

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADVAIR DISKUS safely and effectively. See full prescribing information for ADVAIR DISKUS.

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)

FOR ORAL INHALATION USE

Initial U.S. Approval: 2000

WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- Long-acting beta₂-adrenergic agonists (LABA), such as salmeterol, one of the active ingredients in ADVAIR DISKUS, increase the risk of asthma-related death. A US trial showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 out of 13,179 subjects on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. (5.1)
- When treating patients with asthma, only prescribe ADVAIR DISKUS for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. (1.1, 5.1)

INDICATIONS AND USAGE

ADVAIR DISKUS is a combination product containing a corticosteroid and a LABA indicated for:

- Treatment of asthma in patients aged 4 years and older. (1.1)
- Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). (1.2)

Important limitation:

- Not indicated for the relief of acute bronchospasm. (1.1, 1.2)

DOSAGE AND ADMINISTRATION

For oral inhalation only.

- Treatment of asthma in patients aged 12 years and older: 1 inhalation of ADVAIR DISKUS 100/50, 250/50, or 500/50 twice daily. Starting dosage is based on asthma severity. (2.1)
- Treatment of asthma in patients aged 4 to 11 years: 1 inhalation of ADVAIR DISKUS 100/50 twice daily. (2.1)
- Maintenance treatment of COPD: 1 inhalation of ADVAIR DISKUS 250/50 twice daily. (2.2)

DOSAGE FORMS AND STRENGTHS

Inhalation Powder. Inhaler containing a combination of fluticasone propionate (100, 250, or 500 mcg) and salmeterol (50 mcg) as a powder formulation for oral inhalation. (3)

CONTRAINDICATIONS

- Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins. (4)

WARNINGS and PRECAUTIONS

- LABA increase the risk of asthma-related death and asthma-related hospitalizations. Prescribe only for recommended patient populations. (5.1)
- Do not initiate in acutely deteriorating asthma or COPD. Do not use to treat acute symptoms. (5.2)
- Do not use in combination with an additional medicine containing LABA because of risk of overdose. (5.3)
- Candida albicans* infection of the mouth and pharynx may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk. (5.4)
- Increased risk of pneumonia in patients with COPD. Monitor patients for signs and symptoms of pneumonia. (5.5)
- Potential worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infection; ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)
- Risk of impaired adrenal function when transferring from systemic corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to ADVAIR DISKUS. (5.7)
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue ADVAIR DISKUS slowly. (5.8)
- If paradoxical bronchospasm occurs, discontinue ADVAIR DISKUS and institute alternative therapy. (5.10)
- Use with caution in patients with cardiovascular or central nervous system disorders because of beta-adrenergic stimulation. (5.12)
- Assess for decrease in bone mineral density initially and periodically thereafter. (5.13)
- Monitor growth of pediatric patients. (5.14)
- Close monitoring for glaucoma and cataracts is warranted. (5.15)
- Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.16, 5.18)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.17)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 3\%$) include:

- Asthma: Upper respiratory tract infection or inflammation, pharyngitis, dysphonia, oral candidiasis, bronchitis, cough, headaches, nausea and vomiting. (6.1)
- COPD: Pneumonia, oral candidiasis, throat irritation, dysphonia, viral respiratory infections, headaches, musculoskeletal pain. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): Use not recommended. May increase risk of systemic corticosteroid and cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of salmeterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

USE IN SPECIFIC POPULATIONS

Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2014

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1 FULL PRESCRIBING INFORMATION

2 **WARNING: ASTHMA-RELATED DEATH**

3 **Long-acting beta₂-adrenergic agonists (LABA), such as salmeterol, one of the active**
4 **ingredients in ADVAIR DISKUS[®], increase the risk of asthma-related death. Data from a**
5 **large placebo-controlled US trial that compared the safety of salmeterol with placebo**
6 **added to usual asthma therapy showed an increase in asthma-related deaths in subjects**
7 **receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol**
8 **versus 3 deaths out of 13,179 subjects on placebo). Currently available data are inadequate**
9 **to determine whether concurrent use of inhaled corticosteroids or other long-term asthma**
10 **control drugs mitigates the increased risk of asthma-related death from LABA. Available**
11 **data from controlled clinical trials suggest that LABA increase the risk of asthma-related**
12 **hospitalization in pediatric and adolescent patients.**

13 **Therefore, when treating patients with asthma, physicians should only prescribe**
14 **ADVAIR DISKUS for patients not adequately controlled on a long-term asthma control**
15 **medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants**
16 **initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma**
17 **control is achieved and maintained, assess the patient at regular intervals and step down**
18 **therapy (e.g., discontinue ADVAIR DISKUS) if possible without loss of asthma control and**
19 **maintain the patient on a long-term asthma control medication, such as an inhaled**
20 **corticosteroid. Do not use ADVAIR DISKUS for patients whose asthma is adequately**
21 **controlled on low- or medium-dose inhaled corticosteroids [see Warnings and Precautions**
22 **(5.1)].**

23 **1 INDICATIONS AND USAGE**

24 **1.1 Treatment of Asthma**

25 ADVAIR DISKUS is indicated for the treatment of asthma in patients aged 4 years and
26 older.

27 LABA, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, increase
28 the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA
29 increase the risk of asthma-related hospitalization in pediatric and adolescent patients [*see*
30 *Warnings and Precautions (5.1)*]. Therefore, when treating patients with asthma, physicians
31 should only prescribe ADVAIR DISKUS for patients not adequately controlled on a long-term
32 asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly
33 warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma
34 control is achieved and maintained, assess the patient at regular intervals and step down therapy
35 (e.g., discontinue ADVAIR DISKUS) if possible without loss of asthma control and maintain
36 the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not
37 use ADVAIR DISKUS for patients whose asthma is adequately controlled on low- or medium-
38 dose inhaled corticosteroids.

39 Important Limitation of Use: ADVAIR DISKUS is NOT indicated for the relief of
40 acute bronchospasm.

41 **1.2 Maintenance Treatment of Chronic Obstructive Pulmonary Disease**

42 ADVAIR DISKUS 250/50 is indicated for the twice-daily maintenance treatment of
43 airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including
44 chronic bronchitis and/or emphysema. ADVAIR DISKUS 250/50 is also indicated to reduce
45 exacerbations of COPD in patients with a history of exacerbations. ADVAIR DISKUS 250/50
46 twice daily is the only approved dosage for the treatment of COPD because an efficacy
47 advantage of the higher strength ADVAIR DISKUS 500/50 over ADVAIR DISKUS 250/50 has
48 not been demonstrated.

49 Important Limitation of Use: ADVAIR DISKUS is NOT indicated for the relief of
50 acute bronchospasm.

51 **2 DOSAGE AND ADMINISTRATION**

52 ADVAIR DISKUS should be administered as 1 inhalation twice daily by the orally
53 inhaled route only. After inhalation, the patient should rinse his/her mouth with water without
54 swallowing to help reduce the risk of oropharyngeal candidiasis.

55 More frequent administration or a greater number of inhalations (more than 1 inhalation
56 twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some
57 patients are more likely to experience adverse effects with higher doses of salmeterol. Patients
58 using ADVAIR DISKUS should not use additional LABA for any reason. [*See Warnings and*
59 *Precautions (5.3, 5.12).*]

60 **2.1 Asthma**

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

63 Adult and Adolescent Patients Aged 12 Years and Older: For patients aged 12 years
64 and older, the dosage is 1 inhalation twice daily, approximately 12 hours apart.

65 The recommended starting dosages for ADVAIR DISKUS for patients aged 12 years and
66 older are based upon patients' asthma severity.

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

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

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

75 If a previously effective dosage regimen fails to provide adequate improvement in asthma
76 control, the therapeutic regimen should be reevaluated and additional therapeutic options (e.g.,
77 replacing the current strength of ADVAIR DISKUS with a higher strength, adding additional
78 inhaled corticosteroid, initiating oral corticosteroids) should be considered.

79 Pediatric Patients Aged 4 to 11 Years: For patients with asthma aged 4 to 11 years
80 who are not controlled on an inhaled corticosteroid, the dosage is 1 inhalation of ADVAIR
81 DISKUS 100/50 twice daily, approximately 12 hours apart.

82 **2.2 Chronic Obstructive Pulmonary Disease**

83 The recommended dosage for patients with COPD is 1 inhalation of ADVAIR DISKUS
84 250/50 twice daily, approximately 12 hours apart.

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

87 **3 DOSAGE FORMS AND STRENGTHS**

88 Inhalation Powder. Inhaler containing a foil blister strip of powder formulation for oral
89 inhalation. The strip contains a combination of fluticasone propionate 100, 250, or 500 mcg and
90 salmeterol 50 mcg per blister.

91

92 **4 CONTRAINDICATIONS**

93 The use of ADVAIR DISKUS is contraindicated in the following conditions:

- 94 • Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where
95 intensive measures are required [*see Warnings and Precautions (5.2)*]
- 96 • Severe hypersensitivity to milk proteins [*see Warnings and Precautions (5.11), Adverse*
97 *Reactions (6.3), Description (11)*]

98 **5 WARNINGS AND PRECAUTIONS**

99 **5.1 Asthma-Related Death**

100 LABA, such as salmeterol, one of the active ingredients in ADVAIR DISKUS,
101 increase the risk of asthma-related death. Currently available data are inadequate to
102 determine whether concurrent use of inhaled corticosteroids or other long-term asthma
103 control drugs mitigates the increased risk of asthma-related death from LABA. Available
104 data from controlled clinical trials suggest that LABA increase the risk of asthma-related
105 hospitalization in pediatric and adolescent patients. Therefore, when treating patients with
106 asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately
107 controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or
108 whose disease severity clearly warrants initiation of treatment with both an inhaled
109 corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the
110 patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS) if
111 possible without loss of asthma control and maintain the patient on a long-term asthma
112 control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS for
113 patients whose asthma is adequately controlled on low- or medium-dose inhaled
114 corticosteroids.

115 A large placebo-controlled US trial that compared the safety of salmeterol with placebo,
116 each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects
117 receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a
118 randomized double-blind trial that enrolled LABA-naive subjects with asthma to assess the
119 safety of salmeterol 42 mcg twice daily over 28 weeks compared with placebo when added to
120 usual asthma therapy. A planned interim analysis was conducted when approximately half of the
121 intended number of subjects had been enrolled (N = 26,355), which led to premature termination
122 of the trial. The results of the interim analysis showed that subjects receiving salmeterol were at
123 increased risk for fatal asthma events (see Table 1 and Figure 1). In the total population, a higher
124 rate of asthma-related death occurred in subjects treated with salmeterol than those treated with
125 placebo (0.10% versus 0.02%; relative risk: 4.37 [95% CI: 1.25, 15.34]).

126 Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death
127 occurred at a higher rate in subjects treated with salmeterol than in subjects treated with placebo
128 (0.07% versus 0.01%; relative risk: 5.82 [95% CI: 0.70, 48.37]). In African Americans also,
129 asthma-related death occurred at a higher rate in subjects treated with salmeterol than those
130 treated with placebo (0.31% versus 0.04%; relative risk: 7.26 [95% CI: 0.89, 58.94]). Although
131 the relative risks of asthma-related death were similar in Caucasians and African Americans, the
132 estimate of excess deaths in subjects treated with salmeterol was greater in African Americans
133 because there was a higher overall rate of asthma-related death in African American subjects (see
134 Table 1). Given the similar basic mechanisms of action of beta₂-agonists, the findings seen in the
135 SMART trial are considered a class effect.

136 Post-hoc analyses in pediatric subjects aged 12 to 18 years were also performed. Pediatric
137 subjects accounted for approximately 12% of subjects in each treatment arm. Respiratory-related

138 death or life-threatening experience occurred at a similar rate in the salmeterol group (0.12%
139 [2/1,653]) and the placebo group (0.12% [2/1,622]; relative risk: 1.0 [95% CI: 0.1, 7.2]). All-
140 cause hospitalization, however, was increased in the salmeterol group (2% [35/1,653]) versus the
141 placebo group (<1% [16/1,622]; relative risk: 2.1 [95% CI: 1.1, 3.7]).

142 The data from the SMART trial are not adequate to determine whether concurrent use of
143 inhaled corticosteroids, such as fluticasone propionate, the other active ingredient in ADVAIR
144 DISKUS, or other long-term asthma control therapy mitigates the risk of asthma-related death.
145

146 **Table 1. Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research**
147 **Trial (SMART)**

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

148 ^a Life-table 28-week estimate, adjusted according to the subjects' actual lengths of exposure to
149 trial treatment to account for early withdrawal of subjects from the trial.

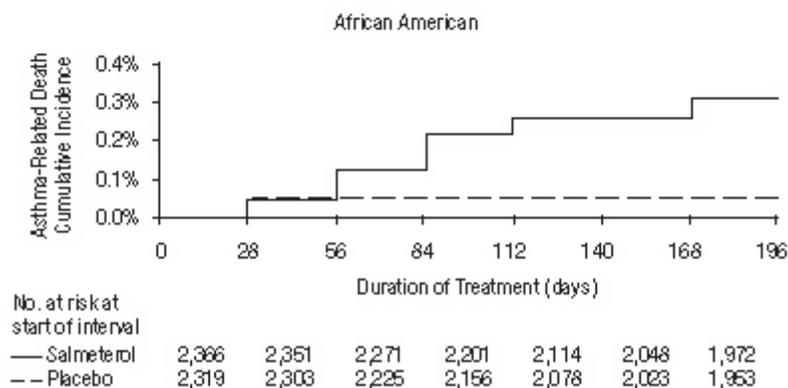
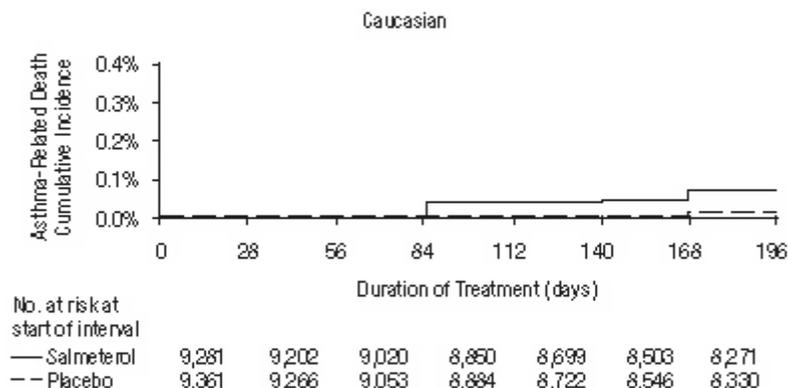
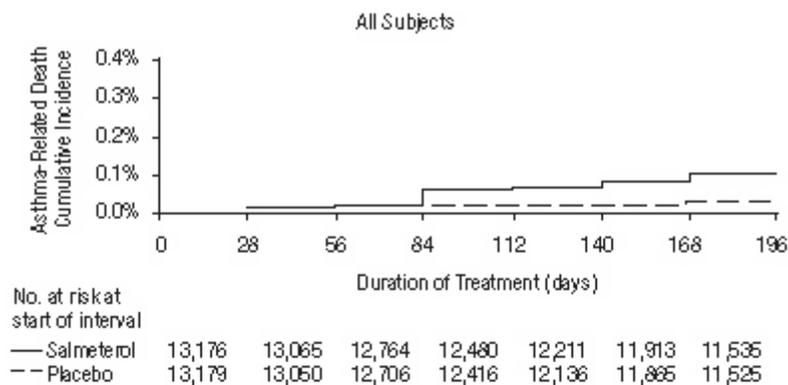
150 ^b Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the
151 rate in the placebo group. The relative risk indicates how many more times likely an asthma-
152 related death occurred in the salmeterol group than in the placebo group in a 28-week
153 treatment period.

154 ^c Estimate of the number of additional asthma-related deaths in subjects treated with salmeterol
155 in SMART, assuming 10,000 subjects received salmeterol for a 28-week treatment period.
156 Estimate calculated as the difference between the salmeterol and placebo groups in the rates
157 of asthma-related death multiplied by 10,000.

158 ^d The Total Population includes the following ethnic origins listed on the case report form:
159 Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population
160 includes those subjects whose ethnic origin was not reported. The results for Caucasian and
161 African American subpopulations are shown above. No asthma-related deaths occurred in the
162 Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149),
163 or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death

164 occurred in the placebo group in the subpopulation whose ethnic origin was not reported
 165 (salmeterol n = 130, placebo n = 127).
 166

167 **Figure 1. Cumulative Incidence of Asthma-Related**
 168 **Deaths in the 28-Week Salmeterol Multi-center Asthma**
 169 **Research Trial (SMART), by Duration of Treatment**
 170



171
 172

173 A 16-week clinical trial performed in the United Kingdom, the Salmeterol Nationwide
174 Surveillance (SNS) trial, showed results similar to the SMART trial. In the SNS trial, the rate of
175 asthma-related death was numerically, though not statistically significantly, greater in subjects
176 with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol
177 (180 mcg 4 times daily) added to usual asthma therapy.

178 *The SNS and SMART trials enrolled subjects with asthma. No trials have been conducted*
179 *that were primarily designed to determine whether the rate of death in patients with COPD is*
180 *increased by LABA.*

181 **5.2 Deterioration of Disease and Acute Episodes**

182 ADVAIR DISKUS should not be initiated in patients during rapidly deteriorating or
183 potentially life-threatening episodes of asthma or COPD. ADVAIR DISKUS has not been
184 studied in subjects with acutely deteriorating asthma or COPD. The initiation of ADVAIR
185 DISKUS in this setting is not appropriate.

186 Serious acute respiratory events, including fatalities, have been reported when salmeterol,
187 a component of ADVAIR DISKUS, has been initiated in patients with significantly worsening or
188 acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma
189 (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation,
190 mechanical ventilation, frequent hospitalizations, previous life-threatening acute asthma
191 exacerbations) and in some patients with acutely deteriorating asthma (e.g., patients with
192 significantly increasing symptoms; increasing need for inhaled, short-acting beta₂-agonists;
193 decreasing response to usual medications; increasing need for systemic corticosteroids; recent
194 emergency room visits; deteriorating lung function). However, these events have occurred in a
195 few patients with less severe asthma as well. It was not possible from these reports to determine
196 whether salmeterol contributed to these events.

197 Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma.
198 In this situation, the patient requires immediate reevaluation with reassessment of the treatment
199 regimen, giving special consideration to the possible need for replacing the current strength of
200 ADVAIR DISKUS with a higher strength, adding additional inhaled corticosteroid, or initiating
201 systemic corticosteroids. Patients should not use more than 1 inhalation twice daily of ADVAIR
202 DISKUS.

203 ADVAIR DISKUS should not be used for the relief of acute symptoms, i.e., as rescue
204 therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting
205 beta₂-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms such as
206 shortness of breath. When prescribing ADVAIR DISKUS, the healthcare provider should also
207 prescribe an inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of acute symptoms,
208 despite regular twice-daily use of ADVAIR DISKUS.

209 When beginning treatment with ADVAIR DISKUS, patients who have been taking oral
210 or inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed
211 to discontinue the regular use of these drugs.

212 **5.3 Excessive Use of ADVAIR DISKUS and Use With Other Long-Acting Beta₂-**
213 **Agonists**

214 ADVAIR DISKUS should not be used more often than recommended, at higher doses
215 than recommended, or in conjunction with other medicines containing LABA, as an overdose
216 may result. Clinically significant cardiovascular effects and fatalities have been reported in
217 association with excessive use of inhaled sympathomimetic drugs. Patients using ADVAIR
218 DISKUS should not use another medicine containing a LABA (e.g., salmeterol, formoterol
219 fumarate, arformoterol tartrate, indacaterol) for any reason.

220 **5.4 Local Effects of Inhaled Corticosteroids**

221 In clinical trials, the development of localized infections of the mouth and pharynx with
222 *Candida albicans* has occurred in subjects treated with ADVAIR DISKUS. When such an
223 infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal
224 therapy while treatment with ADVAIR DISKUS continues, but at times therapy with ADVAIR
225 DISKUS may need to be interrupted. Advise the patient to rinse his/her mouth with water
226 without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

227 **5.5 Pneumonia**

228 Physicians should remain vigilant for the possible development of pneumonia in patients
229 with COPD as the clinical features of pneumonia and exacerbations frequently overlap.

230 Lower respiratory tract infections, including pneumonia, have been reported in patients
231 with COPD following the inhaled administration of corticosteroids, including fluticasone
232 propionate and ADVAIR DISKUS. In 2 replicate 1-year trials in 1,579 subjects with COPD,
233 there was a higher incidence of pneumonia reported in subjects receiving ADVAIR DISKUS
234 250/50 (7%) than in those receiving salmeterol 50 mcg (3%). The incidence of pneumonia in the
235 subjects treated with ADVAIR DISKUS was higher in subjects older than 65 years (9%)
236 compared with the incidence in subjects younger than 65 years (4%). [See *Adverse Reactions*
237 (6.2), *Use in Specific Populations* (8.5).]

238 In a 3-year trial in 6,184 subjects with COPD, there was a higher incidence of pneumonia
239 reported in subjects receiving ADVAIR DISKUS 500/50 compared with placebo (16% with
240 ADVAIR DISKUS 500/50, 14% with fluticasone propionate 500 mcg, 11% with salmeterol 50
241 mcg, and 9% with placebo). Similar to what was seen in the 1-year trials with ADVAIR
242 DISKUS 250/50, the incidence of pneumonia was higher in subjects older than 65 years (18%
243 with ADVAIR DISKUS 500/50 versus 10% with placebo) compared with subjects younger than
244 65 years (14% with ADVAIR DISKUS 500/50 versus 8% with placebo). [See *Adverse Reactions*
245 (6.2), *Use in Specific Populations* (8.5).]

246 **5.6 Immunosuppression**

247 Persons who are using drugs that suppress the immune system are more susceptible to
248 infections than healthy individuals. Chickenpox and measles, for example, can have a more
249 serious or even fatal course in susceptible children or adults using corticosteroids. In such
250 children or adults who have not had these diseases or been properly immunized, particular care
251 should be taken to avoid exposure. How the dose, route, and duration of corticosteroid

252 administration affect the risk of developing a disseminated infection is not known. The
253 contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not
254 known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin
255 (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled
256 intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for
257 complete VZIG and IG prescribing information.) If chickenpox develops, treatment with
258 antiviral agents may be considered.

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

262 **5.7 Transferring Patients From Systemic Corticosteroid Therapy**

263 Particular care is needed for patients who have been transferred from systemically active
264 corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have
265 occurred in patients with asthma during and after transfer from systemic corticosteroids to less
266 systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a
267 number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

268 Patients who have been previously maintained on 20 mg or more of prednisone (or its
269 equivalent) may be most susceptible, particularly when their systemic corticosteroids have been
270 almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs
271 and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection
272 (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although
273 ADVAIR DISKUS may control asthma symptoms during these episodes, in recommended doses
274 it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT
275 provide the mineralocorticoid activity that is necessary for coping with these emergencies.

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

281 Patients requiring oral corticosteroids should be weaned slowly from systemic
282 corticosteroid use after transferring to ADVAIR DISKUS. Prednisone reduction can be
283 accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy
284 with ADVAIR DISKUS. Lung function (mean forced expiratory volume in 1 second [FEV₁] or
285 morning peak expiratory flow [AM PEF]), beta-agonist use, and asthma symptoms should be
286 carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be
287 observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness,
288 nausea and vomiting, and hypotension.

289 Transfer of patients from systemic corticosteroid therapy to ADVAIR DISKUS may
290 unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g.,
291 rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

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

295 **5.8 Hypercorticism and Adrenal Suppression**

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

306 Because of the possibility of significant systemic absorption of inhaled corticosteroids in
307 sensitive patients, patients treated with ADVAIR DISKUS should be observed carefully for any
308 evidence of systemic corticosteroid effects. Particular care should be taken in observing patients
309 postoperatively or during periods of stress for evidence of inadequate adrenal response.

310 It is possible that systemic corticosteroid effects such as hypercorticism and adrenal
311 suppression (including adrenal crisis) may appear in a small number of patients who are sensitive
312 to these effects. If such effects occur, ADVAIR DISKUS should be reduced slowly, consistent
313 with accepted procedures for reducing systemic corticosteroids, and other treatments for
314 management of asthma symptoms should be considered.

315 **5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors**

316 The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir,
317 clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole,
318 telithromycin) with ADVAIR DISKUS is not recommended because increased systemic
319 corticosteroid and increased cardiovascular adverse effects may occur [*see Drug Interactions*
320 (7.1), *Clinical Pharmacology* (12.3)].

321 **5.10 Paradoxical Bronchospasm and Upper Airway Symptoms**

322 As with other inhaled medicines, ADVAIR DISKUS can produce paradoxical
323 bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following
324 dosing with ADVAIR DISKUS, it should be treated immediately with an inhaled, short-acting
325 bronchodilator; ADVAIR DISKUS should be discontinued immediately; and alternative therapy
326 should be instituted. Upper airway symptoms of laryngeal spasm, irritation, or swelling, such as
327 stridor and choking, have been reported in patients receiving ADVAIR DISKUS.

328 **5.11 Immediate Hypersensitivity Reactions**

329 Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm,
330 hypotension), including anaphylaxis, may occur after administration of ADVAIR DISKUS.

331 There have been reports of anaphylactic reactions in patients with severe milk protein allergy

332 after inhalation of powder products containing lactose; therefore, patients with severe milk
333 protein allergy should not use ADVAIR DISKUS [*see Contraindications (4)*].

334 **5.12 Cardiovascular and Central Nervous System Effects**

335 Excessive beta-adrenergic stimulation has been associated with seizures, angina,
336 hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias,
337 nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia
338 [*see Overdosage (10)*]. Therefore, ADVAIR DISKUS, like all products containing
339 sympathomimetic amines, should be used with caution in patients with cardiovascular disorders,
340 especially coronary insufficiency, cardiac arrhythmias, and hypertension.

341 Salmeterol, a component of ADVAIR DISKUS, can produce a clinically significant
342 cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or
343 symptoms. Although such effects are uncommon after administration of salmeterol at
344 recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-
345 agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of
346 the T wave, prolongation of the QTc interval, and ST segment depression. The clinical
347 significance of these findings is unknown. Large doses of inhaled or oral salmeterol (12 to 20
348 times the recommended dose) have been associated with clinically significant prolongation of the
349 QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been
350 reported in association with excessive use of inhaled sympathomimetic drugs.

351 **5.13 Reduction in Bone Mineral Density**

352 Decreases in bone mineral density (BMD) have been observed with long-term
353 administration of products containing inhaled corticosteroids. The clinical significance of small
354 changes in BMD with regard to long-term consequences such as fracture is unknown. Patients
355 with major risk factors for decreased bone mineral content, such as prolonged immobilization,
356 family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition,
357 or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids)
358 should be monitored and treated with established standards of care. Since patients with COPD
359 often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to
360 initiating ADVAIR DISKUS and periodically thereafter. If significant reductions in BMD are
361 seen and ADVAIR DISKUS is still considered medically important for that patient's COPD
362 therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.

363 2-Year Fluticasone Propionate Trial: A 2-year trial in 160 subjects (females aged 18
364 to 40 years, males 18 to 50) with asthma receiving CFC-propelled fluticasone propionate
365 inhalation aerosol 88 or 440 mcg twice daily demonstrated no statistically significant changes in
366 BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by
367 dual-energy x-ray absorptiometry at lumbar regions L1 through L4.

368 3-Year Bone Mineral Density Trial: Effects of treatment with ADVAIR DISKUS
369 250/50 or salmeterol 50 mcg on BMD at the L₁-L₄ lumbar spine and total hip were evaluated in
370 186 subjects with COPD (aged 43 to 87 years) in a 3-year double-blind trial. Of those enrolled,
371 108 subjects (72 males and 36 females) were followed for the entire 3 years. BMD evaluations

372 were conducted at baseline and at 6-month intervals. Conclusions cannot be drawn from this trial
373 regarding BMD decline in subjects treated with ADVAIR DISKUS versus salmeterol due to the
374 inconsistency of treatment differences across gender and between lumbar spine and total hip.

375 In this trial there were 7 non-traumatic fractures reported in 5 subjects treated with
376 ADVAIR DISKUS and 1 non-traumatic fracture in 1 subject treated with salmeterol. None of the
377 non-traumatic fractures occurred in the vertebrae, hip, or long bones.

378 **3-Year Survival Trial:** Effects of treatment with ADVAIR DISKUS 500/50, fluticasone
379 propionate 500 mcg, salmeterol 50 mcg, or placebo on BMD was evaluated in a subset of 658
380 subjects (females and males aged 40 to 80 years) with COPD in the 3-year survival trial. BMD
381 evaluations were conducted at baseline and at 48, 108, and 158 weeks. Conclusions cannot be
382 drawn from this trial because of the large number of dropouts (>50%) before the end of the
383 follow-up and the maldistribution of covariates among the treatment groups that can affect BMD.

384 Fracture risk was estimated for the entire population of subjects with COPD in the
385 survival trial (N = 6,184). The probability of a fracture over 3 years was 6.3% for ADVAIR
386 DISKUS, 5.4% for fluticasone propionate, 5.1% for salmeterol, and 5.1% for placebo.

387 **5.14 Effect on Growth**

388 Orally inhaled corticosteroids may cause a reduction in growth velocity when
389 administered to pediatric patients. Monitor the growth of pediatric patients receiving ADVAIR
390 DISKUS routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled
391 corticosteroids, including ADVAIR DISKUS, titrate each patient's dosage to the lowest dosage
392 that effectively controls his/her symptoms [*see Dosage and Administration (2.1), Use in Specific*
393 *Populations (8.4)*].

394 **5.15 Glaucoma and Cataracts**

395 Glaucoma, increased intraocular pressure, and cataracts have been reported in patients
396 with asthma and COPD following the long-term administration of inhaled corticosteroids,
397 including fluticasone propionate, a component of ADVAIR DISKUS. Therefore, close
398 monitoring is warranted in patients with a change in vision or with a history of increased
399 intraocular pressure, glaucoma, and/or cataracts.

400 Effects of treatment with ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg,
401 salmeterol 50 mcg, or placebo on development of cataracts or glaucoma was evaluated in a
402 subset of 658 subjects with COPD in the 3-year survival trial. Ophthalmic examinations were
403 conducted at baseline and at 48, 108, and 158 weeks. Conclusions about cataracts cannot be
404 drawn from this trial because the high incidence of cataracts at baseline (61% to 71%) resulted in
405 an inadequate number of subjects treated with ADVAIR DISKUS 500/50 who were eligible and
406 available for evaluation of cataracts at the end of the trial (n = 53). The incidence of newly
407 diagnosed glaucoma was 2% with ADVAIR DISKUS 500/50, 5% with fluticasone propionate,
408 0% with salmeterol, and 2% with placebo.

409 **5.16 Eosinophilic Conditions and Churg-Strauss Syndrome**

410 In rare cases, patients on inhaled fluticasone propionate, a component of ADVAIR
411 DISKUS, may present with systemic eosinophilic conditions. Some of these patients have

412 clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often
413 treated with systemic corticosteroid therapy. These events usually, but not always, have been
414 associated with the reduction and/or withdrawal of oral corticosteroid therapy following the
415 introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been
416 reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to
417 eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or
418 neuropathy presenting in their patients. A causal relationship between fluticasone propionate and
419 these underlying conditions has not been established.

420 **5.17 Coexisting Conditions**

421 ADVAIR DISKUS, like all medicines containing sympathomimetic amines, should be
422 used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are
423 unusually responsive to sympathomimetic amines. Doses of the related beta₂-adrenoceptor
424 agonist albuterol, when administered intravenously, have been reported to aggravate preexisting
425 diabetes mellitus and ketoacidosis.

426 **5.18 Hypokalemia and Hyperglycemia**

427 Beta-adrenergic agonist medicines may produce significant hypokalemia in some
428 patients, possibly through intracellular shunting, which has the potential to produce adverse
429 cardiovascular effects [*see Clinical Pharmacology (12.2)*]. The decrease in serum potassium is
430 usually transient, not requiring supplementation. Clinically significant changes in blood glucose
431 and/or serum potassium were seen infrequently during clinical trials with ADVAIR DISKUS at
432 recommended doses.

433 **6 ADVERSE REACTIONS**

434 **LABA, such as salmeterol, one of the active ingredients in ADVAIR DISKUS,**
435 **increase the risk of asthma-related death. Data from a large placebo-controlled US trial**
436 **that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added**
437 **to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving**
438 **salmeterol [*see Warnings and Precautions (5.1)*]. Currently available data are inadequate to**
439 **determine whether concurrent use of inhaled corticosteroids or other long-term asthma**
440 **control drugs mitigates the increased risk of asthma-related death from LABA. Available**
441 **data from controlled clinical trials suggest that LABA increase the risk of asthma-related**
442 **hospitalization in pediatric and adolescent patients [*see Warnings and Precautions (5.1)*].**

443 Systemic and local corticosteroid use may result in the following:

- 444 • *Candida albicans* infection [*see Warnings and Precautions (5.4)*]
- 445 • Pneumonia in patients with COPD [*see Warnings and Precautions (5.5)*]
- 446 • Immunosuppression [*see Warnings and Precautions (5.6)*]
- 447 • Hypercorticism and adrenal suppression [*see Warnings and Precautions (5.8)*]
- 448 • Reduction in bone mineral density [*see Warnings and Precautions (5.13)*]
- 449 • Growth effects [*see Warnings and Precautions (5.14)*]
- 450 • Glaucoma and cataracts [*see Warnings and Precautions (5.15)*]

451 Because clinical trials are conducted under widely varying conditions, adverse reaction
452 rates observed in the clinical trials of a drug cannot be directly compared with rates in the
453 clinical trials of another drug and may not reflect the rates observed in practice.

454 **6.1 Clinical Trials Experience in Asthma**

455 Adult and Adolescent Subjects Aged 12 Years and Older: The incidence of adverse
456 reactions associated with ADVAIR DISKUS in Table 2 is based upon two 12-week, placebo-
457 controlled, US clinical trials (Trials 1 and 2). A total of 705 adult and adolescent subjects (349
458 females and 356 males) previously treated with salmeterol or inhaled corticosteroids were treated
459 twice daily with ADVAIR DISKUS (100/50- or 250/50-mcg doses), fluticasone propionate
460 inhalation powder (100- or 250-mcg doses), salmeterol inhalation powder 50 mcg, or placebo.
461 The average duration of exposure was 60 to 79 days in the active treatment groups compared
462 with 42 days in the placebo group.

463
464 **Table 2. Adverse Reactions With ADVAIR DISKUS With ≥3% Incidence and More Common**
465 **Than Placebo in Adult and Adolescent Subjects With Asthma**

Adverse Event	ADVAIR DISKUS 100/50 (n = 92) %	ADVAIR DISKUS 250/50 (n = 84) %	Fluticasone Propionate 100 mcg (n = 90) %	Fluticasone Propionate 250 mcg (n = 84) %	Salmeterol 50 mcg (n = 180) %	Placebo (n = 175) %
Ear, nose, and throat						
Upper respiratory tract infection	27	21	29	25	19	14
Pharyngitis	13	10	7	12	8	6
Upper respiratory inflammation	7	6	7	8	8	5
Sinusitis	4	5	6	1	3	4
Hoarseness/dysphonia	5	2	2	4	<1	<1
Oral candidiasis	1	4	2	2	0	0
Lower respiratory						
Viral respiratory infections	4	4	4	10	6	3
Bronchitis	2	8	1	2	2	2
Cough	3	6	0	0	3	2
Neurology						
Headaches	12	13	14	8	10	7
Gastrointestinal						
Nausea and vomiting	4	6	3	4	1	1
Gastrointestinal discomfort and pain	4	1	0	2	1	1
Diarrhea	4	2	2	2	1	1

Viral gastrointestinal infections	3	0	3	1	2	2
Non-site specific Candidiasis unspecified site	3	0	1	4	0	1
Musculoskeletal Musculoskeletal pain	4	2	1	5	3	3

466

467 The types of adverse reactions and events reported in Trial 3, a 28-week non-US clinical
468 trial in 503 subjects previously treated with inhaled corticosteroids who were treated twice daily
469 with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and
470 salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation
471 powder 500 mcg, were similar to those reported in Table 2.

472 Additional Adverse Reactions: Other adverse reactions not previously listed, whether
473 considered drug-related or not by the investigators, that were reported more frequently by
474 subjects with asthma treated with ADVAIR DISKUS compared with subjects treated with
475 placebo include the following: lymphatic signs and symptoms; muscle injuries; fractures;
476 wounds and lacerations; contusions and hematomas; ear signs and symptoms; nasal signs and
477 symptoms; nasal sinus disorders; keratitis and conjunctivitis; dental discomfort and pain;
478 gastrointestinal signs and symptoms; oral ulcerations; oral discomfort and pain; lower respiratory
479 signs and symptoms; pneumonia; muscle stiffness, tightness, and rigidity; bone and cartilage
480 disorders; sleep disorders; compressed nerve syndromes; viral infections; pain; chest symptoms;
481 fluid retention; bacterial infections; unusual taste; viral skin infections; skin flakiness and
482 acquired ichthyosis; disorders of sweat and sebum.

483 Pediatric Subjects Aged 4 to 11 Years: The safety data for pediatric subjects aged 4
484 to 11 years is based upon 1 US trial of 12 weeks' treatment duration. A total of 203 subjects (74
485 females and 129 males) who were receiving inhaled corticosteroids at trial entry were
486 randomized to either ADVAIR DISKUS 100/50 or fluticasone propionate inhalation powder 100
487 mcg twice daily. Common adverse reactions ($\geq 3\%$ and greater than placebo) seen in the pediatric
488 subjects but not reported in the adult and adolescent clinical trials include: throat irritation and
489 ear, nose, and throat infections.

490 Laboratory Test Abnormalities: Elevation of hepatic enzymes was reported in $\geq 1\%$ of
491 subjects in clinical trials. The elevations were transient and did not lead to discontinuation from
492 the trials. In addition, there were no clinically relevant changes noted in glucose or potassium.

493 **6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease**

494 Short-Term (6 Months to 1 Year) Trials: The short-term safety data are based on
495 exposure to ADVAIR DISKUS 250/50 twice daily in one 6-month and two 1-year clinical trials.
496 In the 6-month trial, a total of 723 adult subjects (266 females and 457 males) were treated twice
497 daily with ADVAIR DISKUS 250/50, fluticasone propionate inhalation powder 250 mcg,
498 salmeterol inhalation powder, or placebo. The mean age of the subjects was 64, and the majority
499 (93%) was Caucasian. In this trial, 70% of the subjects treated with ADVAIR DISKUS reported

500 an adverse reaction compared with 64% on placebo. The average duration of exposure to
501 ADVAIR DISKUS 250/50 was 141.3 days compared with 131.6 days for placebo. The incidence
502 of adverse reactions in the 6-month trial is shown in Table 3.

503

504 **Table 3. Overall Adverse Reactions With ≥3% Incidence With ADVAIR DISKUS 250/50**
505 **in Subjects With Chronic Obstructive Pulmonary Disease Associated With Chronic**
506 **Bronchitis**

Adverse Event	ADVAIR DISKUS 250/50 (n = 178) %	Fluticasone Propionate 250 mcg (n = 183) %	Salmeterol 50 mcg (n = 177) %	Placebo (n = 185) %
Ear, nose, and throat				
Candidiasis mouth/throat	10	6	3	1
Throat irritation	8	5	4	7
Hoarseness/dysphonia	5	3	<1	0
Sinusitis	3	8	5	3
Lower respiratory				
Viral respiratory infections	6	4	3	3
Neurology				
Headaches	16	11	10	12
Dizziness	4	<1	3	2
Non-site specific				
Fever	4	3	0	3
Malaise and fatigue	3	2	2	3
Musculoskeletal				
Musculoskeletal pain	9	8	12	9
Muscle cramps and spasms	3	3	1	1

507

508 In the two 1-year trials, ADVAIR DISKUS 250/50 was compared with salmeterol in
509 1,579 subjects (863 males and 716 females). The mean age of the subjects was 65 years, and the
510 majority (94%) was Caucasian. To be enrolled, all of the subjects had to have had a COPD
511 exacerbation in the previous 12 months. In this trial, 88% of the subjects treated with ADVAIR
512 DISKUS and 86% of the subjects treated with salmeterol reported an adverse event. The most
513 common events that occurred with a frequency of >5% and more frequently in the subjects
514 treated with ADVAIR DISKUS were nasopharyngitis, upper respiratory tract infection, nasal
515 congestion, back pain, sinusitis, dizziness, nausea, pneumonia, candidiasis, and dysphonia.
516 Overall, 55 (7%) of the subjects treated with ADVAIR DISKUS and 25 (3%) of the subjects
517 treated with salmeterol developed pneumonia.

518 The incidence of pneumonia was higher in subjects older than 65 years, 9% in the
519 subjects treated with ADVAIR DISKUS compared with 4% in the subjects treated with
520 ADVAIR DISKUS younger than 65 years. In the subjects treated with salmeterol, the incidence
521 of pneumonia was the same (3%) in both age-groups. [See *Warnings and Precautions (5.5), Use*
522 *in Specific Populations (8.5).*]

523 Long-Term (3 Years) Trial: The safety of ADVAIR DISKUS 500/50 was evaluated in a
524 randomized, double-blind, placebo-controlled, multicenter, international, 3-year trial in 6,184
525 adult subjects with COPD (4,684 males and 1,500 females). The mean age of the subjects was 65
526 years, and the majority (82%) was Caucasian. The distribution of adverse events was similar to
527 that seen in the 1-year trials with ADVAIR DISKUS 250/50. In addition, pneumonia was
528 reported in a significantly increased number of subjects treated with ADVAIR DISKUS 500/50
529 and fluticasone propionate 500 mcg (16% and 14%, respectively) compared with subjects treated
530 with salmeterol 50 mcg or placebo (11% and 9%, respectively). When adjusted for time on
531 treatment, the rates of pneumonia were 84 and 88 events per 1,000 treatment-years in the groups
532 treated with fluticasone propionate 500 mcg and with ADVAIR DISKUS 500/50, respectively,
533 compared with 52 events per 1,000 treatment-years in the salmeterol and placebo groups. Similar
534 to what was seen in the 1-year trials with ADVAIR DISKUS 250/50, the incidence of pneumonia
535 was higher in subjects older than 65 years (18% with ADVAIR DISKUS 500/50 versus 10%
536 with placebo) compared with subjects younger than 65 years (14% with ADVAIR DISKUS
537 500/50 versus 8% with placebo). [See *Warnings and Precautions (5.5), Use in Specific*
538 *Populations (8.5).*]

539 Additional Adverse Reactions: Other adverse reactions not previously listed, whether
540 considered drug-related or not by the investigators, that were reported more frequently by
541 subjects with COPD treated with ADVAIR DISKUS compared with subjects treated with
542 placebo include the following: syncope; ear, nose, and throat infections; ear signs and symptoms;
543 laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection;
544 hypothyroidism; dry eyes; eye infections; gastrointestinal signs and symptoms; oral lesions;
545 abnormal liver function tests; bacterial infections; edema and swelling; viral infections.

546 Laboratory Abnormalities: There were no clinically relevant changes in these trials.
547 Specifically, no increased reporting of neutrophilia or changes in glucose or potassium were
548 noted.

549 **6.3 Postmarketing Experience**

550 In addition to adverse reactions reported from clinical trials, the following adverse
551 reactions have been identified during postapproval use of any formulation of ADVAIR,
552 fluticasone propionate, and/or salmeterol regardless of indication. Because these reactions are
553 reported voluntarily from a population of uncertain size, it is not always possible to reliably
554 estimate their frequency or establish a causal relationship to drug exposure. These events have
555 been chosen for inclusion due to either their seriousness, frequency of reporting, or causal
556 connection to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol or a combination of
557 these factors.

558 Cardiac Disorders: Arrhythmias (including atrial fibrillation, extrasystoles,
559 supraventricular tachycardia), ventricular tachycardia.

560 Endocrine Disorders: Cushing's syndrome, Cushingoid features, growth velocity
561 reduction in children/adolescents, hypercorticism.

562 Eye Disorders: Glaucoma.

563 Gastrointestinal Disorders: Abdominal pain, dyspepsia, xerostomia.

564 Immune System Disorders: Immediate and delayed hypersensitivity reaction
565 (including very rare anaphylactic reaction). Very rare anaphylactic reaction in patients with
566 severe milk protein allergy.

567 Metabolic and Nutrition Disorders: Hyperglycemia, weight gain.

568 Musculoskeletal, Connective Tissue, and Bone Disorders: Arthralgia, cramps,
569 myositis, osteoporosis.

570 Nervous System Disorders: Paresthesia, restlessness.

571 Psychiatric Disorders: Agitation, aggression, depression. Behavioral changes, including
572 hyperactivity and irritability, have been reported very rarely and primarily in children.

573 Reproductive System and Breast Disorders: Dysmenorrhea.

574 Respiratory, Thoracic, and Mediastinal Disorders: Chest congestion; chest tightness;
575 dyspnea; facial and oropharyngeal edema, immediate bronchospasm; paradoxical bronchospasm;
576 tracheitis; wheezing; reports of upper respiratory symptoms of laryngeal spasm, irritation, or
577 swelling such as stridor or choking.

578 Skin and Subcutaneous Tissue Disorders: Ecchymoses, photodermatitis.

579 Vascular Disorders: Pallor.

580 **7 DRUG INTERACTIONS**

581 ADVAIR DISKUS has been used concomitantly with other drugs, including short-acting
582 beta₂-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with
583 asthma or COPD, without adverse drug reactions [see *Clinical Pharmacology (12.2)*]. No formal
584 drug interaction trials have been performed with ADVAIR DISKUS.

585 **7.1 Inhibitors of Cytochrome P450 3A4**

586 Fluticasone propionate and salmeterol, the individual components of ADVAIR DISKUS,
587 are substrates of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir,
588 clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole,
589 telithromycin) with ADVAIR DISKUS is not recommended because increased systemic
590 corticosteroid and increased cardiovascular adverse effects may occur.

591 Ritonavir: Fluticasone Propionate: A drug interaction trial with fluticasone propionate
592 aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4 inhibitor) can
593 significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced
594 serum cortisol concentrations [see *Clinical Pharmacology (12.3)*]. During postmarketing use,
595 there have been reports of clinically significant drug interactions in patients receiving fluticasone

596 propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's
597 syndrome and adrenal suppression.

598 **Ketoconazole: Fluticasone Propionate:** Coadministration of orally inhaled fluticasone
599 propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in
600 plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the
601 curve (AUC), but had no effect on urinary excretion of cortisol.

602 **Salmeterol:** In a drug interaction trial in 20 healthy subjects, coadministration of
603 inhaled salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days
604 resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased
605 1.4-fold). Three (3) subjects were withdrawn due to beta₂-agonist side effects (2 with prolonged
606 QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on
607 the mean QTc, coadministration of salmeterol and ketoconazole was associated with more
608 frequent increases in QTc duration compared with salmeterol and placebo administration.

609 **7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants**

610 ADVAIR DISKUS should be administered with extreme caution to patients being treated
611 with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of
612 discontinuation of such agents, because the action of salmeterol, a component of ADVAIR
613 DISKUS, on the vascular system may be potentiated by these agents.

614 **7.3 Beta-Adrenergic Receptor Blocking Agents**

615 Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a
616 component of ADVAIR DISKUS, but may also produce severe bronchospasm in patients with
617 asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with
618 beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to
619 the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could
620 be considered, although they should be administered with caution.

621 **7.4 Non-Potassium-Sparing Diuretics**

622 The ECG changes and/or hypokalemia that may result from the administration of non-
623 potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-
624 agonists, such as salmeterol, a component of ADVAIR DISKUS, especially when the
625 recommended dose of the beta-agonist is exceeded. Although the clinical significance of these
626 effects is not known, caution is advised in the coadministration of ADVAIR DISKUS with non-
627 potassium-sparing diuretics.

628 **8 USE IN SPECIFIC POPULATIONS**

629 **8.1 Pregnancy**

630 **Teratogenic Effects:** Pregnancy Category C. There are no adequate and well-controlled
631 trials with ADVAIR DISKUS in pregnant women. Corticosteroids and beta₂-agonists have been
632 shown to be teratogenic in laboratory animals when administered systemically at relatively low
633 dosage levels. Because animal reproduction studies are not always predictive of human response,
634 ADVAIR DISKUS should be used during pregnancy only if the potential benefit justifies the

635 potential risk to the fetus. Women should be advised to contact their physicians if they become
636 pregnant while taking ADVAIR DISKUS.

637 *Fluticasone Propionate and Salmeterol:* In the mouse reproduction assay,
638 fluticasone propionate by the subcutaneous route at a dose approximately 3/5 the maximum
639 recommended human daily inhalation dose (MRHDID) (on a mg/m² basis at a maternal
640 subcutaneous dose of 150 mcg/kg/day) combined with oral salmeterol at a dose approximately
641 410 times the MRHDID (on a mg/m² basis at a maternal oral dose of 10 mg/kg/day) produced
642 cleft palate, fetal death, increased implantation loss, and delayed ossification. These observations
643 are characteristic of glucocorticoids. No developmental toxicity was observed at combination
644 doses of fluticasone propionate subcutaneously up to approximately 1/6 the MRHDID (on a
645 mg/m² basis at a maternal subcutaneous dose of 40 mcg/kg/day) and doses of salmeterol up to
646 approximately 55 times the MRHDID (on a mg/m² basis at a maternal oral dose of 1.4
647 mg/kg/day). In rats, combining fluticasone propionate subcutaneously at a dose equivalent to the
648 MRHDID (on a mg/m² basis at a maternal subcutaneous dose of 100 mcg/kg/day) and a dose of
649 salmeterol at approximately 810 times the MRHDID (on a mg/m² basis at a maternal oral dose of
650 10 mg/kg/day) produced decreased fetal weight, umbilical hernia, delayed ossification, and
651 changes in the occipital bone. No such effects were seen when combining fluticasone propionate
652 subcutaneously at a dose less than the MRHDID (on a mg/m² basis at a maternal subcutaneous
653 dose of 30 mcg/kg/day) and an oral dose of salmeterol at approximately 80 times the MRHDID
654 (on a mg/m² basis at a maternal oral dose of 1 mg/kg/day).

655 *Fluticasone Propionate:* Mice and rats at fluticasone propionate doses less than or
656 equivalent to the MRHDID (on a mg/m² basis at a maternal subcutaneous dose of 45 and 100
657 mcg/kg/day, respectively) showed fetal toxicity characteristic of potent corticosteroid
658 compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded
659 cranial ossification. No teratogenicity was seen in rats at doses approximately equivalent to the
660 MRHDID (on a mcg/m² basis at maternal inhaled doses up to 68.7 mg/kg/day).

661 In rabbits, fetal weight reduction and cleft palate were observed at a fluticasone
662 propionate dose less than the MRHDID (on a mg/m² basis at a maternal subcutaneous dose of 4
663 mcg/kg/day). However, no teratogenic effects were reported at fluticasone propionate doses up to
664 approximately 5 times the MRHDID (on a mg/m² basis at a maternal oral dose up to
665 300 mcg/kg/day). No fluticasone propionate was detected in the plasma in this study, consistent
666 with the established low bioavailability following oral administration [*see Clinical*
667 *Pharmacology (12.3)*].

668 Fluticasone propionate crossed the placenta following subcutaneous administration to
669 mice and rats and oral administration to rabbits.

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

675 *Salmeterol*: No teratogenic effects occurred in rats at salmeterol doses approximately
676 160 times the MRHDID (on a mg/m² basis at maternal oral doses up to 2 mg/kg/day). In
677 pregnant Dutch rabbits administered salmeterol doses approximately 50 times the MRHDID (on
678 an AUC basis at maternal oral doses of 1 mg/kg/day and higher), fetal toxic effects were
679 observed characteristically resulting from beta-adrenoceptor stimulation. These included
680 precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed
681 ossification of the frontal cranial bones. No such effects occurred at a salmeterol dose
682 approximately 20 times the MRHDID (on an AUC basis at a maternal oral dose of 0.6
683 mg/kg/day).

684 New Zealand White rabbits were less sensitive since only delayed ossification of the
685 frontal cranial bones was seen at a salmeterol dose approximately 1,600 times the MRHDID on a
686 mg/m² basis at a maternal oral dose of 10 mg/kg/day). Salmeterol xinafoate crossed the placenta
687 following oral administration to mice and rats.

688 Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers
689 receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

690 **8.2 Labor and Delivery**

691 There are no well-controlled human trials that have investigated effects of ADVAIR
692 DISKUS on preterm labor or labor at term. Because of the potential for beta-agonist interference
693 with uterine contractility, use of ADVAIR DISKUS during labor should be restricted to those
694 patients in whom the benefits clearly outweigh the risks.

695 **8.3 Nursing Mothers**

696 Plasma levels of salmeterol, a component of ADVAIR DISKUS, after inhaled therapeutic
697 doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There are no data from
698 controlled trials on the use of salmeterol by nursing mothers. It is not known whether fluticasone
699 propionate, a component of ADVAIR DISKUS, is excreted in human breast milk. However,
700 other corticosteroids have been detected in human milk. Subcutaneous administration to lactating
701 rats of tritiated fluticasone propionate resulted in measurable radioactivity in milk.

702 Since there are no data from controlled trials on the use of ADVAIR DISKUS by nursing
703 mothers, caution should be exercised when ADVAIR DISKUS is administered to a nursing
704 woman.

705 **8.4 Pediatric Use**

706 Use of ADVAIR DISKUS 100/50 in patients aged 4 to 11 years is supported by
707 extrapolation of efficacy data from older subjects and by safety and efficacy data from a trial of
708 ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years [*see Adverse Reactions*
709 (6.1), *Clinical Pharmacology* (12.3), *Clinical Studies* (14.1)]. The safety and effectiveness of
710 ADVAIR DISKUS in children with asthma younger than 4 years have not been established.

711 Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR
712 DISKUS, may cause a reduction in growth velocity in children and adolescents [*see Warnings*
713 *and Precautions* (5.14)]. The growth of pediatric patients receiving orally inhaled
714 corticosteroids, including ADVAIR DISKUS, should be monitored.

715 A 52-week placebo-controlled trial to assess the potential growth effects of fluticasone
716 propionate inhalation powder (FLOVENT[®] ROTADISK[®]) at 50 and 100 mcg twice daily was
717 conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to
718 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were
719 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and
720 5.66 cm/year in the 100-mcg group (n = 89). An imbalance in the proportion of children entering
721 puberty between groups and a higher dropout rate in the placebo group due to poorly controlled
722 asthma may be confounding factors in interpreting these data. A separate subset analysis of
723 children who remained prepubertal during the trial revealed growth rates at 52 weeks of
724 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and
725 5.67 cm/year in the 100-mcg group (n = 79). In children aged 8.5 years, the mean age of children
726 in this trial, the range for expected growth velocity is: boys – 3rd percentile = 3.8 cm/year, 50th
727 percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year,
728 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year. The clinical relevance of these
729 growth data is not certain.

730 If a child or adolescent on any corticosteroid appears to have growth suppression, the
731 possibility that he/she is particularly sensitive to this effect of corticosteroids should be
732 considered. The potential growth effects of prolonged treatment should be weighed against the
733 clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids,
734 including ADVAIR DISKUS, each patient should be titrated to the lowest strength that
735 effectively controls his/her asthma [*see Dosage and Administration (2.1)*].

736 **8.5 Geriatric Use**

737 Clinical trials of ADVAIR DISKUS for asthma did not include sufficient numbers of
738 subjects aged 65 years and older to determine whether older subjects with asthma respond
739 differently than younger subjects.

740 Of the total number of subjects in clinical trials receiving ADVAIR DISKUS for COPD,
741 1,621 were aged 65 years and older and 379 were aged 75 years and older. Subjects with COPD
742 aged 65 years and older had a higher incidence of serious adverse events compared with subjects
743 younger than 65 years. Although the distribution of adverse events was similar in the 2 age-
744 groups, subjects older than 65 years experienced more severe events. In two 1-year trials, the
745 excess risk of pneumonia that was seen in subjects treated with ADVAIR DISKUS compared
746 with those treated with salmeterol was greater in subjects older than 65 years than in subjects
747 younger than 65 years [*see Adverse Reactions (6.2)*]. As with other products containing beta₂-
748 agonists, special caution should be observed when using ADVAIR DISKUS in geriatric patients
749 who have concomitant cardiovascular disease that could be adversely affected by beta₂-agonists.
750 Based on available data for ADVAIR DISKUS or its active components, no adjustment of
751 dosage of ADVAIR DISKUS in geriatric patients is warranted.

752 No relationship between fluticasone propionate systemic exposure and age was observed
753 in 57 subjects with COPD (aged 40 to 82 years) given 250 or 500 mcg twice daily.

754 **8.6 Hepatic Impairment**

755 Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in
756 patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are
757 predominantly cleared by hepatic metabolism, impairment of liver function may lead to
758 accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with
759 hepatic disease should be closely monitored.

760 **8.7 Renal Impairment**

761 Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in
762 patients with renal impairment.

763 **10 OVERDOSAGE**

764 No human overdosage data has been reported for ADVAIR DISKUS.

765 ADVAIR DISKUS contains both fluticasone propionate and salmeterol; therefore, the
766 risks associated with overdosage for the individual components described below apply to
767 ADVAIR DISKUS. Treatment of overdosage consists of discontinuation of ADVAIR DISKUS
768 together with institution of appropriate symptomatic and/or supportive therapy. The judicious use
769 of a cardioselective beta-receptor blocker may be considered, bearing in mind that such
770 medication can produce bronchospasm. Cardiac monitoring is recommended in cases of
771 overdosage.

772 **10.1 Fluticasone Propionate**

773 Chronic overdosage of fluticasone propionate may result in signs/symptoms of
774 hypercorticism [*see Warnings and Precautions (5.7)*]. Inhalation by healthy volunteers of a
775 single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or
776 3,520 mcg of fluticasone propionate CFC inhalation aerosol was well tolerated. Fluticasone
777 propionate given by inhalation aerosol at dosages of 1,320 mcg twice daily for 7 to 15 days to
778 healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for
779 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in subjects
780 were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were
781 similar in active and placebo treatment groups.

782 **10.2 Salmeterol**

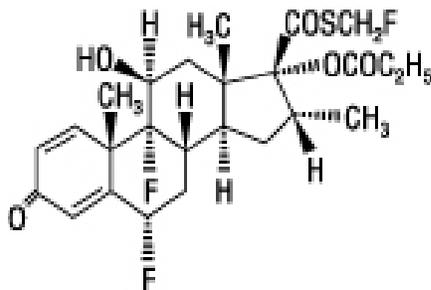
783 The expected signs and symptoms with overdosage of salmeterol are those of excessive
784 beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms
785 of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia
786 with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry
787 mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia,
788 metabolic acidosis). Overdosage with salmeterol can lead to clinically significant prolongation of
789 the QTc interval, which can produce ventricular arrhythmias.

790 As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be
791 associated with an overdose of salmeterol.

792 **11 DESCRIPTION**

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

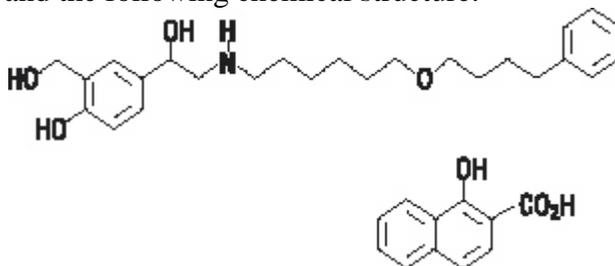
795 One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid
796 having the chemical name *S*-(fluoromethyl) 6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-
797 oxoandrost-1,4-diene-17 β -carbothioate, 17-propionate and the following chemical structure:



798

799 Fluticasone propionate is a white powder with a molecular weight of 500.6, and the
800 empirical formula is C₂₅H₃₁F₃O₅S. It is practically insoluble in water, freely soluble in dimethyl
801 sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

802 The other active component of ADVAIR DISKUS is salmeterol xinafoate, a
803 beta₂-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-
804 naphthoic acid salt of salmeterol. It has the chemical name 4-hydroxy- α ¹-[[[6-(4-
805 phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-
806 naphthalenecarboxylate and the following chemical structure:



807

808 Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the
809 empirical formula is C₂₅H₃₇NO₄•C₁₁H₈O₃. It is freely soluble in methanol; slightly soluble in
810 ethanol, chloroform, and isopropanol; and sparingly soluble in water.

811 ADVAIR DISKUS is a purple plastic inhaler containing a foil blister strip. Each blister
812 on the strip contains a white powder mix of micronized fluticasone propionate (100, 250, or
813 500 mcg) and micronized salmeterol xinafoate salt (72.5 mcg, equivalent to 50 mcg of salmeterol
814 base) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins).
815 After the inhaler is activated, the powder is dispersed into the airstream created by the patient
816 inhaling through the mouthpiece.

817 Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and
818 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR

819 DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50, respectively, when
820 tested at a flow rate of 60 L/min for 2 seconds.

821 In adult subjects with obstructive lung disease and severely compromised lung function
822 (mean FEV₁ 20% to 30% of predicted), mean peak inspiratory flow (PIF) through the DISKUS®
823 inhaler was 82.4 L/min (range: 46.1 to 115.3 L/min).

824 Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged
825 18 to 50 years) subjects with asthma inhaling maximally through the DISKUS device show mean
826 PIF of 122.2 L/min (range: 81.6 to 152.1 L/min). Inhalation profiles for pediatric subjects with
827 asthma inhaling maximally through the DISKUS device show a mean PIF of 75.5 L/min (range:
828 49.0 to 104.8 L/min) for the 4-year-old subject set (N = 20) and 107.3 L/min (range: 82.8 to
829 125.6 L/min) for the 8-year-old subject set (N = 20).

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

832 **12 CLINICAL PHARMACOLOGY**

833 **12.1 Mechanism of Action**

834 ADVAIR DISKUS: ADVAIR DISKUS contains both fluticasone propionate and
835 salmeterol. The mechanisms of action described below for the individual components apply to
836 ADVAIR DISKUS. These drugs represent 2 different classes of medications (a synthetic
837 corticosteroid and a LABA) that have different effects on clinical, physiologic, and inflammatory
838 indices.

839 Fluticasone Propionate: Fluticasone propionate is a synthetic trifluorinated
840 corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown in vitro to
841 exhibit a binding affinity for the human glucocorticoid receptor that is 18 times that of
842 dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active
843 metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the
844 McKenzie vasoconstrictor assay in man are consistent with these results. The clinical
845 significance of these findings is unknown.

846 Inflammation is an important component in the pathogenesis of asthma. Corticosteroids
847 have been shown to have a wide range of actions on multiple cell types (e.g., mast cells,
848 eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids,
849 leukotrienes, cytokines) involved in inflammation. These anti-inflammatory actions of
850 corticosteroids contribute to their efficacy in asthma.

851 Inflammation is also a component in the pathogenesis of COPD. In contrast to asthma,
852 however, the predominant inflammatory cells in COPD include neutrophils, CD8+
853 T-lymphocytes, and macrophages. The effects of corticosteroids in the treatment of COPD are
854 not well defined and inhaled corticosteroids and fluticasone propionate when used apart from
855 ADVAIR DISKUS are not indicated for the treatment of COPD.

856 Salmeterol Xinafoate: Salmeterol is a selective LABA. In vitro studies show salmeterol
857 to be at least 50 times more selective for beta₂-adrenoceptors than albuterol. Although

858 beta₂-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and
859 beta₁-adrenoceptors are the predominant receptors in the heart, there are also beta₂-adrenoceptors
860 in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function
861 of these receptors has not been established, but their presence raises the possibility that even
862 selective beta₂-agonists may have cardiac effects.

863 The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including salmeterol, are
864 at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that
865 catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine
866 monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial
867 smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells,
868 especially from mast cells.

869 In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of
870 mast cell mediators, such as histamine, leukotrienes, and prostaglandin D₂, from human lung.
871 Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-
872 activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered
873 by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol
874 attenuate allergen-induced bronchial hyper-responsiveness.

875 **12.2 Pharmacodynamics**

876 ADVAIR DISKUS: Healthy Subjects: Cardiovascular Effects: Since systemic
877 pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher
878 doses were used to produce measurable effects. Four (4) trials were conducted with healthy adult
879 subjects: (1) a single-dose crossover trial using 2 inhalations of ADVAIR DISKUS 500/50,
880 fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or
881 fluticasone propionate powder 500 mcg given alone, (2) a cumulative dose trial using 50 to
882 400 mcg of salmeterol powder given alone or as ADVAIR DISKUS 500/50, (3) a repeat-dose
883 trial for 11 days using 2 inhalations twice daily of ADVAIR DISKUS 250/50, fluticasone
884 propionate powder 250 mcg, or salmeterol powder 50 mcg, and (4) a single-dose trial using
885 5 inhalations of ADVAIR DISKUS 100/50, fluticasone propionate powder 100 mcg alone, or
886 placebo. In these trials no significant differences were observed in the pharmacodynamic effects
887 of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the
888 salmeterol was given as ADVAIR DISKUS, concurrently with fluticasone propionate from
889 separate inhalers, or as salmeterol alone. The systemic pharmacodynamic effects of salmeterol
890 were not altered by the presence of fluticasone propionate in ADVAIR DISKUS. The potential
891 effect of salmeterol on the effects of fluticasone propionate on the HPA axis was also evaluated
892 in these trials.

893 Hypothalamic-Pituitary-Adrenal Axis Effects: No significant differences across
894 treatments were observed in 24-hour urinary cortisol excretion and, where measured, 24-hour
895 plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone propionate were not
896 altered by the presence of salmeterol in ADVAIR DISKUS in healthy subjects.

897 *Subjects With Asthma: Adult and Adolescent Subjects: Cardiovascular*
898 *Effects:* In clinical trials with ADVAIR DISKUS in adult and adolescent subjects aged 12 years
899 and older with asthma, no significant differences were observed in the systemic
900 pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and
901 glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adult and
902 adolescent subjects with asthma given either ADVAIR DISKUS 100/50 or ADVAIR DISKUS
903 250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose
904 and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

905 *Hypothalamic-Pituitary-Adrenal Axis Effects:* In a 28-week trial in adult and
906 adolescent subjects with asthma, ADVAIR DISKUS 500/50 twice daily was compared with the
907 concurrent use of salmeterol powder 50 mcg plus fluticasone propionate powder 500 mcg from
908 separate inhalers or fluticasone propionate powder 500 mcg alone. No significant differences
909 across treatments were observed in serum cortisol AUC after 12 weeks of dosing or in 24-hour
910 urinary cortisol excretion after 12 and 28 weeks.

911 In a 12-week trial in adult and adolescent subjects with asthma, ADVAIR DISKUS
912 250/50 twice daily was compared with fluticasone propionate powder 250 mcg alone, salmeterol
913 powder 50 mcg alone, and placebo. For most subjects, the ability to increase cortisol production
914 in response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with
915 ADVAIR DISKUS. One subject (3%) who received ADVAIR DISKUS 250/50 had an abnormal
916 response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 subjects (6%) who
917 received placebo, 2 subjects (6%) who received fluticasone propionate 250 mcg, and no subjects
918 who received salmeterol.

919 In a repeat-dose, 3-way crossover trial, 1 inhalation twice daily of ADVAIR DISKUS
920 100/50, FLOVENT[®] DISKUS[®] 100 mcg (fluticasone propionate inhalation powder, 100 mcg),
921 or placebo was administered to 20 adult and adolescent subjects with asthma. After 28 days of
922 treatment, geometric mean serum cortisol AUC over 12 hours showed no significant difference
923 between ADVAIR DISKUS and FLOVENT DISKUS or between either active treatment and
924 placebo.

925 *Pediatric Subjects: Hypothalamic-Pituitary-Adrenal Axis Effects:* In a
926 12-week trial in subjects with asthma aged 4 to 11 years who were receiving inhaled
927 corticosteroids at trial entry, ADVAIR DISKUS 100/50 twice daily was compared with
928 fluticasone propionate inhalation powder 100 mcg administered twice daily via the DISKUS.
929 The values for 24-hour urinary cortisol excretion at trial entry and after 12 weeks of treatment
930 were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was
931 also similar between the 2 groups.

932 *Subjects With Chronic Obstructive Pulmonary Disease: Cardiovascular*
933 *Effects:* In clinical trials with ADVAIR DISKUS in subjects with COPD, no significant
934 differences were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR
935 DISKUS, the individual components of ADVAIR DISKUS, and placebo. In a trial of ADVAIR
936 DISKUS 250/50, 8 subjects (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in

937 the fluticasone propionate 250-mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the
938 placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5)
939 of these 8 subjects had a prolonged QTc interval at baseline.

940 In a 24-week trial, 130 subjects with COPD received continuous 24-hour
941 electrocardiographic monitoring prior to the first dose and after 4 weeks of twice-daily treatment
942 with either ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg, salmeterol
943 powder 50 mcg, or placebo. No significant differences in ventricular or supraventricular
944 arrhythmias and heart rate were observed among the groups treated with ADVAIR DISKUS
945 500/50, the individual components, or placebo. One (1) subject in the fluticasone propionate
946 group experienced atrial flutter/atrial fibrillation, and 1 subject in the group given ADVAIR
947 DISKUS 500/50 experienced heart block. There were 3 cases of nonsustained ventricular
948 tachycardia (1 each in the placebo, salmeterol, and fluticasone propionate 500-mcg treatment
949 groups).

950 In 24-week clinical trials in subjects with COPD, the incidence of clinically significant
951 ECG abnormalities (myocardial ischemia, ventricular hypertrophy, clinically significant
952 conduction abnormalities, clinically significant arrhythmias) was lower for subjects who
953 received salmeterol (1%, 9 of 688 subjects who received either salmeterol 50 mcg or ADVAIR
954 DISKUS) compared with placebo (3%, 10 of 370 subjects).

955 No significant differences with salmeterol 50 mcg alone or in combination with
956 fluticasone propionate as ADVAIR DISKUS 500/50 were observed on pulse rate and systolic
957 and diastolic blood pressure in a subset of subjects with COPD who underwent 12-hour serial
958 vital sign measurements after the first dose (n = 183) and after 12 weeks of therapy (n = 149).
959 Median changes from baseline in pulse rate and systolic and diastolic blood pressure were
960 similar to those seen with placebo.

961 *Hypothalamic-Pituitary-Adrenal Axis Effects:* Short-cosyntropin stimulation
962 testing was performed both at Day 1 and Endpoint in 101 subjects with COPD receiving twice-
963 daily ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, salmeterol powder
964 50 mcg, or placebo. For most subjects, the ability to increase cortisol production in response to
965 stress, as assessed by short cosyntropin stimulation, remained intact with ADVAIR DISKUS
966 250/50. One (1) subject (3%) who received ADVAIR DISKUS 250/50 had an abnormal
967 stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by high-performance liquid
968 chromatography) after dosing, compared with 2 subjects (9%) who received fluticasone
969 propionate 250 mcg, 2 subjects (7%) who received salmeterol 50 mcg, and 1 subject (4%) who
970 received placebo following 24 weeks of treatment or early discontinuation from trial.

971 After 36 weeks of dosing, serum cortisol concentrations in a subset of subjects with
972 COPD (n = 83) were 22% lower in subjects receiving ADVAIR DISKUS 500/50 and 21% lower
973 in subjects receiving fluticasone propionate 500 mcg than in subjects receiving placebo.

974 Other Fluticasone Propionate Products: *Subjects With Asthma: Hypothalamic-*
975 *Pituitary-Adrenal Axis Effects:* In clinical trials with fluticasone propionate inhalation powder
976 using dosages up to and including 250 mcg twice daily, occasional abnormal short cosyntropin

977 tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted both in
978 subjects receiving fluticasone propionate and in subjects receiving placebo. The incidence of
979 abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year trial carried out with
980 the DISKHALER[®] inhalation device in 64 subjects with mild, persistent asthma (mean FEV₁
981 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no
982 subject receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin
983 infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1
984 subject receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing
985 at 18 months and 2 years was normal. Another subject receiving fluticasone propionate (5%) had
986 an abnormal response at 2 years. No subject on placebo had an abnormal response at 1 or
987 2 years.

988 *Subjects With Chronic Obstructive Pulmonary Disease: Hypothalamic-*
989 *Pituitary-Adrenal Axis Effects:* After 4 weeks of dosing, the steady-state fluticasone
990 propionate pharmacokinetics and serum cortisol levels were described in a subset of subjects
991 with COPD (n = 86) randomized to twice-daily fluticasone propionate inhalation powder via the
992 DISKUS 500 mcg, fluticasone propionate inhalation powder 250 mcg, or placebo. Serial serum
993 cortisol concentrations were measured across a 12-hour dosing interval. Serum cortisol
994 concentrations following 250- and 500-mcg twice-daily dosing were 10% and 21% lower than
995 placebo, respectively, indicating a dose-dependent increase in systemic exposure to fluticasone
996 propionate.

997 Other Salmeterol Xinafoate Products: *Subjects With Asthma: Cardiovascular*
998 *Effects:* Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related
999 cardiovascular effects and effects on blood glucose and/or serum potassium [*see Warnings and*
1000 *Precautions (5.12, 5.18)].* The cardiovascular effects (heart rate, blood pressure) associated with
1001 salmeterol inhalation aerosol occur with similar frequency, and are of similar type and severity,
1002 as those noted following albuterol administration.

1003 The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol
1004 were studied in volunteers and in subjects with asthma. Salmeterol doses up to 84 mcg
1005 administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the
1006 same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adult and
1007 adolescent subjects receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent
1008 continuous electrocardiographic monitoring during two 12-hour periods after the first dose and
1009 after 1 month of therapy, and no clinically significant dysrhythmias were noted.

1010 Concomitant Use of ADVAIR DISKUS With Other Respiratory Medications:
1011 *Short-Acting Beta₂-Agonists:* In clinical trials in subjects with asthma, the mean daily need for
1012 albuterol by 166 adult and adolescent subjects aged 12 years and older using ADVAIR DISKUS
1013 was approximately 1.3 inhalations/day and ranged from 0 to 9 inhalations/day. Five percent (5%)
1014 of subjects using ADVAIR DISKUS in these trials averaged 6 or more inhalations per day over
1015 the course of the 12-week trials. No increase in frequency of cardiovascular adverse events was
1016 observed among subjects who averaged 6 or more inhalations per day.

1017 In a clinical trial in subjects with COPD, the mean daily need for albuterol for subjects
1018 using ADVAIR DISKUS 250/50 was 4.1 inhalations/day. Twenty-six percent (26%) of subjects
1019 using ADVAIR DISKUS 250/50 averaged 6 or more inhalations of albuterol per day over the
1020 course of the 24-week trial. No increase in frequency of cardiovascular adverse reactions was
1021 observed among subjects who averaged 6 or more inhalations per day.

1022 **Methylxanthines:** The concurrent use of intravenously or orally administered
1023 methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent subjects aged 12
1024 years and older receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials
1025 in subjects with asthma, 39 subjects receiving ADVAIR DISKUS 100/50, 250/50, or 500/50
1026 twice daily concurrently with a theophylline product had adverse event rates similar to those in
1027 304 subjects receiving ADVAIR DISKUS without theophylline. Similar results were observed in
1028 subjects receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily
1029 concurrently with a theophylline product (n = 39) or without theophylline (n = 132).

1030 In a clinical trial in subjects with COPD, 17 subjects receiving ADVAIR DISKUS 250/50
1031 twice daily concurrently with a theophylline product had adverse event rates similar to those in
1032 161 subjects receiving ADVAIR DISKUS without theophylline. Based on the available data, the
1033 concomitant administration of methylxanthines with ADVAIR DISKUS did not alter the
1034 observed adverse event profile.

1035 **Fluticasone Propionate Nasal Spray:** In adult and adolescent subjects aged 12
1036 years and older taking ADVAIR DISKUS in clinical trials, no difference in the profile of adverse
1037 events or HPA axis effects was noted between subjects who were taking FLONASE[®]
1038 (fluticasone propionate) Nasal Spray, 50 mcg concurrently (n = 46) and those who were not
1039 (n = 130).

1040 **12.3 Pharmacokinetics**

1041 **Absorption: Fluticasone Propionate: Healthy Subjects:** Fluticasone propionate acts
1042 locally in the lung; therefore, plasma levels do not predict therapeutic effect. Trials using oral
1043 dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of
1044 fluticasone propionate is negligible (less than 1%), primarily due to incomplete absorption and
1045 presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone
1046 propionate delivered to the lung is systemically absorbed.

1047 Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma
1048 concentrations of fluticasone propionate were achieved in 1 to 2 hours. In a single-dose
1049 crossover trial, a higher-than-recommended dose of ADVAIR DISKUS was administered to 14
1050 healthy adult subjects. Two (2) inhalations of the following treatments were administered:
1051 ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder
1052 50 mcg given concurrently, and fluticasone propionate powder 500 mcg alone. Mean peak
1053 plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL, respectively,
1054 indicating no significant changes in systemic exposures of fluticasone propionate.

1055 In 15 healthy subjects, systemic exposure to fluticasone propionate from 4 inhalations of
1056 ADVAIR[®] HFA 230/21 (fluticasone propionate 230 mcg and salmeterol 21 mcg) Inhalation

1057 Aerosol (920/84 mcg) and 2 inhalations of ADVAIR DISKUS 500/50 (1,000/100 mcg) were
1058 similar between the 2 inhalers (i.e., 799 versus 832 pg•h/mL, respectively), but approximately
1059 half the systemic exposure from 4 inhalations of fluticasone propionate CFC inhalation aerosol
1060 220 mcg (880 mcg, AUC = 1,543 pg•h/mL). Similar results were observed for peak fluticasone
1061 propionate plasma concentrations (186 and 182 pg/mL from ADVAIR HFA and ADVAIR
1062 DISKUS, respectively, and 307 pg/mL from the fluticasone propionate CFC inhalation aerosol).
1063 Absolute bioavailability of fluticasone propionate was 5.3% and 5.5% following administration
1064 of ADVAIR HFA and ADVAIR DISKUS, respectively.

1065 *Subjects With Asthma and COPD:* Peak steady-state fluticasone propionate
1066 plasma concentrations in adult subjects with asthma (N = 11) ranged from undetectable to
1067 266 pg/mL after a 500-mcg twice-daily dose of fluticasone propionate inhalation powder using
1068 the DISKUS device. The mean fluticasone propionate plasma concentration was 110 pg/mL.

1069 Full pharmacokinetic profiles were obtained from 9 female and 16 male subjects with
1070 asthma given fluticasone propionate inhalation powder 500 mcg twice daily using the DISKUS
1071 device and from 14 female and 43 male subjects with COPD given 250 or 500 mcg twice daily.
1072 No overall differences in fluticasone propionate pharmacokinetics were observed.

1073 Peak steady-state fluticasone propionate plasma concentrations in subjects with COPD
1074 averaged 53 pg/mL (range: 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily
1075 (n = 30) and 84 pg/mL (range: 24.3 to 197.1 pg/mL) after treatment with 500 mcg twice daily
1076 (n = 27) via the fluticasone propionate DISKUS device. In another trial in subjects with COPD,
1077 peak steady-state fluticasone propionate plasma concentrations averaged 115 pg/mL (range: 52.6
1078 to 366.0 pg/mL) after treatment with 500 mcg twice daily via the fluticasone propionate
1079 DISKUS device (n = 15) and 105 pg/mL (range: 22.5 to 299.0 pg/mL) via ADVAIR DISKUS
1080 (n = 24).

1081 *Salmeterol Xinafoate: Healthy Subjects:* Salmeterol xinafoate, an ionic salt,
1082 dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate)
1083 moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts
1084 locally in the lung; therefore, plasma levels do not predict therapeutic effect.

1085 Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma
1086 concentrations of salmeterol were achieved in about 5 minutes.

1087 In 15 healthy subjects receiving ADVAIR HFA 230/21 Inhalation Aerosol (920/84 mcg)
1088 and ADVAIR DISKUS 500/50 (1,000/100 mcg), systemic exposure to salmeterol was higher
1089 (317 versus 169 pg•h/mL) and peak salmeterol concentrations were lower (196 versus
1090 223 pg/mL) following ADVAIR HFA compared with ADVAIR DISKUS, although
1091 pharmacodynamic results were comparable.

1092 *Subjects With Asthma:* Because of the small therapeutic dose, systemic levels
1093 of salmeterol are low or undetectable after inhalation of recommended doses (50 mcg of
1094 salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose
1095 of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within

1096 5 to 45 minutes in 7 subjects with asthma; plasma concentrations were very low, with mean peak
1097 concentrations of 167 pg/mL at 20 minutes and no accumulation with repeated doses.

1098 Distribution: Fluticasone Propionate: Following intravenous administration, the initial
1099 disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility
1100 and tissue binding. The volume of distribution averaged 4.2 L/kg.

1101 The percentage of fluticasone propionate bound to human plasma proteins averages 99%.
1102 Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly
1103 bound to human transcortin.

1104 Salmeterol: The percentage of salmeterol bound to human plasma proteins averages
1105 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much
1106 higher concentrations than those achieved following therapeutic doses of salmeterol.

1107 Metabolism: Fluticasone Propionate: The total clearance of fluticasone propionate is
1108 high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total.
1109 The only circulating metabolite detected in man is the 17 β -carboxylic acid derivative of
1110 fluticasone propionate, which is formed through the CYP3A4 pathway. This metabolite had less
1111 affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human
1112 lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites
1113 detected in vitro using cultured human hepatoma cells have not been detected in man.

1114 Salmeterol: Salmeterol base is extensively metabolized by hydroxylation, with
1115 subsequent elimination predominantly in the feces. No significant amount of unchanged
1116 salmeterol base was detected in either urine or feces.

1117 An in vitro study using human liver microsomes showed that salmeterol is extensively
1118 metabolized to α -hydroxysalmeterol (aliphatic oxidation) by CYP3A4. Ketoconazole, a strong
1119 inhibitor of CYP3A4, essentially completely inhibited the formation of α -hydroxysalmeterol in
1120 vitro.

1121 Elimination: Fluticasone Propionate: Following intravenous dosing, fluticasone
1122 propionate showed polyexponential kinetics and had a terminal elimination half-life of
1123 approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as
1124 metabolites, with the remainder excreted in the feces as parent drug and metabolites. Terminal
1125 half-life estimates of fluticasone propionate for ADVAIR HFA, ADVAIR DISKUS, and
1126 fluticasone propionate CFC inhalation aerosol were similar and averaged 5.6 hours.

1127 Salmeterol: In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol
1128 (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was
1129 eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination
1130 half-life was about 5.5 hours (1 volunteer only).

1131 The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is
1132 highly protein bound (greater than 99%) and has a long elimination half-life of 11 days. No
1133 terminal half-life estimates were calculated for salmeterol following administration of ADVAIR
1134 DISKUS.

1135 **Special Populations:** A population pharmacokinetic analysis was performed for
1136 fluticasone propionate and salmeterol utilizing data from 9 controlled clinical trials that included
1137 350 subjects with asthma aged 4 to 77 years who received treatment with ADVAIR DISKUS, the
1138 combination of HFA-propelled fluticasone propionate and salmeterol inhalation aerosol
1139 (ADVAIR HFA), fluticasone propionate inhalation powder (FLOVENT DISKUS), HFA-
1140 propelled fluticasone propionate inhalation aerosol (FLOVENT[®] HFA), or CFC-propelled
1141 fluticasone propionate inhalation aerosol. The population pharmacokinetic analyses for
1142 fluticasone propionate and salmeterol showed no clinically relevant effects of age, gender, race,
1143 body weight, body mass index, or percent of predicted FEV₁ on apparent clearance and apparent
1144 volume of distribution.

1145 **Age:** When the population pharmacokinetic analysis for fluticasone propionate was
1146 divided into subgroups based on fluticasone propionate strength, formulation, and age
1147 (adolescents/adults and children), there were some differences in fluticasone propionate
1148 exposure. Higher fluticasone propionate exposure from ADVAIR DISKUS 100/50 compared
1149 with FLOVENT DISKUS 100 mcg was observed in adolescents and adults (ratio 1.52 [90% CI:
1150 1.08, 2.13]). However, in clinical trials of up to 12 weeks' duration comparing ADVAIR
1151 DISKUS 100/50 and FLOVENT DISKUS 100 mcg in adolescents and adults, no differences in
1152 systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed. Similar
1153 fluticasone propionate exposure was observed from ADVAIR DISKUS 500/50 and FLOVENT
1154 DISKUS 500 mcg (ratio 0.83 [90% CI: 0.65, 1.07]) in adolescents and adults.

1155 Steady-state systemic exposure to salmeterol when delivered as ADVAIR DISKUS
1156 100/50, ADVAIR DISKUS 250/50, or ADVAIR HFA 115/21 (fluticasone propionate 115 mcg
1157 and salmeterol 21 mcg) Inhalation Aerosol was evaluated in 127 subjects aged 4 to 57 years. The
1158 geometric mean AUC was 325 pg•h/mL (90% CI: 309, 341) in adolescents and adults.

1159 The population pharmacokinetic analysis included 160 subjects with asthma aged 4 to
1160 11 years who received ADVAIR DISKUS 100/50 or FLOVENT DISKUS 100 mcg. Higher
1161 fluticasone propionate exposure (AUC) was observed in children from ADVAIR DISKUS
1162 100/50 compared with FLOVENT DISKUS 100 mcg (ratio 1.20 [90% CI: 1.06, 1.37]). Higher
1163 fluticasone propionate exposure (AUC) from ADVAIR DISKUS 100/50 was observed in
1164 children compared with adolescents and adults (ratio 1.63 [90% CI: 1.35, 1.96]). However, in
1165 clinical trials of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and FLOVENT
1166 DISKUS 100 mcg in both adolescents and adults and in children, no differences in systemic
1167 effects of corticosteroid treatment (e.g., HPA axis effects) were observed.

1168 Exposure to salmeterol was higher in children compared with adolescents and adults who
1169 received ADVAIR DISKUS 100/50 (ratio 1.23 [90% CI: 1.10, 1.38]). However, in clinical trials
1170 of up to 12 weeks' duration with ADVAIR DISKUS 100/50 in both adolescents and adults and
1171 in children, no differences in systemic effects of beta₂-agonist treatment (e.g., cardiovascular
1172 effects, tremor) were observed.

1173 *Gender:* The population pharmacokinetic analysis involved 202 males and 148
1174 females with asthma who received fluticasone propionate alone or in combination with
1175 salmeterol and showed no gender differences for fluticasone propionate pharmacokinetics.

1176 The population pharmacokinetic analysis involved 76 males and 51 females with asthma
1177 who received salmeterol in combination with fluticasone propionate and showed no gender
1178 differences for salmeterol pharmacokinetics.

1179 *Hepatic and Renal Impairment:* Formal pharmacokinetic studies using ADVAIR
1180 DISKUS have not been conducted in patients with hepatic or renal impairment. However, since
1181 both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism,
1182 impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol
1183 in plasma. Therefore, patients with hepatic disease should be closely monitored.

1184 Drug Interactions: In the repeat- and single-dose trials, there was no evidence of
1185 significant drug interaction in systemic exposure between fluticasone propionate and salmeterol
1186 when given alone or in combination via the DISKUS. The population pharmacokinetic analysis
1187 from 9 controlled clinical trials in 350 subjects with asthma showed no significant effects on
1188 fluticasone propionate or salmeterol pharmacokinetics following co-administration with beta₂-
1189 agonists, corticosteroids, antihistamines, or theophyllines.

1190 *Inhibitors of Cytochrome P450 3A4: Ritonavir: Fluticasone Propionate:*
1191 Fluticasone propionate is a substrate of CYP3A4. Coadministration of fluticasone propionate and
1192 the strong CYP3A4 inhibitor ritonavir is not recommended based upon a multiple-dose,
1193 crossover drug interaction trial in 18 healthy subjects. Fluticasone propionate aqueous nasal
1194 spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily).
1195 Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal
1196 spray alone were undetectable (less than 10 pg/mL) in most subjects, and when concentrations
1197 were detectable peak levels (C_{max}) averaged 11.9 pg/mL (range: 10.8 to 14.1 pg/mL) and $AUC_{(0-}$
1198 $_{\tau)}$ averaged 8.43 pg•h/mL (range: 4.2 to 18.8 pg•h/mL). Fluticasone propionate C_{max} and $AUC_{(0-}$
1199 $_{\tau)}$ increased to 318 pg/mL (range: 110 to 648 pg/mL) and 3,102.6 pg•h/mL (range: 1,207.1 to
1200 5,662.0 pg•h/mL), respectively, after coadministration of ritonavir with fluticasone propionate
1201 aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted
1202 in a significant decrease (86%) in serum cortisol AUC.

1203 *Ketoconazole: Fluticasone Propionate:* In a placebo-controlled crossover trial
1204 in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone
1205 propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in
1206 increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no
1207 effect on urinary excretion of cortisol.

1208 *Salmeterol:* In a placebo-controlled crossover drug interaction trial in 20
1209 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the
1210 strong CYP3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant
1211 increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with
1212 and without ketoconazole 15.76 [90% CI: 10.66, 23.31]) mainly due to increased bioavailability

1213 of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by
1214 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20 subjects (15%) were withdrawn from
1215 salmeterol and ketoconazole coadministration due to beta-agonist-mediated systemic effects (2
1216 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of
1217 salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate,
1218 mean blood potassium, or mean blood glucose. Although there was no statistical effect on the
1219 mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent
1220 increases in QTc duration compared with salmeterol and placebo administration.

1221 *Erythromycin: Fluticasone Propionate:* In a multiple-dose drug interaction
1222 trial, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and
1223 erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

1224 *Salmeterol:* In a repeat-dose trial in 13 healthy subjects, concomitant
1225 administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol
1226 resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with and without erythromycin
1227 1.4 [90% CI: 0.96, 2.03], *P* = 0.12), a 3.6-beat/min increase in heart rate ([95% CI: 0.19, 7.03],
1228 *P* < 0.04), a 5.8-msec increase in QTc interval ([95% CI: -6.14, 17.77], *P* = 0.34), and no change
1229 in plasma potassium.

1230 **13 NONCLINICAL TOXICOLOGY**

1231 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

1232 Fluticasone Propionate: Fluticasone propionate demonstrated no tumorigenic potential
1233 in mice at oral doses up to 1,000 mcg/kg (approximately 4 and 10 times the MRHDID for adults
1234 and children, respectively, on a mg/m² basis) for 78 weeks or in rats at inhalation doses up to
1235 57 mcg/kg (less than and approximately equivalent to the MRHDID for adults and children,
1236 respectively, on a mg/m² basis) for 104 weeks.

1237 Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in
1238 vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in
1239 vitro or in the in vivo mouse micronucleus test.

1240 No evidence of impairment of fertility was observed in rats at subcutaneous doses up to
1241 50 mcg/kg (less than the MRHDID on a mg/m² basis). Prostate weight was significantly reduced.

1242 Salmeterol: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses
1243 of 1.4 mg/kg and above (approximately 20 times the MRHDID for adults and children based on
1244 comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth
1245 muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts.
1246 No tumors were seen at 0.2 mg/kg (approximately 3 times the MRHDID for adults and children
1247 based on comparison of the AUCs).

1248 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats,
1249 salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and
1250 ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 and 25 times the MRHDID
1251 for adults and children, respectively, on a mg/m² basis). No tumors were seen at 0.21 mg/kg

1252 (approximately 15 and 8 times the MRHDID for adults and children, respectively, on a mg/m²
1253 basis). These findings in rodents are similar to those reported previously for other
1254 beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

1255 Salmeterol produced no detectable or reproducible increases in microbial and mammalian
1256 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo
1257 in a rat micronucleus test. No effects on fertility were identified in rats treated with salmeterol at
1258 oral doses up to 2 mg/kg (approximately 160 times the MRHDID for adults on a mg/m² basis).

1259 **13.2 Animal Toxicology and/or Pharmacology**

1260 Preclinical: Studies in laboratory animals (minipigs, rodents, and dogs) have
1261 demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence
1262 of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently.
1263 The clinical relevance of these findings is unknown.

1264 **14 CLINICAL STUDIES**

1265 **14.1 Asthma**

1266 Adult and Adolescent Subjects Aged 12 Years and Older: In clinical trials
1267 comparing ADVAIR DISKUS with its individual components, improvements in most efficacy
1268 endpoints were greater with ADVAIR DISKUS than with the use of either fluticasone propionate
1269 or salmeterol alone. In addition, clinical trials showed similar results between ADVAIR DISKUS
1270 and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from
1271 separate inhalers.

1272 *Trials Comparing ADVAIR DISKUS to Fluticasone Propionate Alone or*
1273 *Salmeterol Alone*: Three (3) double-blind, parallel-group clinical trials were conducted with
1274 ADVAIR DISKUS in 1,208 adolescent and adult subjects (aged 12 years and older, baseline
1275 FEV₁ 63% to 72% of predicted normal) with asthma that was not optimally controlled on their
1276 current therapy. All treatments were inhalation powders given as 1 inhalation from the DISKUS
1277 device twice daily, and other maintenance therapies were discontinued.

1278 *Trial 1: Clinical Trial With ADVAIR DISKUS 100/50*: This placebo-controlled,
1279 12-week, US trial compared ADVAIR DISKUS 100/50 with its individual components,
1280 fluticasone propionate 100 mcg and salmeterol 50 mcg. The trial was stratified according to
1281 baseline asthma maintenance therapy; subjects were using either inhaled corticosteroids
1282 (n = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg;
1283 fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg)
1284 or salmeterol (n = 106). Baseline FEV₁ measurements were similar across treatments: ADVAIR
1285 DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and
1286 placebo, 2.15 L.

1287 Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma,
1288 were utilized for this placebo-controlled trial. Worsening asthma was defined as a clinically
1289 important decrease in FEV₁ or PEF, increase in use of VENTOLIN[®] (albuterol, USP) Inhalation
1290 Aerosol, increase in night awakenings due to asthma, emergency intervention or hospitalization

1291 due to asthma, or requirement for asthma medication not allowed by the protocol. As shown in
1292 Table 4, statistically significantly fewer subjects receiving ADVAIR DISKUS 100/50 were
1293 withdrawn due to worsening asthma compared with fluticasone propionate, salmeterol, and
1294 placebo.

1295

1296 **Table 4. Percent of Subjects Withdrawn Due to Worsening Asthma in Subjects Previously**
1297 **Treated With Either Inhaled Corticosteroids or Salmeterol (Trial 1)**

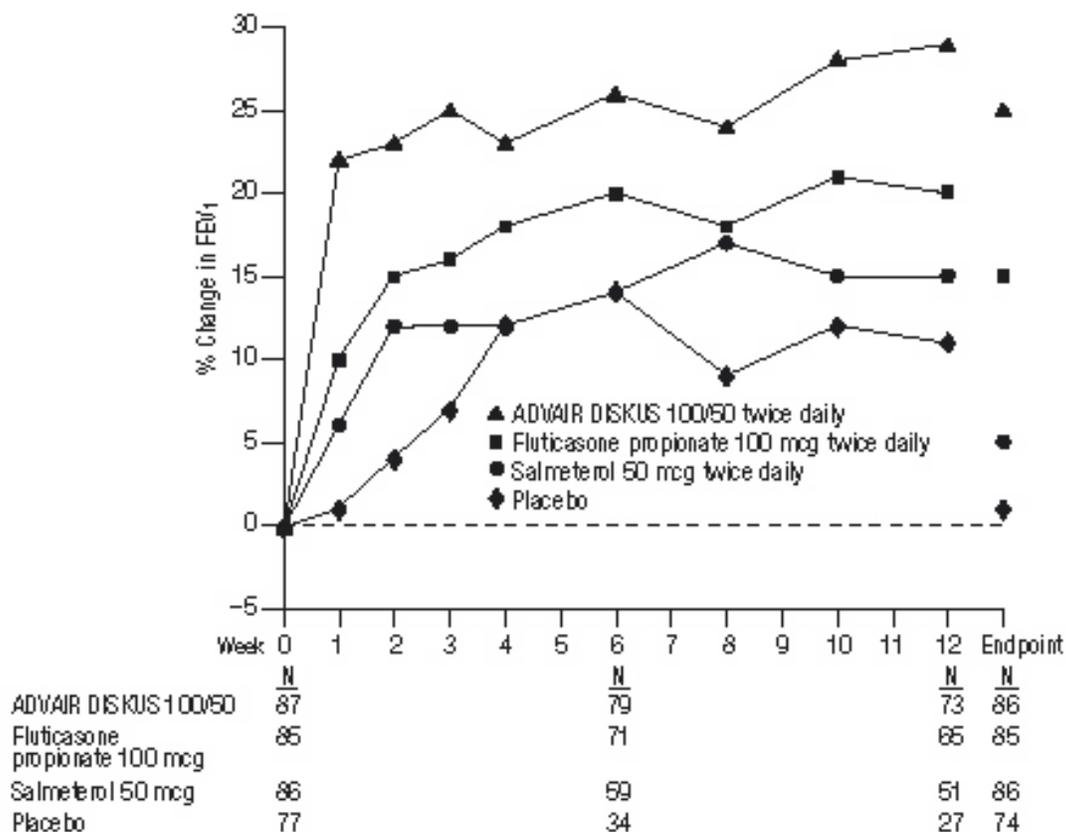
ADVAIR DISKUS 100/50 (n = 87)	Fluticasone Propionate 100 mcg (n = 85)	Salmeterol 50 mcg (n = 86)	Placebo (n = 77)
3%	11%	35%	49%

1298

1299 The FEV₁ results are displayed in Figure 2. Because this trial used predetermined criteria
1300 for worsening asthma, which caused more subjects in the placebo group to be withdrawn, FEV₁
1301 results at Endpoint (last available FEV₁ result) are also provided. Subjects receiving ADVAIR
1302 DISKUS 100/50 had significantly greater improvements in FEV₁ (0.51 L, 25%) compared with
1303 fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L,
1304 1%). These improvements in FEV₁ with ADVAIR DISKUS were achieved regardless of baseline
1305 asthma maintenance therapy (inhaled corticosteroids or salmeterol).

1306

1307 **Figure 2. Mean Percent Change From Baseline in FEV₁ in Subjects With Asthma**
1308 **Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Trial 1)**
1309



1310
1311

1312 The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is
1313 shown in Table 5.

1314

1315 **Table 5. Peak Expiratory Flow Results for Subjects With Asthma Previously Treated With**
1316 **Either Inhaled Corticosteroids or Salmeterol (Trial 1)**

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

1317

^a Change from baseline = change from baseline at Endpoint (last available data).

1318

1319 The subjective impact of asthma on subjects' perception of health was evaluated through
1320 use of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-
1321 point scale where 1 = maximum impairment and 7 = none). Subjects receiving ADVAIR
1322 DISKUS 100/50 had clinically meaningful improvements in overall asthma-specific quality of
1323 life as defined by a difference between groups of ≥ 0.5 points in change from baseline AQLQ
1324 scores (difference in AQLQ score of 1.25 compared with placebo).

1325 *Trial 2: Clinical Trial With ADVAIR DISKUS 250/50:* This placebo-controlled,
1326 12-week, US trial compared ADVAIR DISKUS 250/50 with its individual components,
1327 fluticasone propionate 250 mcg and salmeterol 50 mcg, in 349 subjects with asthma using
1328 inhaled corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide
1329 1,250 to 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone
1330 acetonide 1,100 to 1,600 mcg). Baseline FEV₁ measurements were similar across treatments:
1331 ADVAIR DISKUS 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L;
1332 and placebo, 2.19 L.

1333 Efficacy results in this trial were similar to those observed in Trial 1. Subjects receiving
1334 ADVAIR DISKUS 250/50 had significantly greater improvements in FEV₁ (0.48 L, 23%)
1335 compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and
1336 placebo (decrease of 0.11 L, decrease of 5%). Statistically significantly fewer subjects receiving
1337 ADVAIR DISKUS 250/50 were withdrawn from this trial for worsening asthma (4%) compared
1338 with fluticasone propionate (22%), salmeterol (38%), and placebo (62%). In addition, ADVAIR
1339 DISKUS 250/50 was superior to fluticasone propionate, salmeterol, and placebo for
1340 improvements in morning and evening PEF. Subjects receiving ADVAIR DISKUS 250/50 also
1341 had clinically meaningful improvements in overall asthma-specific quality of life as described in
1342 Trial 1 (difference in AQLQ score of 1.29 compared with placebo).

1343 *Trial 3: Clinical Trial With ADVAIR DISKUS 500/50:* This 28-week, non-US
1344 trial compared ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and
1345 concurrent therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from
1346 separate inhalers) twice daily in 503 subjects with asthma using inhaled corticosteroids (daily
1347 doses of beclomethasone dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg;
1348 flunisolide 1,500 to 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750
1349 to 1,000 mcg inhalation powder]). The primary efficacy parameter, morning PEF, was collected
1350 daily for the first 12 weeks of the trial. The primary purpose of weeks 13 to 28 was to collect
1351 safety data.

1352 Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50,
1353 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min.
1354 Morning PEF improved significantly with ADVAIR DISKUS 500/50 compared with fluticasone
1355 propionate 500 mcg over the 12-week treatment period. Improvements in morning PEF observed
1356 with ADVAIR DISKUS 500/50 were similar to improvements observed with concurrent therapy.

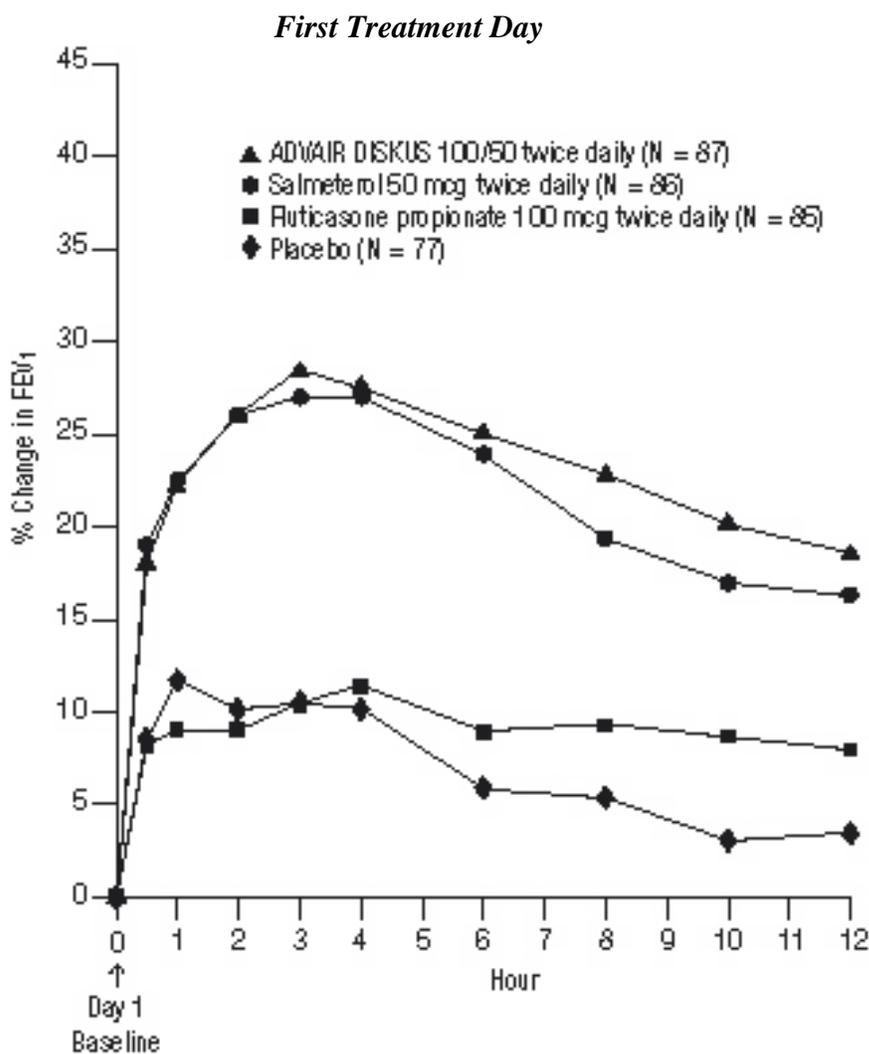
1357 *Onset of Action and Progression of Improvement in Asthma Control:* The onset
1358 of action and progression of improvement in asthma control were evaluated in the 2 placebo-
1359 controlled US trials. Following the first dose, the median time to onset of clinically significant
1360 bronchodilatation ($\geq 15\%$ improvement in FEV₁) in most subjects was seen within 30 to
1361 60 minutes. Maximum improvement in FEV₁ generally occurred within 3 hours, and clinically
1362 significant improvement was maintained for 12 hours (see Figure 3). Following the initial dose,
1363 predose FEV₁ relative to Day 1 baseline improved markedly over the first week of treatment and
1364 continued to improve over the 12 weeks of treatment in both trials. No diminution in the 12-hour
1365 bronchodilator effect was observed with either ADVAIR DISKUS 100/50 (Figures 3 and 4) or
1366 ADVAIR DISKUS 250/50 as assessed by FEV₁ following 12 weeks of therapy.

1367

1368 **Figure 3. Percent Change in Serial 12-hour FEV₁ in Subjects**
1369 **With Asthma Previously Using Either Inhaled Corticosteroids**
1370 **or Salmeterol (Trial 1)**

1371

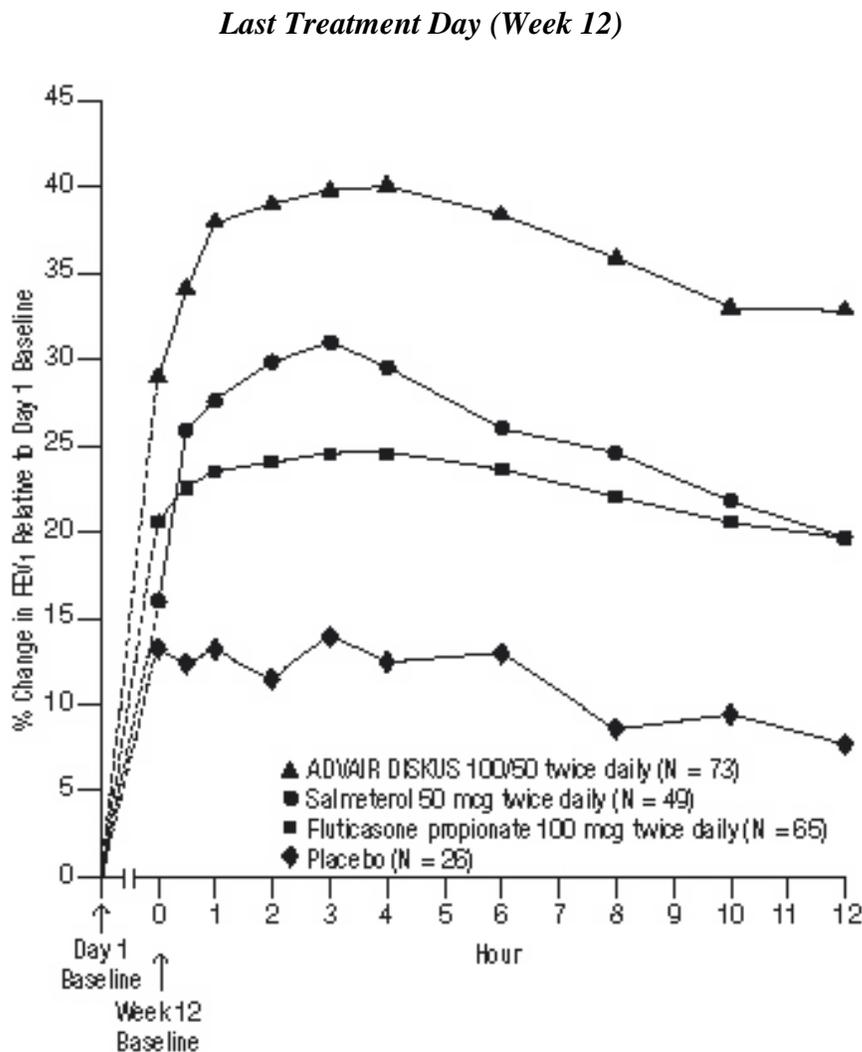
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Figure 4. Percent Change in Serial 12-hour FEV₁ in Subjects With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Trial 1)



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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 trials.

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

1392 the safety of ADVAIR DISKUS 100/50 compared with fluticasone propionate inhalation powder
1393 100 mcg in this age-group; however, the trial also included secondary efficacy measures of
1394 pulmonary function. Morning predose FEV₁ was obtained at baseline and Endpoint (last
1395 available FEV₁ result) in children aged 6 to 11 years. In subjects receiving ADVAIR DISKUS
1396 100/50, FEV₁ increased from 1.70 L at baseline (n = 79) to 1.88 L at Endpoint (n = 69)
1397 compared with an increase from 1.65 L at baseline (n = 83) to 1.77 L at Endpoint (n = 75) in
1398 subjects receiving fluticasone propionate 100 mcg.

1399 The findings of this trial, along with extrapolation of efficacy data from subjects aged
1400 12 years and older, support the overall conclusion that ADVAIR DISKUS 100/50 is efficacious
1401 in the treatment of asthma in subjects aged 4 to 11 years.

1402 **14.2 Chronic Obstructive Pulmonary Disease**

1403 The efficacy of ADVAIR DISKUS 250/50 and ADVAIR DISKUS 500/50 in the
1404 treatment of subjects with COPD was evaluated in 6 randomized, double-blind, parallel-group
1405 clinical trials in adult subjects aged 40 years and older. These trials were primarily designed to
1406 evaluate the efficacy of ADVAIR DISKUS on lung function (3 trials), exacerbations (2 trials),
1407 and survival (1 trial).

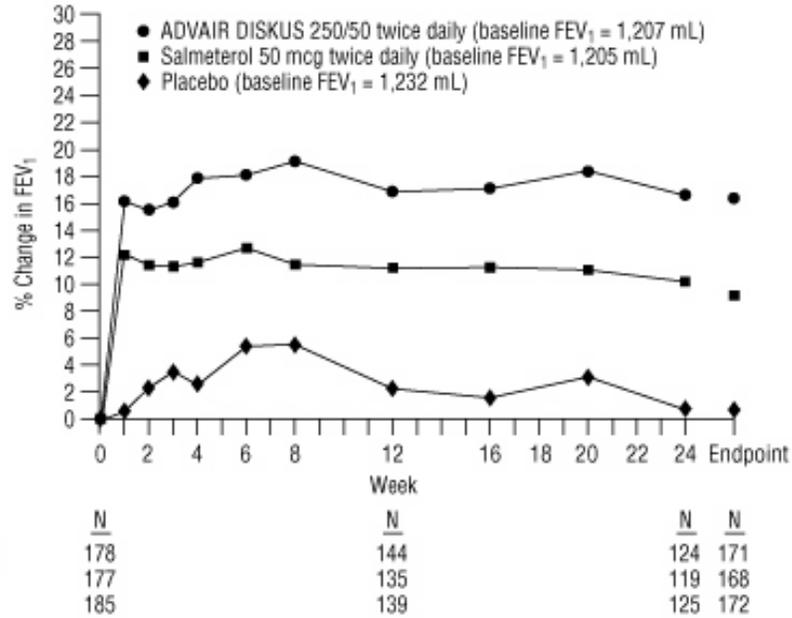
1408 Lung Function: Two of the 3 clinical trials primarily designed to evaluate the efficacy of
1409 ADVAIR DISKUS on lung function were conducted in 1,414 subjects with COPD associated
1410 with chronic bronchitis. In these 2 trials, all the subjects had a history of cough productive of
1411 sputum that was not attributable to another disease process on most days for at least 3 months of
1412 the year for at least 2 years. The trials were randomized, double-blind, parallel-group, 24-week
1413 treatment duration. One trial evaluated the efficacy of ADVAIR DISKUS 250/50 compared with
1414 its components fluticasone propionate 250 mcg and salmeterol 50 mcg and with placebo, and the
1415 other trial evaluated the efficacy of ADVAIR DISKUS 500/50 compared with its components
1416 fluticasone propionate 500 mcg and salmeterol 50 mcg and with placebo. Trial treatments were
1417 inhalation powders given as 1 inhalation from the DISKUS device twice daily. Maintenance
1418 COPD therapies were discontinued, with the exception of theophylline. The subjects had a mean
1419 pre-bronchodilator FEV₁ of 41% and 20% reversibility at trial entry. Percent reversibility was
1420 calculated as 100 times (FEV₁ post-albuterol minus FEV₁ pre-albuterol)/FEV₁ pre-albuterol.

1421 Improvements in lung function (as defined by predose and postdose FEV₁) were
1422 significantly greater with ADVAIR DISKUS than with fluticasone propionate, salmeterol, or
1423 placebo. The improvement in lung function with ADVAIR DISKUS 500/50 was similar to the
1424 improvement seen with ADVAIR DISKUS 250/50.

1425 Figures 5 and 6 display predose and 2-hour postdose, respectively, FEV₁ results for the
1426 trial with ADVAIR DISKUS 250/50. To account for subject withdrawals during the trial, FEV₁
1427 at Endpoint (last evaluable FEV₁) was evaluated. Subjects receiving ADVAIR DISKUS 250/50
1428 had significantly greater improvements in predose FEV₁ at Endpoint (165 mL, 17%) compared
1429 with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL, 1%), demonstrating the contribution of
1430 fluticasone propionate to the improvement in lung function with ADVAIR DISKUS (Figure 5).
1431 Subjects receiving ADVAIR DISKUS 250/50 had significantly greater improvements in

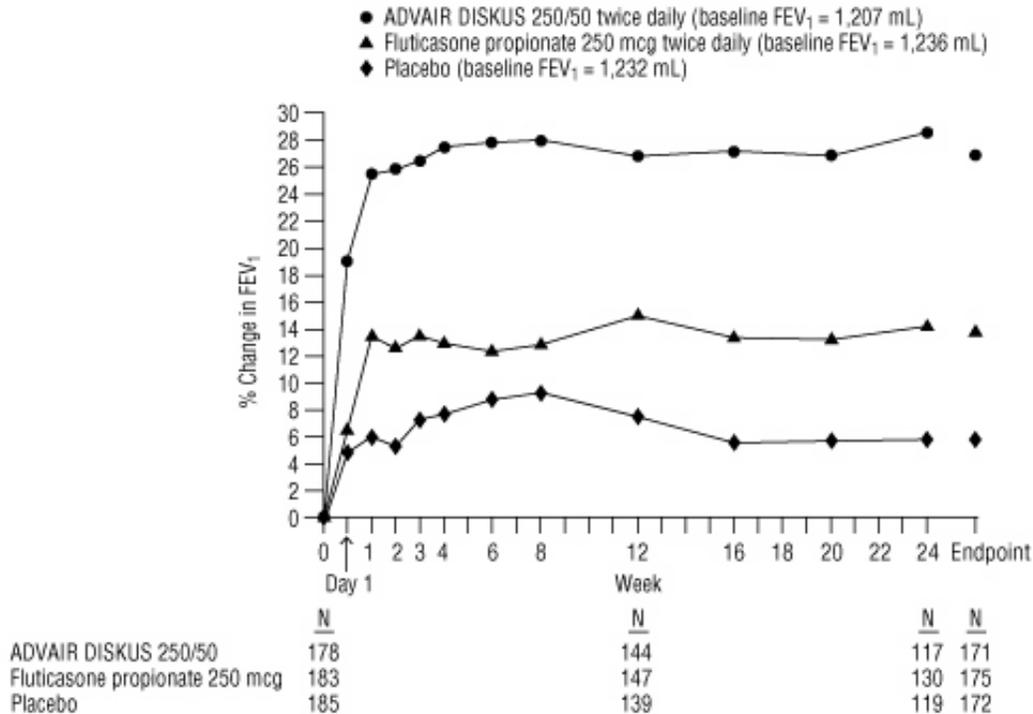
1432 postdose FEV₁ at Endpoint (281 mL, 27%) compared with fluticasone propionate 250 mcg
 1433 (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the contribution of salmeterol to the
 1434 improvement in lung function with ADVAIR DISKUS (Figure 6).
 1435

1436 **Figure 5. Predose FEV₁: Mean Percent Change From Baseline in Subjects**
 1437 **With Chronic Obstructive Pulmonary Disease**
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1441 **Figure 6. Two-Hour Postdose FEV₁: Mean Percent Changes From Baseline**
 1442 **Over Time in Subjects With Chronic Obstructive Pulmonary Disease**
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1446 The third trial was a 1-year trial that evaluated ADVAIR DISKUS 500/50, fluticasone
 1447 propionate 500 mcg, salmeterol 50 mcg, and placebo in 1,465 subjects. The subjects had an
 1448 established history of COPD and exacerbations, a pre-bronchodilator FEV₁ <70% of predicted at
 1449 trial entry, and 8.3% reversibility. The primary endpoint was the comparison of pre-
 1450 bronchodilator FEV₁ in the groups receiving ADVAIR DISKUS 500/50 or placebo. Subjects
 1451 treated with ADVAIR DISKUS 500/50 had greater improvements in FEV₁ (113 mL, 10%)
 1452 compared with fluticasone propionate 500 mcg (7 mL, 2%), salmeterol (15 mL, 2%), and
 1453 placebo (-60 mL, -3%).

1454 **Exacerbations:** Two trials were primarily designed to evaluate the effect of ADVAIR
 1455 DISKUS 250/50 on exacerbations. In these 2 trials, exacerbations were defined as worsening of
 1456 2 or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of
 1457 any 1 major symptom together with any 1 of the following minor symptoms: sore throat, colds
 1458 (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or
 1459 wheeze for at least 2 consecutive days. COPD exacerbations were considered of moderate
 1460 severity if treatment with systemic corticosteroids and/or antibiotics was required and were
 1461 considered severe if hospitalization was required.

1462 Exacerbations were also evaluated as a secondary outcome in the 1- and 3-year trials with
 1463 ADVAIR DISKUS 500/50. There was not a symptomatic definition of exacerbation in these 2

1464 trials. Exacerbations were defined in terms of severity requiring treatment with antibiotics and/or
1465 systemic corticosteroids (moderately severe) or requiring hospitalization (severe).

1466 The 2 exacerbation trials with ADVAIR DISKUS 250/50 were identical trials designed to
1467 evaluate the effect of ADVAIR DISKUS 250/50 and salmeterol 50 mcg, each given twice daily,
1468 on exacerbations of COPD over a 12-month period. A total of 1,579 subjects had an established
1469 history of COPD (but no other significant respiratory disorders). Subjects had a pre-
1470 bronchodilator FEV₁ of 33% of predicted, a mean reversibility of 23% at baseline, and a history
1471 of ≥1 COPD exacerbation in the previous year that was moderate or severe. All subjects were
1472 treated with ADVAIR DISKUS 250/50 twice daily during a 4-week run-in period prior to being
1473 assigned trial treatment with twice-daily ADVAIR DISKUS 250/50 or salmeterol 50 mcg. In
1474 both trials, treatment with ADVAIR DISKUS 250/50 resulted in a significantly lower annual rate
1475 of moderate/severe COPD exacerbations compared with salmeterol (30.5% reduction [95% CI:
1476 17.0, 41.8], *P*<0.001) in the first trial and (30.4% reduction [95% CI: 16.9, 41.7], *P*<0.001) in
1477 the second trial. Subjects treated with ADVAIR DISKUS 250/50 also had a significantly lower
1478 annual rate of exacerbations requiring treatment with oral corticosteroids compared with subjects
1479 treated with salmeterol (39.7% reduction [95% CI: 22.8, 52.9], *P*<0.001) in the first trial and
1480 (34.3% reduction [95% CI: 18.6, 47.0], *P*<0.001) in the second trial. Secondary endpoints
1481 including pulmonary function and symptom scores improved more in subjects treated with
1482 ADVAIR DISKUS 250/50 than with salmeterol 50 mcg in both trials.

1483 Exacerbations were evaluated in the 1- and the 3-year trials with ADVAIR DISKUS
1484 500/50 as 1 of the secondary efficacy endpoints. In the 1-year trial, the group receiving ADVAIR
1485 DISKUS 500/50 had a significantly lower rate of moderate and severe exacerbations compared
1486 with placebo (25.4% reduction compared with placebo [95% CI: 13.5, 35.7]) but not when
1487 compared with its components (7.5% reduction compared with fluticasone propionate [95% CI:
1488 -7.3, 20.3] and 7% reduction compared with salmeterol [95% CI: -8.0, 19.9]). In the 3-year trial,
1489 the group receiving ADVAIR DISKUS 500/50 had a significantly lower rate of moderate and
1490 severe exacerbations compared with each of the other treatment groups (25.1% reduction
1491 compared with placebo [95% CI: 18.6, 31.1], 9.0% reduction compared with fluticasone
1492 propionate [95% CI: 1.2, 16.2], and 12.2% reduction compared with salmeterol [95% CI: 4.6,
1493 19.2]).

1494 There were no trials conducted to directly compare the efficacy of ADVAIR DISKUS
1495 250/50 with ADVAIR DISKUS 500/50 on exacerbations. Across trials, the reduction in
1496 exacerbations seen with ADVAIR DISKUS 500/50 was not greater than the reduction in
1497 exacerbations seen with ADVAIR DISKUS 250/50.

1498 **Survival:** A 3-year multicenter, international trial evaluated the efficacy of ADVAIR
1499 DISKUS 500/50 compared with fluticasone propionate 500 mcg, salmeterol 50 mcg, and placebo
1500 on survival in 6,112 subjects with COPD. During the trial subjects were permitted usual COPD
1501 therapy with the exception of other inhaled corticosteroids and long-acting bronchodilators. The
1502 subjects were aged 40 to 80 years with an established history of COPD, a pre-bronchodilator
1503 FEV₁ <60% of predicted at trial entry, and <10% of predicted reversibility. Each subject who

1504 withdrew from double-blind treatment for any reason was followed for the full 3-year trial period
1505 to determine survival status. The primary efficacy endpoint was all-cause mortality. Survival
1506 with ADVAIR DISKUS 500/50 was not significantly improved compared with placebo or the
1507 individual components (all-cause mortality rate 12.6% ADVAIR DISKUS versus 15.2%
1508 placebo). The rates for all-cause mortality were 13.5% and 16.0% in the groups treated with
1509 salmeterol 50 mcg and fluticasone propionate 500 mcg, respectively. Secondary outcomes,
1510 including pulmonary function (post-bronchodilator FEV₁), improved with ADVAIR DISKUS
1511 500/50, salmeterol, and fluticasone propionate 500/50 compared with placebo.

1512 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1513 ADVAIR DISKUS 100/50 is supplied as a disposable purple plastic inhaler containing a
1514 foil blister strip with 60 blisters. The inhaler is packaged in a plastic-coated, moisture-protective
1515 foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional
1516 pack containing 14 blisters (NDC 0173-0695-04).

1517 ADVAIR DISKUS 250/50 is supplied as a disposable purple plastic inhaler containing a
1518 foil blister strip with 60 blisters. The inhaler is packaged in a plastic-coated, moisture-protective
1519 foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional
1520 pack containing 14 blisters (NDC 0173-0696-04).

1521 ADVAIR DISKUS 500/50 is supplied as a disposable purple plastic inhaler containing a
1522 foil blister strip with 60 blisters. The inhaler is packaged in a plastic-coated, moisture-protective
1523 foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional
1524 pack containing 14 blisters (NDC 0173-0697-04).

1525 Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions
1526 permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in
1527 a dry place away from direct heat or sunlight. Keep out of reach of children.

1528 ADVAIR DISKUS should be stored inside the unopened moisture-protective foil pouch
1529 and only removed from the pouch immediately before initial use. Discard ADVAIR DISKUS 1
1530 month after opening the foil pouch or when the counter reads “0” (after all blisters have been
1531 used), whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler
1532 apart.

1533 **17 PATIENT COUNSELING INFORMATION**

1534 Advise the patient to read the FDA-approved patient labeling (Medication Guide and
1535 Instructions for Use).

1536 **Asthma-Related Death: Inform patients with asthma that salmeterol, one of the**
1537 **active ingredients in ADVAIR DISKUS, increases the risk of asthma-related death and**
1538 **may increase the risk of asthma-related hospitalization in pediatric and adolescent patients.**
1539 **Also inform them that currently available data are inadequate to determine whether**
1540 **concurrent use of inhaled corticosteroids or other long-term asthma control drugs**
1541 **mitigates the increased risk of asthma-related death from LABA.**

1542 Not for Acute Symptoms: Inform patients that ADVAIR DISKUS is not meant to
1543 relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for
1544 that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta₂-agonist
1545 such as albuterol. Provide patients with such medication and instruct them in how it should be
1546 used.

1547 Instruct patients to seek medical attention immediately if they experience any of the
1548 following:

- 1549 • Decreasing effectiveness of inhaled, short-acting beta₂-agonists
- 1550 • Need for more inhalations than usual of inhaled, short-acting beta₂-agonists
- 1551 • Significant decrease in lung function as outlined by the physician

1552 Tell patients they should not stop therapy with ADVAIR DISKUS without
1553 physician/provider guidance since symptoms may recur after discontinuation.

1554 Do Not Use Additional Long-Acting Beta₂-Agonists: Instruct patients not to use other
1555 LABA for asthma and COPD.

1556 Local Effects: Inform patients that localized infections with *Candida albicans* occurred
1557 in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, treat it with
1558 appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with
1559 ADVAIR DISKUS, but at times therapy with ADVAIR DISKUS may need to be temporarily
1560 interrupted under close medical supervision. Rinsing the mouth with water without swallowing
1561 after inhalation is advised to help reduce the risk of thrush.

1562 Pneumonia: Patients with COPD have a higher risk of pneumonia; instruct them to
1563 contact their healthcare provider if they develop symptoms of pneumonia.

1564 Immunosuppression: Warn patients who are on immunosuppressant doses of
1565 corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their
1566 physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal,
1567 bacterial, viral, or parasitic infections; or ocular herpes simplex.

1568 Hypercorticism and Adrenal Suppression: Advise patients that ADVAIR DISKUS
1569 may cause systemic corticosteroid effects of hypercorticism and adrenal suppression.
1570 Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and
1571 after transfer from systemic corticosteroids. Patients should taper slowly from systemic
1572 corticosteroids if transferring to ADVAIR DISKUS.

1573 Immediate Hypersensitivity Reactions: Advise patients that immediate
1574 hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension),
1575 including anaphylaxis, may occur after administration of ADVAIR DISKUS. Patients should
1576 discontinue ADVAIR DISKUS if such reactions occur. There have been reports of anaphylactic
1577 reactions in patients with severe milk protein allergy after inhalation of powder products
1578 containing lactose; therefore, patients with severe milk protein allergy should not take ADVAIR
1579 DISKUS.

1580 Reduction in Bone Mineral Density: Advise patients who are at an increased risk for
1581 decreased BMD that the use of corticosteroids may pose an additional risk.

1582 **Reduced Growth Velocity:** Inform patients that orally inhaled corticosteroids, including
1583 fluticasone propionate, may cause a reduction in growth velocity when administered to pediatric
1584 patients. Physicians should closely follow the growth of children and adolescents taking
1585 corticosteroids by any route.

1586 **Ocular Effects:** Long-term use of inhaled corticosteroids may increase the risk of some
1587 eye problems (cataracts or glaucoma); consider regular eye examinations.

1588 **Risks Associated With Beta-Agonist Therapy:** Inform patients of adverse effects
1589 associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or
1590 nervousness.

1591

1592 ADVAIR, ADVAIR DISKUS, DISKHALER, DISKUS, FLONASE, FLOVENT, ROTADISK,
1593 SEREVENT, and VENTOLIN are registered trademarks of the GSK group of companies.

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1597 GlaxoSmithKline

1598 Research Triangle Park, NC 27709

1599

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1602 ADD:xPI

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MEDICATION GUIDE

1605

ADVAIR DISKUS[®] [ad' vair disk' us] 100/50

1606

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

1607

1608

ADVAIR DISKUS[®] 250/50

1609

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

1610

1611

ADVAIR DISKUS[®] 500/50

1612

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

1613

1614

1615 Read the Medication Guide that comes with ADVAIR DISKUS before you start using
1616 it and each time you get a refill. There may be new information. This Medication
1617 Guide does not take the place of talking to your healthcare provider about your
1618 medical condition or treatment.

1619

1620 **What is the most important information I should know about ADVAIR**
1621 **DISKUS?**

1622 **ADVAIR DISKUS can cause serious side effects, including:**

- 1623 • **People with asthma who take long-acting beta₂-adrenergic agonist**
1624 **(LABA) medicines, such as salmeterol (one of the medicines in ADVAIR**
1625 **DISKUS), have an increased risk of death from asthma problems.** It is
1626 not known whether fluticasone propionate, the other medicine in ADVAIR
1627 DISKUS, reduces the risk of death from asthma problems seen with LABA
1628 medicines.
- 1629 • **It is not known if LABA medicines such as salmeterol increase the risk**
1630 **of death in people with COPD.**
- 1631 • **Call your healthcare provider if breathing problems worsen over time**
1632 **while using ADVAIR DISKUS.** You may need different treatment.
- 1633 • **Get emergency medical care if:**
 - 1634 • your breathing problems worsen quickly.
 - 1635 • you use your rescue inhaler, but it does not relieve your breathing problems.
- 1636 • ADVAIR DISKUS should be used only if your healthcare provider decides that
1637 your asthma is not well controlled with a long-term asthma control medicine,
1638 such as an inhaled corticosteroid. When your asthma is well controlled, your
1639 healthcare provider may tell you to stop taking ADVAIR DISKUS. Your
1640 healthcare provider will decide if you can stop ADVAIR DISKUS without loss of
1641 asthma control. Your healthcare provider may prescribe a different asthma
1642 control medicine for you, such as an inhaled corticosteroid.
- 1643 • Children and adolescents who take LABA medicines may have an increased risk
1644 of being hospitalized for asthma problems.

1645

1646 **What is ADVAIR DISKUS?**

- 1647 • ADVAIR DISKUS combines the inhaled corticosteroid (ICS) medicine fluticasone
1648 propionate and the LABA medicine salmeterol.
- 1649 • ICS medicines such as fluticasone propionate help to decrease inflammation in
1650 the lungs. Inflammation in the lungs can lead to breathing problems.
- 1651 • LABA medicines such as salmeterol help the muscles around the airways in your
1652 lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest
1653 tightness, and shortness of breath. These symptoms can happen when the
1654 muscles around the airways tighten. This makes it hard to breathe.

- 1655 • ADVAIR DISKUS is not used to relieve sudden breathing problems.
- 1656 • It is not known if ADVAIR DISKUS is safe and effective in children younger than
1657 4 years.
- 1658 • ADVAIR DISKUS is used for asthma and COPD as follows:
- 1659 **Asthma:**
- 1660 ADVAIR DISKUS is a prescription medicine used to control symptoms of asthma
1661 and to prevent symptoms such as wheezing in adults and children aged 4 years
1662 and older.
- 1663 ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT).
1664 LABA medicines, such as salmeterol, increase the risk of death from asthma
1665 problems.
- 1666 ADVAIR DISKUS is not for adults and children with asthma who are well
1667 controlled with an asthma control medicine, such as a low to medium dose of an
1668 inhaled corticosteroid medicine.
- 1669 **COPD:**
- 1670 ADVAIR DISKUS 250/50 is a prescription medicine used to treat COPD. COPD is
1671 a chronic lung disease that includes chronic bronchitis, emphysema, or both.
1672 ADVAIR DISKUS 250/50 is used long term as 1 inhalation 2 times each day to
1673 improve symptoms of COPD for better breathing and to reduce the number of
1674 flare-ups (the worsening of your COPD symptoms for several days).
1675
- 1676 **Who should not use ADVAIR DISKUS?**
- 1677 Do not use ADVAIR DISKUS if you:
- 1678 • have a severe allergy to milk proteins. Ask your healthcare provider if you are
1679 not sure.
- 1680 • are allergic to fluticasone propionate, salmeterol, or any of the ingredients in
1681 ADVAIR DISKUS. See “What are the ingredients in ADVAIR DISKUS?” below for
1682 a complete list of ingredients.
1683
- 1684 **What should I tell my healthcare provider before using ADVAIR DISKUS?**
- 1685 **Tell your healthcare provider about all of your health conditions, including**
1686 **if you:**
- 1687 • have heart problems.
- 1688 • have high blood pressure.

- 1689 • have seizures.
- 1690 • have thyroid problems.
- 1691 • have diabetes.
- 1692 • have liver problems.
- 1693 • have weak bones (osteoporosis).
- 1694 • have an immune system problem.
- 1695 • have eye problems such as glaucoma or cataracts.
- 1696 • are allergic to any of the ingredients in ADVAIR DISKUS, any other medicines, or
- 1697 food products. See “What are the ingredients in ADVAIR DISKUS?” below for a
- 1698 complete list of ingredients.
- 1699 • have any type of viral, bacterial, or fungal infection.
- 1700 • are exposed to chickenpox or measles.
- 1701 • have any other medical conditions.
- 1702 • are pregnant or planning to become pregnant. It is not known if ADVAIR
- 1703 DISKUS may harm your unborn baby.
- 1704 • are breastfeeding. It is not known if the medicines in ADVAIR DISKUS pass into
- 1705 your milk and if they can harm your baby.
- 1706 **Tell your healthcare provider about all the medicines you take**, including
- 1707 prescription and over-the-counter medicines, vitamins, and herbal supplements.
- 1708 ADVAIR DISKUS and certain other medicines may interact with each other. This
- 1709 may cause serious side effects. Especially, tell your healthcare provider if you take
- 1710 antifungal or anti-HIV medicines.
- 1711 Know the medicines you take. Keep a list of them to show your healthcare provider
- 1712 and pharmacist when you get a new medicine.
- 1713
- 1714 **How should I use ADVAIR DISKUS?**
- 1715 **Read the step-by-step instructions for using ADVAIR DISKUS at the end of**
- 1716 **this Medication Guide.**
- 1717 • **Do not** use ADVAIR DISKUS unless your healthcare provider has taught you
- 1718 how to use the inhaler and you understand how to use it correctly.
- 1719 • Children should use ADVAIR DISKUS with an adult’s help, as instructed by the
- 1720 child’s healthcare provider.
- 1721 • ADVAIR DISKUS comes in 3 different strengths. Your healthcare provider

- 1722 prescribed the strength that is best for you.
- 1723 • Use ADVAIR DISKUS exactly as your healthcare provider tells you to use it. **Do**
1724 **not** use ADVAIR DISKUS more often than prescribed.
- 1725 • Use 1 inhalation of ADVAIR DISKUS 2 times each day. Use ADVAIR DISKUS at
1726 the same time each day, about 12 hours apart.
- 1727 • If you miss a dose of ADVAIR DISKUS, just skip that dose. Take your next dose
1728 at your usual time. Do not take 2 doses at 1 time.
- 1729 • If you take too much ADVAIR DISKUS, call your healthcare provider or go to the
1730 nearest hospital emergency room right away if you have any unusual symptoms,
1731 such as worsening shortness of breath, chest pain, increased heart rate, or
1732 shakiness.
- 1733 • **Do not use other medicines that contain a LABA for any reason.** Ask your
1734 healthcare provider or pharmacist if any of your other medicines are LABA
1735 medicines.
- 1736 • Do not stop using ADVAIR DISKUS unless told to do so by your healthcare
1737 provider because your symptoms might get worse. Your healthcare provider will
1738 change your medicines as needed.
- 1739 • **ADVAIR DISKUS does not relieve sudden symptoms.** Always have a rescue
1740 inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler,
1741 call your healthcare provider to have one prescribed for you.
- 1742 • Call your healthcare provider or get medical care right away if:
1743 • your breathing problems get worse.
1744 • you need to use your rescue inhaler more often than usual.
1745 • your rescue inhaler does not work as well to relieve your symptoms.
1746 • you need to use 4 or more inhalations of your rescue inhaler in 24 hours for
1747 2 or more days in a row.
1748 • you use 1 whole canister of your rescue inhaler in 8 weeks.
1749 • your peak flow meter results decrease. Your healthcare provider will tell you
1750 the numbers that are right for you.
1751 • you have asthma and your symptoms do not improve after using ADVAIR
1752 DISKUS regularly for 1 week.

1753

1754 **What are the possible side effects with ADVAIR DISKUS?**

1755 **ADVAIR DISKUS can cause serious side effects, including:**

- 1756 • **See “What is the most important information I should know about**
1757 **ADVAIR DISKUS?”**

- 1758 • **fungal infection in your mouth or throat (thrush).** Rinse your mouth with
1759 water without swallowing after using ADVAIR DISKUS to help reduce your
1760 chance of getting thrush.
- 1761 • **pneumonia.** People with COPD have a higher chance of getting pneumonia.
1762 ADVAIR DISKUS may increase the chance of getting pneumonia. Call your
1763 healthcare provider if you notice any of the following symptoms:
- 1764 • increase in mucus (sputum) production
 - 1765 • change in mucus color
 - 1766 • fever
 - 1767 • chills
 - 1768 • increased cough
 - 1769 • increased breathing problems
- 1770 • **weakened immune system and increased chance of getting infections**
1771 **(immunosuppression)**
- 1772 • **reduced adrenal function (adrenal insufficiency).** Adrenal insufficiency is a
1773 condition where the adrenal glands do not make enough steroid hormones. This
1774 can happen when you stop taking oral corticosteroid medicines (such as
1775 prednisone) and start taking a medicine containing an inhaled steroid (such as
1776 ADVAIR DISKUS). When your body is under stress such as from fever, trauma
1777 (such as a car accident), infection, surgery, or worse COPD symptoms, adrenal
1778 insufficiency can get worse and may cause death.
- 1779 Symptoms of adrenal insufficiency include:
- 1780 • feeling tired
 - 1781 • lack of energy
 - 1782 • weakness
 - 1783 • nausea and vomiting
 - 1784 • low blood pressure
- 1785 • **sudden breathing problems immediately after inhaling your medicine**
- 1786 • **serious allergic reactions.** Call your healthcare provider or get emergency
1787 medical care if you get any of the following symptoms of a serious allergic
1788 reaction:
- 1789 • rash
 - 1790 • hives
 - 1791 • swelling of your face, mouth, and tongue
 - 1792 • breathing problems
- 1793 • **effects on heart**
- 1794 • increased blood pressure

- 1795 • a fast or irregular heartbeat
- 1796 • chest pain
- 1797 • **effects on nervous system**
- 1798 • tremor
- 1799 • nervousness
- 1800 • **bone thinning or weakness (osteoporosis)**
- 1801 • **slowed growth in children.** A child's growth should be checked often.
- 1802 • **eye problems including glaucoma and cataracts.** You should have regular
- 1803 eye exams while using ADVAIR DISKUS.
- 1804 • **changes in laboratory blood values (sugar, potassium, certain types of**
- 1805 **white blood cells)**
- 1806 **Common side effects of ADVAIR DISKUS include:**
- 1807 **Asthma:**
- 1808 • upper respiratory tract infection
- 1809 • throat irritation
- 1810 • hoarseness and voice changes
- 1811 • thrush in your mouth or throat. Rinse your mouth with water without swallowing
- 1812 after use to help prevent this.
- 1813 • bronchitis
- 1814 • cough
- 1815 • headache
- 1816 • nausea and vomiting
- 1817 In children with asthma, infections in the ear, nose, and throat are common.
- 1818 **COPD:**
- 1819 • thrush in your mouth or throat. Rinse your mouth with water without swallowing
- 1820 after use to help prevent this.
- 1821 • throat irritation
- 1822 • hoarseness and voice changes
- 1823 • viral respiratory infections
- 1824 • headache
- 1825 • muscle and bone pain
- 1826 Tell your healthcare provider about any side effect that bothers you or that does
- 1827 not go away.
- 1828 These are not all the side effects with ADVAIR DISKUS. Ask your healthcare
- 1829 provider or pharmacist for more information.

1830 Call your doctor for medical advice about side effects. You may report side effects
1831 to FDA at 1-800-FDA-1088.

1832

1833 **How should I store ADVAIR DISKUS?**

- 1834 • Store ADVAIR DISKUS at room temperature between 68°F and 77°F (20°C and
1835 25°C). Keep in a dry place away from heat and sunlight.
- 1836 • Store ADVAIR DISKUS in the unopened foil pouch and only open when ready for
1837 use.
- 1838 • Safely throw away ADVAIR DISKUS in the trash 1 month after you open the foil
1839 pouch or when the counter reads **0**, whichever comes first.
- 1840 • **Keep ADVAIR DISKUS and all medicines out of the reach of children.**

1841

1842 **General information about ADVAIR DISKUS**

1843 Medicines are sometimes prescribed for purposes not mentioned in a Medication
1844 Guide. Do not use ADVAIR DISKUS for a condition for which it was not prescribed.
1845 Do not give your ADVAIR DISKUS to other people, even if they have the same
1846 condition that you have. It may harm them.

1847 This Medication Guide summarizes the most important information about ADVAIR
1848 DISKUS. If you would like more information, talk with your healthcare provider or
1849 pharmacist. You can ask your healthcare provider or pharmacist for information
1850 about ADVAIR DISKUS that was written for healthcare professionals.

1851 For more information about ADVAIR DISKUS, call 1-888-825-5249 or visit our
1852 website at www.advair.com.

1853

1854 **What are the ingredients in ADVAIR DISKUS?**

1855 Active ingredients: fluticasone propionate, salmeterol xinafoate

1856 Inactive ingredient: lactose monohydrate (contains milk proteins)

1857

1858

Instructions for Use

1859 **For Oral Inhalation Only**

1860

1861 **Your ADVAIR DISKUS inhaler**

1862



Figure A

1863
1864
1865
1866
1867

Read this information before you start using your ADVAIR DISKUS inhaler:

- 1868 • Take ADVAIR DISKUS out of the foil pouch just before you use it for the first
1869 time. Safely throw away the pouch. The DISKUS will be in the closed position.
- 1870 • Write the date you opened the foil pouch in the first blank line on the label. **See**
1871 **Figure A.**
- 1872 • Write the “use by” date in the second blank line on the label. **See Figure A.**
1873 That date is 1 month after the date you wrote in the first line.
- 1874 • The counter should read **60**. If you have a sample (with “Sample” on the back
1875 label) or institutional (with “INSTITUTIONAL PACK” on the foil pouch) pack, the
1876 counter should read **14**.

1877
1878

How to use your ADVAIR DISKUS inhaler

1879 **Follow these steps every time you use ADVAIR DISKUS.**

1880 **Step 1. Open your ADVAIR DISKUS.**

- 1881 • Hold the DISKUS in your left hand and place the thumb of your right hand in the
1882 thumb grip. Push the thumb grip away from you as far as it will go until the
1883 mouthpiece shows and snaps into place. **See Figure B.**

1884 **Step 2. Slide the lever until you hear it click.**

- 1885 • **Hold the DISKUS in a level, flat position** with the mouthpiece towards you.
1886 Slide the lever away from the mouthpiece as far as it will go until it **clicks**. **See**
1887 **Figure C.**
- 1888 • The number on the counter will count down by 1. The DISKUS is now ready to
1889 use.



1890
1891 **Figure B**



Figure C

1892 Follow the instructions below so you will not accidentally waste a dose:

- 1893 • **Do not** close the DISKUS.
- 1894 • **Do not** tilt the DISKUS.
- 1895 • **Do not** move the lever on the DISKUS.

1896 **Step 3. Inhale your medicine.**

- 1897 • Before you breathe in your dose from the DISKUS, breathe out (exhale) as long
1898 as you can while you hold the DISKUS level and away from your mouth. **See**
1899 **Figure D**. Do not breathe into the mouthpiece.
- 1900 • Put the mouthpiece to your lips. **See Figure E**. Breathe in quickly and deeply
1901 through the DISKUS. Do not breathe in through your nose.



1902
1903 **Figure D**



Figure E

- 1904 • Remove the DISKUS from your mouth **and hold your breath for about**
1905 **10 seconds**, or for as long as is comfortable for you.
- 1906 • **Breathe out slowly as long as you can. See Figure D.**
- 1907 • The DISKUS delivers your dose of medicine as a very fine powder that you may
1908 or may not taste or feel. **Do not** take an extra dose from the DISKUS even if
1909 you do not taste or feel the medicine.

1910 **Step 4. Close the DISKUS.**

- 1911 • Place your thumb in the thumb grip and slide it back towards you as far as it will
1912 go. **See Figure F**. Make sure the DISKUS clicks shut and you cannot see the
1913 mouthpiece.

- 1914 • The DISKUS is now ready for you to take your next scheduled dose in about
1915 12 hours. **When you are ready to take your next dose, repeat Steps 1**
1916 **through 4.**



1917
1918 **Figure F**

1919
1920 **Step 5. Rinse your mouth.**

- 1921 • **Rinse your mouth with water after breathing in the medicine.** Spit out the
1922 water. Do not swallow it. **See Figure G.**



1924
1925 **Figure G**

1926
1927 **When should you get a refill?**

- 1928 The counter on top of the DISKUS shows you how many doses are left. After you
1929 have taken **55** doses (**9** doses from the sample or institutional pack), the numbers
1930 **5** to **0** will show in red. **See Figure H.** These numbers warn you there are only a
1931 few doses left and are a reminder to get a refill.



1933
1934 **Figure H**

1935
1936 **For correct use of the DISKUS, remember:**

- 1937 • Always use the DISKUS in a level, flat position.

- 1938 • Make sure the lever firmly clicks into place.
- 1939 • Hold your breath for about 10 seconds after inhaling. Then breathe out fully.
- 1940 • After each dose, rinse your mouth with water and spit it out. Do not swallow the
- 1941 water.
- 1942 • **Do not** take an extra dose, even if you did not taste or feel the powder.
- 1943 • **Do not** take the DISKUS apart.
- 1944 • **Do not** wash the DISKUS.
- 1945 • Always keep the DISKUS in a dry place.
- 1946 • **Do not** use the DISKUS with a spacer device.

1947

1948 If you have questions about ADVAIR DISKUS or how to use your inhaler, call
1949 GlaxoSmithKline (GSK) at 1-888-825-5249 or visit www.advair.com.

1950

1951 **This Medication Guide and Instructions for Use have been approved by the**
1952 **U.S. Food and Drug Administration.**

1953

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1968 ADD: xMG