corticosteroids and for management of asthma symptoms.

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

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

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

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

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

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

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

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

570 1. Patients should use ADVAIR DISKUS at regular intervals as directed. Results of clinical trials  
571 indicate significant improvement may occur within the first 30 minutes of taking the first dose;

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- 572 however, the full benefit may not be achieved until treatment has been administered for 1 week or  
573 longer. The patient should not exceed the prescribed dosage and should contact the physician if  
574 symptoms do not improve or if the condition worsens.
- 575 2. The bronchodilation from a single dose of ADVAIR DISKUS may last up to 12 hours or longer.  
576 The recommended dosage (1 inhalation twice daily, morning and evening) should not be exceeded.  
577 Patients who are receiving ADVAIR DISKUS twice daily should not use salmeterol or other  
578 long-acting inhaled beta<sub>2</sub>-agonists for prevention of exercise-induced bronchospasm or maintenance  
579 treatment of asthma.
- 580 3. ADVAIR DISKUS is not meant to relieve acute asthma symptoms and extra doses should not be  
581 used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta<sub>2</sub>-agonist  
582 such as albuterol (the physician should provide the patient with such medication and instruct the  
583 patient in how it should be used).
- 584 4. The physician should be notified immediately if any of the following situations occur, which may  
585 be a sign of seriously worsening asthma:
- 586 • Decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonists
  - 587 • Need for more inhalations than usual of inhaled, short-acting beta<sub>2</sub>-agonists
  - 588 • Significant decrease in peak flow as outlined by the physician
- 589 5. Patients should be cautioned regarding common adverse cardiovascular effects, such as  
590 palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- 591 6. When patients are prescribed ADVAIR DISKUS, other inhaled drugs and asthma medications  
592 should be used only as directed by the physician.
- 593 7. ADVAIR DISKUS should not be used with a spacer device.
- 594 8. If you are pregnant or nursing, contact your physician about the use of ADVAIR DISKUS.
- 595 9. Effective and safe use of ADVAIR DISKUS includes an understanding of the way that it should be  
596 used:
- 597 • Never exhale into the DISKUS.
  - 598 • Never attempt to take the DISKUS apart.
  - 599 • Always activate and use the DISKUS in a level, horizontal position.
  - 600 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
  - 601 • Always keep the DISKUS in a dry place.
  - 602 • Discard 1 month after removal from the moisture-protective foil overwrap pouch or after every  
603 blister has been used (when the dose indicator reads "0"), whichever comes first.
- 604 10. Patients should be warned to avoid exposure to chickenpox or measles and, if they are  
605 exposed, to consult their physicians without delay.
- 606 11. For the proper use of ADVAIR DISKUS and to attain maximum improvement, the patient should  
607 read and follow carefully the accompanying Patient's Instructions for Use.

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608 Drug Interactions: ADVAIR DISKUS has been used concomitantly with other drugs, including  
609 short-acting beta<sub>2</sub>-agonists, methylxanthines, and intranasal corticosteroids, commonly used in  
610 patients with asthma, without adverse drug reactions. No formal drug interaction studies have been  
611 performed with ADVAIR DISKUS.

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

618 **Methylxanthines:** The concurrent use of intravenously or orally administered methylxanthines  
619 (e.g., aminophylline, theophylline) by patients receiving ADVAIR DISKUS has not been completely  
620 evaluated. In clinical trials, 39 patients receiving ADVAIR DISKUS 100/50, 250/50, or 500/50 twice  
621 daily concurrently with a theophylline product had adverse event rates similar to those in 304  
622 patients receiving ADVAIR DISKUS without theophylline. Similar results were observed in patients  
623 receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily concurrently with a  
624 theophylline product (n = 39) or without theophylline (n = 132).

625 **Fluticasone Propionate Nasal Spray:** In patients taking ADVAIR DISKUS in clinical trials, no  
626 difference in the profile of adverse events or HPA axis effects was noted between patients taking  
627 FLONASE® (fluticasone propionate) Nasal Spray, 50 mcg concurrently (n = 46) and those who were  
628 not (n = 130).

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

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

641 **Diuretics:** The ECG changes and/or hypokalemia that may result from the administration of  
642 nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by  
643 beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although

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644 the clinical significance of these effects is not known, caution is advised in the coadministration of  
645 beta-agonists with nonpotassium-sparing diuretics.

646 **Ketoconazole and Other Inhibitors of Cytochrome P450:** In a placebo-controlled, crossover  
647 study in 8 healthy volunteers, coadministration of a single dose of fluticasone propionate  
648 (1000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased  
649 mean fluticasone propionate concentrations, a reduction in plasma cortisol AUC, and no effect on  
650 urinary excretion of cortisol. This interaction may be due to an inhibition of cytochrome P450 3A4 by  
651 ketoconazole, which is also the route of metabolism of fluticasone propionate. Care should be  
652 exercised when ADVAIR DISKUS is coadministered with long-term ketoconazole and other known  
653 cytochrome P450 3A4 inhibitors.

654 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone Propionate:** Fluticasone  
655 propionate demonstrated no tumorigenic potential in mice at oral doses up to 1000 mcg/kg  
656 (approximately 4 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
657 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than the maximum  
658 recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) for 104 weeks.

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

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

666 **Salmeterol:** In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of  
667 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose in  
668 adults based on comparison of the plasma area under the curves (AUCs)) caused a dose-related  
669 increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas  
670 of the uterus, and cysts in the ovaries. The incidence of leiomyosarcomas was not statistically  
671 significant. No tumors were seen at 0.2 mg/kg (approximately 3 times the maximum recommended  
672 daily inhalation doses in adults based on comparison of the AUCs).

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



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

685 **Pregnancy: Teratogenic Effects: ADVAIR DISKUS:** Pregnancy Category C. From the  
686 reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using  
687 combinations of fluticasone propionate and salmeterol compared to toxicity data from the  
688 components administered separately. In mice combining 150 mcg/kg subcutaneously of fluticasone  
689 propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
690 basis) with 10 mg/kg orally of salmeterol (approximately 450 times the maximum recommended  
691 daily inhalation dose in adults on a mg/m<sup>2</sup> basis) were teratogenic. Cleft palate, fetal death,  
692 increased implantation loss and delayed ossification was seen. These observations are  
693 characteristic of glucocorticoids. No developmental toxicity was observed at combination doses up  
694 to 40 mcg/kg subcutaneously of fluticasone propionate (less than the maximum recommended daily  
695 inhalation dose in adults on a mcg/m<sup>2</sup> basis) and up to 1.4 mg/kg orally of salmeterol (approximately  
696 65 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis. In rats, no  
697 teratogenicity was observed at combination doses up to 30 mcg/kg subcutaneously of fluticasone  
698 propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
699 basis) and up to 1 mg/kg of salmeterol (approximately 90 times the maximum recommended daily  
700 inhalation dose in adults on a mg/m<sup>2</sup> basis). Combining 100 mcg/kg subcutaneously of fluticasone  
701 propionate (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
702 basis) with 10 mg/kg orally of salmeterol (approximately 900 times the maximum recommended  
703 daily inhalation dose in adults on a mg/m<sup>2</sup> basis) produced maternal toxicity, decreased placental  
704 weight, decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital  
705 bone. There are no adequate and well-controlled studies with ADVAIR DISKUS in pregnant women.  
706 ADVAIR DISKUS should be used during pregnancy only if the potential benefit justifies the potential  
707 risk to the fetus.

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

713 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of  
714 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis).  
715 However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 5  
716 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) of fluticasone

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717 propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the  
718 established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY).

719 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose of  
720 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a  
721 mcg/m<sup>2</sup> basis) administration of a subcutaneous or an oral dose of 100 mcg/kg to rats,  
722 (approximately equivalent to the maximum recommended daily inhalation dose in adults on a  
723 mcg/m<sup>2</sup> basis) and an oral dose of 300 mcg/kg administered to rabbits (approximately 5 times the  
724 maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis).

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

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

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

741 New Zealand White rabbits were less sensitive since only delayed ossification of the frontal  
742 bones was seen at an oral dose of 10 mg/kg (approximately 1800 times the maximum  
743 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Extensive use of other  
744 beta-agonists has provided no evidence that these class effects in animals are relevant to their use  
745 in humans. There are no adequate and well-controlled studies with salmeterol in pregnant women.  
746 Salmeterol should be used during pregnancy only if the potential benefit justifies the potential risk to  
747 the fetus.

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

751 **Use in Labor and Delivery:** There are no well-controlled human studies that have investigated  
752 effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the potential for  
753 beta-agonist interference with uterine contractility, use of ADVAIR DISKUS for management of

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754 asthma during labor should be restricted to those patients in whom the benefits clearly outweigh the  
755 risks.

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

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

766 Caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.  
767 **Pediatric Use:** The safety and effectiveness of ADVAIR DISKUS in children under 12 years of age  
768 has not been established. In one 12-week study, 257 patients 4 to 11 years inadequately controlled  
769 using inhaled corticosteroids were randomized to ADVAIR DISKUS 100/50 or concurrent therapy  
770 with fluticasone propionate inhalation powder 100 mcg plus salmeterol inhalation powder 50 mcg  
771 twice daily. The pattern of adverse events reported in patients 4 to 11 years of age was similar to  
772 that seen in patients 12 years of age and older treated with ADVAIR DISKUS.

773 Controlled clinical studies have shown that orally inhaled corticosteroids may cause a reduction  
774 in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory  
775 evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of  
776 systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis  
777 function. The long-term effects of this reduction in growth velocity associated with orally inhaled  
778 corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up"  
779 growth following discontinuation of treatment with orally inhaled corticosteroids has not been  
780 adequately studied.

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

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790 **Geriatric Use:** Of the total number of patients in clinical studies of ADVAIR DISKUS, 44 were  
791 65 years of age or older and 3 were 75 years of age or older. No overall differences in safety were  
792 observed between these patients and younger patients, and other reported clinical experience,  
793 including studies of the individual components, has not identified differences in responses between  
794 the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled  
795 out. As with other products containing beta<sub>2</sub>-agonists, special caution should be observed when  
796 using ADVAIR DISKUS in geriatric patients who have concomitant cardiovascular disease that  
797 could be adversely affected by beta<sub>2</sub>-agonists. Based on available data for ADVAIR DISKUS or its  
798 active components, no adjustment of dosage of ADVAIR DISKUS in geriatric patients is warranted.  
799

800 **ADVERSE REACTIONS:** The incidence of common adverse experiences in Table 3 is based upon  
801 2 placebo-controlled, 12-week, US clinical studies (Studies 1 and 2). A total of 705 adolescent and  
802 adult patients (349 females and 356 males) previously treated with salmeterol or inhaled  
803 corticosteroids were treated twice daily with ADVAIR DISKUS (100/50- or 250/50-mcg doses).  
804 fluticasone propionate inhalation powder (100- or 250-mcg doses), salmeterol inhalation powder  
805 50 mcg, or placebo.  
806

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Table 3: Overall Adverse Effects With ≥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) %	Salmetero 150 mcg (n = 180) %	Placebo (n = 175) %
<b>Ear, nose, and throat</b>						
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	4
Oral candidiasis	1	4	2	2	0	0
<b>Lower respiratory</b>						
Viral respiratory infections	4	4	4	10	6	3
Bronchitis	2	8	1	2	2	2
Cough	3	6	0	0	3	2
<b>Neurology</b>						
Headaches	12	13	14	8	10	7
<b>Gastrointestinal</b>						
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
<b>Non-site specific</b>						
Candidiasis unspecified site	3	0	1	4	0	1
<b>Musculoskeletal</b>						
Musculoskeletal pain	4	2	1	5	3	3
<b>Average duration of exposure (days)</b>	<b>77.3</b>	<b>78.7</b>	<b>72.4</b>	<b>70.1</b>	<b>60.1</b>	<b>42.3</b>

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808

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

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

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

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

819 **Cardiovascular:** Palpitations.

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

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

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

826 **Gastrointestinal:** Dental discomfort and pain, gastrointestinal signs and symptoms,  
827 gastrointestinal infections, gastroenteritis, gastrointestinal disorders, oral ulcerations, oral erythema  
828 and rashes, constipation, appendicitis, oral discomfort and pain.

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

830 **Lower Respiratory:** Lower respiratory signs and symptoms, pneumonia, lower respiratory  
831 infections.

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

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

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

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

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

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844 **Observed During Clinical Practice:** In addition to adverse events reported from clinical trials, the  
 845 following events have been identified during postapproval use of ADVAIR DISKUS, fluticasone  
 846 propionate, and/or salmeterol. Because they are reported voluntarily from a population of unknown  
 847 size, estimates of frequency cannot be made. These events have been chosen for inclusion due to  
 848 a combination of their seriousness, frequency of reporting, or potential causal connection to  
 849 ADVAIR DISKUS, fluticasone propionate, and/or salmeterol.

850 In extensive US and worldwide postmarketing experience with salmeterol, a component of  
 851 ADVAIR DISKUS, serious exacerbations of asthma, including some that have been fatal, have been  
 852 reported. In most cases, these have occurred in patients with severe asthma and/or in some  
 853 patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also  
 854 occurred in a few patients with less severe asthma. It was not possible from these reports to  
 855 determine whether salmeterol contributed to these events or simply failed to relieve the  
 856 deteriorating asthma.

857 **Cardiovascular:** Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular  
 858 tachycardia), ventricular tachycardia.

859 **Ear, Nose, and Throat:** Aphonía, earache, paranasal sinus pain, throat soreness and irritation.

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

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

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

864 **Neurology:** Paresthesia, restlessness.

865 **Non-Site Specific:** Immediate and delayed hypersensitivity reaction, pallor.

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

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

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

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

873 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate, a  
 874 component of ADVAIR DISKUS, may present with systemic eosinophilic conditions, with some  
 875 patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a  
 876 condition that is often treated with systemic corticosteroid therapy. These events usually, but not  
 877 always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy  
 878 following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have  
 879 also been reported with other inhaled corticosteroids in this clinical setting. While ADVAIR DISKUS  
 880 should not be used for transferring patients from systemic corticosteroid therapy, physicians should

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

881 be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications,  
882 and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate  
883 and these underlying conditions has not been established (see PRECAUTIONS: Eosinophilic  
884 Conditions).

885

886 **OVERDOSAGE:**

887 **ADVAIR DISKUS:** No deaths occurred in rats given combinations of salmeterol and fluticasone  
888 propionate at acute inhalation doses of 9.6 and 1.9 mg/kg, respectively (approximately 320 and 15  
889 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis).

890 **Fluticasone Propionate:** Chronic overdosage with fluticasone propionate may result in  
891 signs/symptoms of hypercorticism (see PRECAUTIONS). Inhalation by healthy volunteers of a  
892 single dose of 4000 mcg of fluticasone propionate inhalation powder or single doses of 1760 or  
893 3520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate  
894 given by inhalation aerosol at doses of 1320 mcg twice daily for 7 to 15 days to healthy human  
895 volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy  
896 volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated.  
897 Adverse reactions were of mild or moderate severity, and incidences were similar in active and  
898 placebo treatment groups. The oral and subcutaneous median lethal doses in mice and rats were  
899 >1000 mg/kg (>4300 and >8700 times, respectively, the maximum recommended daily inhalation  
900 dose in adults on a mg/m<sup>2</sup> basis).

901 **Salmeterol:** The expected signs and symptoms with overdosage of salmeterol are those of  
902 excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and  
903 symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or  
904 hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache,  
905 tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.  
906 Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic  
907 adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or  
908 arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to  
909 clinically significant prolongation of the QT<sub>c</sub> interval, which can produce ventricular arrhythmias.  
910 Other signs of overdosage may include hypokalemia and hyperglycemia.

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

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



**ADVAIR™ DISKUS® 100/50**  
**(fluticasone propionate 100 mcg and salmeterol® 50 mcg Inhalation powder)**  
**ADVAIR™ DISKUS® 250/50**  
**(fluticasone propionate 250 mcg and salmeterol® 50 mcg Inhalation powder)**  
**ADVAIR™ DISKUS® 500/50**  
**(fluticasone propionate 500 mcg and salmeterol® 50 mcg Inhalation powder)**

918 No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg (approximately  
919 250 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis) and in  
920 dogs at an inhalation dose of 0.7 mg/kg (approximately 200 times the maximum recommended  
921 daily inhalation dose in adults on a mg/m<sup>2</sup> basis). By the oral route, no deaths occurred in mice at  
922 150 mg/kg (approximately 6500 times the maximum recommended daily inhalation dose in adults  
923 on a mg/m<sup>2</sup> basis) and in rats at 1000 mg/kg (approximately 86,000 times the maximum  
924 recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis).

925

926 **DOSAGE AND ADMINISTRATION:** ADVAIR DISKUS is available in 3 strengths, ADVAIR DISKUS  
927 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50, containing 100, 250, and 500 mcg  
928 of fluticasone propionate, respectively, and 50 mcg of salmeterol per inhalation. ADVAIR DISKUS  
929 should be administered by the orally inhaled route only (see PATIENT'S INSTRUCTIONS FOR  
930 USE).

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

933 The recommended starting doses for ADVAIR DISKUS are based upon patients' current asthma  
934 therapy.

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

938 • For patients on an inhaled corticosteroid, Table 4 provides the recommended starting dose.

939 The maximum recommended dose is ADVAIR DISKUS 500/50 twice daily.

940 For all patients it is desirable to titrate to the lowest effective strength after adequate  
941 asthma stability is achieved.

942

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**ADVAIR™ DISKUS® 100/50**  
 (fluticasone propionate 100 mcg and salmeterol\* 50 mcg inhalation powder)  
**ADVAIR™ DISKUS® 250/50**  
 (fluticasone propionate 250 mcg and salmeterol\* 50 mcg inhalation powder)  
**ADVAIR™ DISKUS® 500/50**  
 (fluticasone propionate 500 mcg and salmeterol\* 50 mcg inhalation powder)

943 **Table 4: Recommended Doses of ADVAIR DISKUS for Patients Taking Inhaled Corticosteroids**

Current Daily Dose of Inhaled Corticosteroid		Recommended Strength and Dosing Schedule of ADVAIR DISKUS
Beclomethasone dipropionate	≤420 mcg	100/50 twice daily
	482-840 mcg	250/50 twice daily
Budesonide	≤400 mcg	100/50 twice daily
	800-1200 mcg	250/50 twice daily
	1600 mcg*	500/50 twice daily
Flunisolide	≤1000 mcg	100/50 twice daily
	1250-2000 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
	1000 mcg*	500/50 twice daily
Triamcinolone acetonide	≤1000 mcg	100/50 twice daily
	1100-1600 mcg	250/50 twice daily

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

945

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

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

953 Patients who are receiving ADVAIR DISKUS twice daily should not use salmeterol for prevention  
 954 of exercise-induced bronchospasm, or for any other reason.

955 Improvement in asthma control following inhaled administration of ADVAIR DISKUS can occur  
 956 within 30 minutes of beginning treatment, although maximum benefit may not be achieved for  
 957 1 week or longer after starting treatment. Individual patients will experience a variable time to onset  
 958 and degree of symptom relief.

959 For patients who do not respond adequately to the starting dose after 2 weeks of therapy,  
 960 replacing the current strength of ADVAIR DISKUS with a higher strength may provide additional  
 961 asthma control.

**ADVAIR™ DISKUS® 100/50**  
(fluticasone propionate 100 mcg and salmeterol® 50 mcg Inhalation powder)  
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**ADVAIR™ DISKUS® 500/50**  
(fluticasone propionate 500 mcg and salmeterol® 50 mcg Inhalation powder)

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

966 Rinsing the mouth after inhalation is advised.

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

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

973

974 **HOW SUPPLIED:** ADVAIR DISKUS 100/50 is supplied as a disposable, purple-colored device  
975 containing 60 blisters. The DISKUS Inhalation device is packaged within a purple-colored,  
976 plastic-coated, moisture-protective foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also  
977 supplied in an institutional pack of 1 purple-colored, disposable DISKUS Inhalation device  
978 containing 28 blisters. The DISKUS Inhalation device is packaged within a purple-colored,  
979 plastic-coated, moisture-protective foil pouch (NDC 0173-0695-02).

980 ADVAIR DISKUS 250/50 is supplied as a disposable, purple-colored device containing 60  
981 blisters. The DISKUS Inhalation device is packaged within a purple-colored, plastic-coated,  
982 moisture-protective foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an  
983 institutional pack of 1 purple-colored, disposable DISKUS Inhalation device containing 28 blisters.  
984 The DISKUS Inhalation device is packaged within a purple-colored, plastic-coated,  
985 moisture-protective foil pouch (NDC 0173-0696-02).

986 ADVAIR DISKUS 500/50 is supplied as a disposable, purple-colored device containing 60  
987 blisters. The DISKUS Inhalation device is packaged within a purple-colored, plastic-coated,  
988 moisture-protective foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an  
989 institutional pack of 1 purple-colored, disposable DISKUS Inhalation device containing 28 blisters.  
990 The DISKUS Inhalation device is packaged within a purple-colored, plastic-coated,  
991 moisture-protective foil pouch (NDC 0173-0697-02).

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

997

998

**ADVAIR™ DISKUS® 100/50****(fluticasone propionate 100 mcg and salmeterol™ 50 mcg inhalation powder)****ADVAIR™ DISKUS® 250/50****(fluticasone propionate 250 mcg and salmeterol™ 50 mcg inhalation powder)****ADVAIR™ DISKUS® 500/50****(fluticasone propionate 500 mcg and salmeterol™ 50 mcg inhalation powder)**

999

**GlaxoWellcome**

1000

Glaxo Wellcome Inc.

1001

Research Triangle Park, NC 27709

1002

1003

US Patent Nos. 4,335,121; 4,992,474; 5,225,445; 5,126,375; D342,994; 5,270,305; 5,860,419;

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5,590,645; and 5,873,360

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August 2000

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Product logo

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**ADVAIR™ DISKUS® 100/50**

7

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

8

9

**ADVAIR™ DISKUS® 250/50**

10

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

11

12

**ADVAIR™ DISKUS® 500/50**

13

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

14

15

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

16

17

18

**FOR ORAL INHALATION ONLY**

19

20

(Illustration of device with parts labeled:

21

Outer Case

22

Mouthpiece

23

Lever

24

Thumbgrip

25

Dose Indicator)

26

27

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

28

29

30

31

*For more information ask your doctor or pharmacist.*

32

33

34

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

35

36

37

38

Asthma is a long-term condition affecting the lungs. Symptoms of asthma include shortness of breath, wheezing, chest tightness, and cough. Two main causes of asthma symptoms are bronchoconstriction (tightening of the muscles surrounding the airways) and inflammation (swelling and irritation of the airways).

39

40

41

42

43

ADVAIR DISKUS contains 2 medicines, fluticasone propionate and salmeterol xinafoate, which treat these 2 causes of asthma symptoms. Fluticasone propionate is a synthetic corticosteroid.

44

45 Corticosteroids are natural anti-inflammatory substances found in the body. They are used to treat  
46 asthma because they reduce airway inflammation.  
47

48 Salmeterol is a long-acting bronchodilator that helps prevent and relieve bronchospasm, making it  
49 easier to breathe.  
50

51 When inhaled regularly, ADVAIR DISKUS helps to prevent symptoms of asthma.  
52

53 **Important Points to Remember About Using ADVAIR DISKUS**

54 **1. TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE:**

- 55 • If you are pregnant (or intending to become pregnant),  
56 • If you are breastfeeding a baby,  
57 • If you are allergic to ADVAIR DISKUS, or any other orally inhaled bronchodilator or  
58 corticosteroid. In some circumstances, this medicine may not be suitable and your doctor may  
59 wish to give you a different medicine.  
60 • Make sure that your doctor knows what other medicines you are taking.

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

66 **3. You may feel better after the first dose of ADVAIR DISKUS; however, it may take 1 week or**  
67 **longer to achieve maximum benefit. It is IMPORTANT THAT YOU USE ADVAIR DISKUS**  
68 **REGULARLY. DO NOT STOP TREATMENT EVEN IF YOU ARE FEELING BETTER unless**  
69 **told to do so by your doctor.**

70 **4. If you miss a dose, just take your next scheduled dose when it is due. DO NOT DOUBLE the**  
71 **dose.**

72 **5. DO NOT USE ADVAIR DISKUS TO RELIEVE SUDDEN ASTHMA SYMPTOMS (e.g., sudden**  
73 **severe onset or worsening of wheezing, cough, chest tightness, and/or shortness of breath that**  
74 **has been diagnosed by your doctor as due to asthma). If you experience sudden asthma**  
75 **symptoms, you should not take ADVAIR DISKUS to relieve these symptoms. Sudden**  
76 **asthma symptoms should be treated with an inhaled, short-acting bronchodilator such as**  
77 **albuterol. If you do not have an inhaled, short-acting bronchodilator, contact your doctor to have**  
78 **one prescribed for you.**

79 **6. Tell your doctor immediately if your asthma is getting worse, as indicated by any of the**  
80 **following situations.**

- 81 • Your inhaled, short-acting bronchodilator becomes less effective.  
82 • You need more inhalations than usual of your inhaled, short-acting bronchodilator.  
83 • You have a significant decrease in your peak flow measurement as previously defined by your  
84 doctor.

85 **7. If your symptoms do not improve after using ADVAIR DISKUS regularly for 2 weeks, tell your**  
86 **doctor.**

87 8. While you are taking ADVAIR DISKUS twice daily, you should not use SEREVENT<sup>®</sup>  
88 DISKUS<sup>®</sup> (salmeterol xinafoate Inhalation powder) or SEREVENT<sup>®</sup> (salmeterol xinafoate)  
89 Inhalation Aerosol for any reason, including prevention of exercise-induced asthma or  
90 the maintenance treatment of asthma.

91 9. Use other inhaled medicines only as directed by your doctor.

92 10. Do not use ADVAIR DISKUS with a spacer device.

93

94



95

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

96

97

When you take the ADVAIR DISKUS out of the box and foil overwrap pouch, write the "Pouch  
98 opened" and "Use by" dates on the label in the space provided on the device. The "Use by" date  
99 is 1 month from date of opening.

100

101

The DISKUS<sup>®</sup> inhalation device will be in the closed position when the pouch is opened.

102

103

The dose indicator on the top of the DISKUS tells you how many doses are left. The dose indicator  
104 number will decrease each time you use the DISKUS. After the DISKUS has delivered 55 doses (23  
105 doses for the institutional or sample pack), numbers 5 to 0 will appear in red to warn you that there  
106 are only a few doses left (see Figure 1).

107

108

Figure 1

109

110

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

111

112

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

115

116

Figure 2

117

118

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

121

122

Figure 3

123

124

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

126

127

- do not close the DISKUS,
- do not tilt the DISKUS,
- do not play with the lever,
- do not advance the lever more than once.

129

130

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

133

## Figure 4

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

## Figure 5

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

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

## Figure 6

## REMEMBER:

- Never exhale into the DISKUS.
- Never attempt to take the DISKUS apart.
- Always activate and use the DISKUS in a level, horizontal position.
- Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
- Always keep the DISKUS in a dry place.

**STORING YOUR ADVAIR DISKUS**

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

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

**For more information**

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

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

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



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Glaxo Wellcome Inc.

Research Triangle Park, NC 27709

US Patent Nos. 4,335,121; 4,992,474; 5,225,445; 5,126,375; D342,994;  
5,270,305; 5,880,410; 5,590,645; and 5,873,360

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