

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ADVAIR HFA 45/21 (fluticasone propionate 45 mcg and salmeterol 21 mcg) Inhalation Aerosol  
ADVAIR HFA 115/21 (fluticasone propionate 115 mcg and salmeterol 21 mcg) Inhalation Aerosol  
ADVAIR HFA 230/21 (fluticasone propionate 230 mcg and salmeterol 21 mcg) Inhalation Aerosol  
FOR ORAL INHALATION

Initial U.S. Approval: 2000

### WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- Long-acting beta<sub>2</sub>-adrenergic agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR HFA, increase the risk of asthma-related death. A US study showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 out of 13,179 patients 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 LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients. (5.1)
- When treating patients with asthma, only prescribe ADVAIR HFA 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 HFA) 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 HFA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. (1, 5.1)

### INDICATIONS AND USAGE

ADVAIR HFA is a combination product containing a corticosteroid and a LABA indicated for treatment of asthma in patients aged 12 years and older. Important limitation:

- Not indicated for the relief of acute bronchospasm. (1)

### DOSAGE AND ADMINISTRATION

For oral inhalation only.

Treatment of asthma in patients ≥12 years: 2 inhalations of ADVAIR HFA 45/21, 115/21, or 230/21 twice daily. Starting dosage is based on asthma severity. (2)

### DOSAGE FORMS AND STRENGTHS

Inhalation aerosol: delivers a combination of fluticasone propionate (45, 115, or 230 mcg) and salmeterol (21 mcg) from mouthpiece per actuation. (3)

### CONTRAINDICATIONS

- Primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures. (4)
- Hypersensitivity to any ingredient. (4)

### WARNINGS AND PRECAUTIONS

- Asthma-related death: LABAs increase the risk. Prescribe only for recommended patient populations. (5.1)
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms. (5.2)
- Use with additional LABA: Do not use in combination because of risk of overdose. (5.3)

- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth following inhalation. (5.4)
- Pneumonia: Increased risk in patients with COPD. Monitor patients for signs and symptoms of pneumonia. (5.5)
- Immunosuppression: 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)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to ADVAIR HFA. (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 HFA slowly. (5.8)
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid and cardiovascular effects. Use not recommended with ADVAIR HFA. (5.9)
- Paradoxical bronchospasm: Discontinue ADVAIR HFA and institute alternative therapy if paradoxical bronchospasm occurs. (5.10)
- Patients with cardiovascular or central nervous system disorders: Use with caution because of beta-adrenergic stimulation. (5.12)
- Decreases in bone mineral density: Assess bone mineral density initially and periodically thereafter. (5.13)
- Effects on growth: Monitor growth of pediatric patients. (5.14)
- Glaucoma and cataracts: Close monitoring is warranted. (5.15)
- Metabolic effects: Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.16, 5.18)
- Coexisting conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.17)

### ADVERSE REACTIONS

Most common adverse reactions (incidence ≥3%) are: upper respiratory tract infection or inflammation, throat irritation, dysphonia, headache, dizziness, nausea and vomiting. (6.1)

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

### DRUG INTERACTIONS

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Use not recommended. May cause 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 nonpotassium-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: December 2012

---

**FULL PRESCRIBING INFORMATION: CONTENTS\*****WARNING: ASTHMA-RELATED DEATH****1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION****3 DOSAGE FORMS AND STRENGTHS****4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 Asthma-Related Death
- 5.2 Deterioration of Disease and Acute Episodes
- 5.3 Excessive Use of ADVAIR HFA and Use With Other Long-Acting Beta<sub>2</sub>-Agonists
- 5.4 Local Effects
- 5.5 Pneumonia
- 5.6 Immunosuppression
- 5.7 Transferring Patients From Systemic Corticosteroid Therapy
- 5.8 Hypercorticism and Adrenal Suppression
- 5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
- 5.10 Paradoxical Bronchospasm and Upper Airway Symptoms
- 5.11 Immediate Hypersensitivity Reactions
- 5.12 Cardiovascular and Central Nervous System Effects
- 5.13 Reduction in Bone Mineral Density
- 5.14 Effect on Growth
- 5.15 Glaucoma and Cataracts
- 5.16 Eosinophilic Conditions and Churg-Strauss Syndrome
- 5.17 Coexisting Conditions
- 5.18 Hypokalemia and Hyperglycemia

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

**7 DRUG INTERACTIONS**

- 7.1 Inhibitors of Cytochrome P450 3A4

- 7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

- 7.3 Beta-Adrenergic Receptor Blocking Agents

- 7.4 Diuretics

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment

**10 OVERDOSAGE**

- 10.1 Fluticasone Propionate
- 10.2 Salmeterol

**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

**14 CLINICAL STUDIES**

- 14.1 Studies Comparing ADVAIR HFA With Fluticasone Propionate Alone or Salmeterol Alone
- 14.2 One-Year Safety Study
- 14.3 Onset of Action and Progression of Improvement in Control

**16 HOW SUPPLIED/STORAGE AND HANDLING****17 PATIENT COUNSELING INFORMATION**

- 17.1 Asthma-Related Death
- 17.2 Not for Acute Symptoms
- 17.3 Do Not Use Additional Long-Acting Beta<sub>2</sub>-Agonists
- 17.4 Risks Associated With Corticosteroid Therapy
- 17.5 Risks Associated With Beta-Agonist Therapy

\*Sections or subsections omitted from the full prescribing information are not listed.

---

1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: ASTHMA-RELATED DEATH**

3 **Long-acting beta<sub>2</sub>-adrenergic agonists (LABAs), such as salmeterol, one of the active**  
4 **ingredients in ADVAIR<sup>®</sup> HFA, increase the risk of asthma-related death. Data from a large**  
5 **placebo-controlled US study that compared the safety of salmeterol (SEREVENT<sup>®</sup>**  
6 **Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in**  
7 **asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients**  
8 **treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo).**  
9 **Currently available data are inadequate to determine whether concurrent use of inhaled**  
10 **corticosteroids or other long-term asthma control drugs mitigates the increased risk of**  
11 **asthma-related death from LABAs. Available data from controlled clinical trials suggest**  
12 **that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent**  
13 **patients.**

14 **Therefore, when treating patients with asthma, physicians should only prescribe**  
15 **ADVAIR HFA for patients not adequately controlled on a long-term asthma control**  
16 **medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants**  
17 **initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma**  
18 **control is achieved and maintained, assess the patient at regular intervals and step down**  
19 **therapy (e.g., discontinue ADVAIR HFA) if possible without loss of asthma control and**  
20 **maintain the patient on a long-term asthma control medication, such as an inhaled**  
21 **corticosteroid. Do not use ADVAIR HFA for patients whose asthma is adequately**  
22 **controlled on low- or medium-dose inhaled corticosteroids [see Warnings and Precautions**  
23 **(5.1)].**

24 **1 INDICATIONS AND USAGE**

25 ADVAIR HFA is indicated for the treatment of asthma in patients aged 12 years and  
26 older.

27 Long-acting beta<sub>2</sub>-adrenergic agonists (LABAs), such as salmeterol, one of the active  
28 ingredients in ADVAIR HFA, increase the risk of asthma-related death. Available data from  
29 controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization  
30 in pediatric and adolescent patients [see Warnings and Precautions (5.1)]. Therefore, when  
31 treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not  
32 adequately controlled on a long-term asthma control medication, such as an inhaled  
33 corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an  
34 inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the  
35 patient at regular intervals and step down therapy (e.g., discontinue ADVAIR HFA) if possible  
36 without loss of asthma control and maintain the patient on a long-term asthma control

37 medication, such as an inhaled corticosteroid. Do not use ADVAIR HFA for patients whose  
38 asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.  
39 Important Limitation of Use: ADVAIR HFA is NOT indicated for the relief of acute  
40 bronchospasm.

## 41 **2 DOSAGE AND ADMINISTRATION**

42 ADVAIR HFA should be administered twice daily every day by the orally inhaled route  
43 only. After inhalation, the patient should rinse the mouth with water without swallowing [*see*  
44 *Patient Counseling Information (17.4)*].

45 More frequent administration or a higher number of inhalations (more than 2 inhalations  
46 twice daily) of the prescribed strength of ADVAIR HFA is not recommended as some patients  
47 are more likely to experience adverse effects with higher doses of salmeterol. Patients using  
48 ADVAIR HFA should not use additional LABAs for any reason. [*See Warnings and Precautions*  
49 *(5.3, 5.12)*].

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

52 For patients aged 12 years and older, the dosage is 2 inhalations twice daily (morning and  
53 evening, approximately 12 hours apart).

54 The recommended starting dosages for ADVAIR HFA for patients aged 12 years and  
55 older are based upon patients' asthma severity.

56 The maximum recommended dosage is 2 inhalations of ADVAIR HFA 230/21 twice  
57 daily.

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

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

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

69 ADVAIR HFA should be primed before using for the first time by releasing 4 test sprays  
70 into the air away from the face, shaking well for 5 seconds before each spray. In cases where the  
71 inhaler has not been used for more than 4 weeks or when it has been dropped, prime the inhaler  
72 again by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before  
73 each spray.

74 **3 DOSAGE FORMS AND STRENGTHS**

75 ADVAIR HFA is an inhalation aerosol. Each actuation delivers a combination of  
76 fluticasone propionate (45, 115, or 230 mcg) and salmeterol (21 mcg) from the actuator.  
77 ADVAIR HFA is supplied in 8- and 12-g pressurized aluminum canisters containing 60 and 120  
78 metered inhalations, respectively. Each canister is fitted with a counter and a purple actuator with  
79 a light purple strapcap.

80 **4 CONTRAINDICATIONS**

81 The use of ADVAIR HFA is contraindicated in the following conditions:

- 82 • Primary treatment of status asthmaticus or other acute episodes of asthma where intensive  
83 measures are required.
- 84 • Hypersensitivity to any of the ingredients of these preparations contraindicates their use  
85 [*see Description (11)*].

86 **5 WARNINGS AND PRECAUTIONS**

87 **5.1 Asthma-Related Death**

88 **LABAs, such as salmeterol, one of the active ingredients in ADVAIR HFA, increase**  
89 **the risk of asthma-related death. Currently available data are inadequate to determine**  
90 **whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs**  
91 **mitigates the increased risk of asthma-related death from LABAs. Available data from**  
92 **controlled clinical trials suggest that LABAs increase the risk of asthma-related**  
93 **hospitalization in pediatric and adolescent patients. Therefore, when treating patients with**  
94 **asthma, physicians should only prescribe ADVAIR HFA for patients not adequately**  
95 **controlled on a long-term asthma control medication such as an inhaled corticosteroid, or**  
96 **whose disease severity clearly warrants initiation of treatment with both an inhaled**  
97 **corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the**  
98 **patient at regular intervals and step down therapy (e.g., discontinue ADVAIR HFA) if**  
99 **possible without loss of asthma control and maintain the patient on a long-term asthma**  
100 **control medication, such as an inhaled corticosteroid. Do not use ADVAIR HFA for**  
101 **patients whose asthma is adequately controlled on low- or medium-dose inhaled**  
102 **corticosteroids.**

103 A large placebo-controlled US study that compared the safety of salmeterol with placebo,  
104 each added to usual asthma therapy, showed an increase in asthma-related deaths in patients  
105 receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a  
106 randomized double-blind study that enrolled LABA-naïve patients with asthma to assess the  
107 safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks  
108 compared with placebo when added to usual asthma therapy. A planned interim analysis was  
109 conducted when approximately half of the intended number of patients had been enrolled  
110 (N = 26,355), which led to premature termination of the study. The results of the interim analysis  
111 showed that patients receiving salmeterol were at increased risk for fatal asthma events (see  
112 Table 3 and Figure 5). In the total population, a higher rate of asthma-related death occurred in

113 patients treated with salmeterol than those treated with placebo (0.10% versus 0.02%; relative  
114 risk: 4.37 [95% CI: 1.25, 15.34]).

115 Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death  
116 occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo  
117 (0.07% versus 0.01%; relative risk: 5.82 [95% CI: 0.70, 48.37]). In African Americans also,  
118 asthma-related death occurred at a higher rate in patients treated with salmeterol than those  
119 treated with placebo (0.31% versus 0.04%; relative risk: 7.26 [95% CI: 0.89, 58.94]). Although  
120 the relative risks of asthma-related death were similar in Caucasians and African Americans, the  
121 estimate of excess deaths in patients treated with salmeterol was greater in African Americans  
122 because there was a higher overall rate of asthma-related death in African American patients (see  
123 Table 3). Given the similar basic mechanisms of action of beta<sub>2</sub>-agonists, the findings seen in the  
124 SMART study are considered a class effect.

125 Post-hoc analyses in pediatric patients aged 12 to 18 years were also performed. Pediatric  
126 patients accounted for approximately 12% of patients in each treatment arm. Respiratory-related  
127 death or life-threatening experience occurred at a similar rate in the salmeterol group (0.12%  
128 [2/1,653]) and the placebo group (0.12% [2/1,622]; relative risk: 1.0 [95% CI: 0.1, 7.2]).  
129 All-cause hospitalization, however, was increased in the salmeterol group (2% [35/1,653]) versus  
130 the placebo group (<1% [16/1,622]; relative risk: 2.1 [95% CI: 1.1, 3.7]).

131 The data from the SMART study are not adequate to determine whether concurrent use of  
132 inhaled corticosteroids, such as fluticasone propionate, the other active ingredient in ADVAIR  
133 HFA, or other long-term asthma control therapy mitigates the risk of asthma-related death.

134

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

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

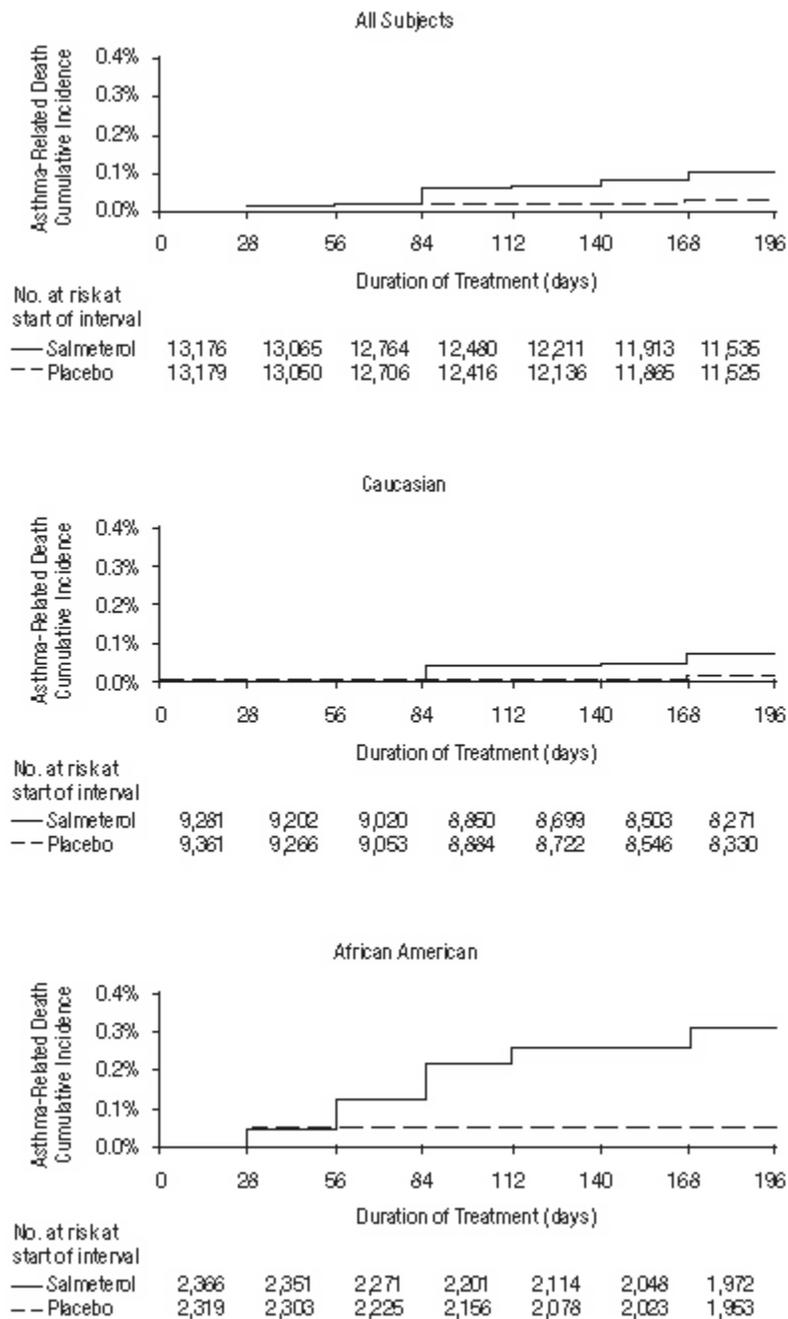
137 <sup>a</sup> Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to  
 138 study treatment to account for early withdrawal of patients from the study.

139 <sup>b</sup> Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the  
 140 rate in the placebo group. The relative risk indicates how many more times likely an asthma-  
 141 related death occurred in the salmeterol group than in the placebo group in a 28-week  
 142 treatment period.

143 <sup>c</sup> Estimate of the number of additional asthma-related deaths in patients treated with salmeterol  
 144 in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period.  
 145 Estimate calculated as the difference between the salmeterol and placebo groups in the rates  
 146 of asthma-related death multiplied by 10,000.

147 <sup>d</sup> The Total Population includes the following ethnic origins listed on the case report form:  
 148 Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population  
 149 includes those patients whose ethnic origin was not reported. The results for Caucasian and  
 150 African American subpopulations are shown above. No asthma-related deaths occurred in the  
 151 Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149),  
 152 or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death  
 153 occurred in the placebo group in the subpopulation whose ethnic origin was not reported  
 154 (salmeterol n = 130, placebo n = 127).  
 155

156 **Figure 1. Cumulative Incidence of Asthma-Related**  
 157 **Deaths in the 28-Week Salmeterol Multi-center Asthma**  
 158 **Research Trial (SMART), by Duration of Treatment**  
 159



160  
 161  
 162 A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide  
 163 Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate  
 164 of asthma-related death was numerically, though not statistically significantly, greater in patients

165 with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol (180  
166 mcg 4 times daily) added to usual asthma therapy.

## 167 **5.2 Deterioration of Disease and Acute Episodes**

168 ADVAIR HFA should not be initiated in patients during rapidly deteriorating or  
169 potentially life-threatening episodes of asthma. ADVAIR HFA has not been studied in patients  
170 with acutely deteriorating asthma. The initiation of ADVAIR HFA in this setting is not  
171 appropriate.

172 Serious acute respiratory events, including fatalities, have been reported when salmeterol,  
173 a component of ADVAIR HFA, has been initiated in patients with significantly worsening or  
174 acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma  
175 (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation,  
176 mechanical ventilation, frequent hospitalizations, previous life-threatening acute asthma  
177 exacerbations) and in some patients with acutely deteriorating asthma (e.g., patients with  
178 significantly increasing symptoms; increasing need for inhaled, short-acting beta<sub>2</sub>-agonists;  
179 decreasing response to usual medications; increasing need for systemic corticosteroids; recent  
180 emergency room visits; deteriorating lung function). However, these events have occurred in a  
181 few patients with less severe asthma as well. It was not possible from these reports to determine  
182 whether salmeterol contributed to these events.

183 Increasing use of inhaled, short-acting beta<sub>2</sub>-agonists is a marker of deteriorating asthma.  
184 In this situation, the patient requires immediate reevaluation with reassessment of the treatment  
185 regimen, giving special consideration to the possible need for replacing the current strength of  
186 ADVAIR HFA with a higher strength, adding additional inhaled corticosteroid, or initiating  
187 systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning  
188 and evening) of ADVAIR HFA.

189 ADVAIR HFA should not be used for the relief of acute symptoms, i.e., as rescue  
190 therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting  
191 beta<sub>2</sub>-agonist, not ADVAIR HFA, should be used to relieve acute symptoms such as shortness of  
192 breath. When prescribing ADVAIR HFA, the physician must also provide the patient with an  
193 inhaled, short-acting beta<sub>2</sub>-agonist (e.g., albuterol) for treatment of acute symptoms, despite  
194 regular twice-daily (morning and evening) use of ADVAIR HFA.

195 When beginning treatment with ADVAIR HFA, patients who have been taking oral or  
196 inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., 4 times a day) should be instructed to  
197 discontinue the regular use of these drugs.

## 198 **5.3 Excessive Use of ADVAIR HFA and Use With Other Long-Acting Beta<sub>2</sub>-** 199 **Agonists**

200 As with other inhaled drugs containing beta<sub>2</sub>-adrenergic agents, ADVAIR HFA should  
201 not be used more often than recommended, at higher doses than recommended, or in conjunction  
202 with other medications containing LABAs, as an overdose may result. Clinically significant  
203 cardiovascular effects and fatalities have been reported in association with excessive use of  
204 inhaled sympathomimetic drugs. Patients using ADVAIR HFA should not use an additional

205 LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including  
206 prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma.

#### 207 **5.4 Local Effects**

208 In clinical studies, the development of localized infections of the mouth and pharynx with  
209 *Candida albicans* has occurred in patients treated with ADVAIR HFA. When such an infection  
210 develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy  
211 while treatment with ADVAIR HFA continues, but at times therapy with ADVAIR HFA may  
212 need to be interrupted. Patients should rinse the mouth after inhalation of ADVAIR HFA.

#### 213 **5.5 Pneumonia**

214 Lower respiratory tract infections, including pneumonia, have been reported in patients  
215 with chronic obstructive pulmonary disease (COPD) following the inhaled administration of  
216 corticosteroids, including fluticasone propionate and ADVAIR DISKUS<sup>®</sup> (fluticasone  
217 propionate and salmeterol inhalation powder). In 2 replicate 1-year studies of 1,579 patients with  
218 COPD, there was a higher incidence of pneumonia reported in patients receiving ADVAIR  
219 DISKUS 250/50 (7%) than in those receiving salmeterol 50 mcg (3%). The incidence of  
220 pneumonia in the patients treated with ADVAIR DISKUS was higher in patients over 65 years  
221 of age (9%) compared with the incidence in patients less than 65 years of age (4%).

222 In a 3-year study of 6,184 patients with COPD, there was a higher incidence of  
223 pneumonia reported in patients receiving ADVAIR DISKUS 500/50 compared with placebo  
224 (16% with ADVAIR DISKUS 500/50, 14% with fluticasone propionate 500 mcg, 11% with  
225 salmeterol 50 mcg, and 9% with placebo). Similar to what was seen in the 1-year studies with  
226 ADVAIR DISKUS 250/50, the incidence of pneumonia was higher in patients over 65 years of  
227 age (18% with ADVAIR DISKUS 500/50 versus 10% with placebo) compared with patients less  
228 than 65 years of age (14% with ADVAIR DISKUS 500/50 versus 8% with placebo).

#### 229 **5.6 Immunosuppression**

230 Persons who are using drugs that suppress the immune system are more susceptible to  
231 infections than healthy individuals. Chickenpox and measles, for example, can have a more  
232 serious or even fatal course in susceptible children or adults using corticosteroids. In such  
233 children or adults who have not had these diseases or been properly immunized, particular care  
234 should be taken to avoid exposure. How the dose, route, and duration of corticosteroid  
235 administration affect the risk of developing a disseminated infection is not known. The  
236 contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not  
237 known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin  
238 (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled  
239 intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for  
240 complete VZIG and IG prescribing information.) If chickenpox develops, treatment with  
241 antiviral agents may be considered.

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

245 **5.7 Transferring Patients From Systemic Corticosteroid Therapy**

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

251 Patients who have been previously maintained on 20 mg or more per day of prednisone  
252 (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have  
253 been almost completely withdrawn. During this period of HPA suppression, patients may exhibit  
254 signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection  
255 (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although  
256 ADVAIR HFA may provide control of asthma symptoms during these episodes, in  
257 recommended doses it supplies less than normal physiologic amounts of glucocorticoid  
258 systemically and does NOT provide the mineralocorticoid activity that is necessary for coping  
259 with these emergencies.

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

265 Patients requiring oral corticosteroids should be weaned slowly from systemic  
266 corticosteroid use after transferring to ADVAIR HFA. Prednisone reduction can be  
267 accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy  
268 with ADVAIR HFA. Lung function (mean forced expiratory volume in 1 second [FEV<sub>1</sub>] or  
269 morning peak expiratory flow [PEF]), beta-agonist use, and asthma symptoms should be  
270 carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma  
271 signs and symptoms, patients should be observed for signs and symptoms of adrenal  
272 insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

273 Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or  
274 ADVAIR HFA may unmask conditions previously suppressed by the systemic corticosteroid  
275 therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients  
276 may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or  
277 muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory  
278 function.

279 **5.8 Hypercorticism and Adrenal Suppression**

280 Fluticasone propionate, a component of ADVAIR HFA, will often help control asthma  
281 symptoms with less suppression of HPA function than therapeutically equivalent oral doses of  
282 prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically  
283 active at higher doses, the beneficial effects of ADVAIR HFA in minimizing HPA dysfunction  
284 may be expected only when recommended dosages are not exceeded and individual patients are

285 titrated to the lowest effective dose. A relationship between plasma levels of fluticasone  
286 propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks  
287 of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects  
288 on cortisol production exists, physicians should consider this information when prescribing  
289 ADVAIR HFA.

290 Because of the possibility of systemic absorption of inhaled corticosteroids, patients  
291 treated with ADVAIR HFA should be observed carefully for any evidence of systemic  
292 corticosteroid effects. Particular care should be taken in observing patients postoperatively or  
293 during periods of stress for evidence of inadequate adrenal response.

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

### 300 **5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors**

301 The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir,  
302 clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole,  
303 telithromycin) with ADVAIR HFA is not recommended because increased systemic  
304 corticosteroid and increased cardiovascular adverse effects may occur [*see Drug Interactions*  
305 (7.1), *Clinical Pharmacology* (12.3)].

### 306 **5.10 Paradoxical Bronchospasm and Upper Airway Symptoms**

307 As with other inhaled medications, ADVAIR HFA can produce paradoxical  
308 bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following  
309 dosing with ADVAIR HFA, it should be treated immediately with an inhaled, short-acting  
310 bronchodilator; ADVAIR HFA should be discontinued immediately; and alternative therapy  
311 should be instituted. Upper airway symptoms of laryngeal spasm, irritation, or swelling, such as  
312 stridor and choking, have been reported in patients receiving fluticasone propionate and  
313 salmeterol.

### 314 **5.11 Immediate Hypersensitivity Reactions**

315 Immediate hypersensitivity reactions may occur after administration of ADVAIR HFA,  
316 as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm [*see Adverse*  
317 *Reactions* (6.2)].

### 318 **5.12 Cardiovascular and Central Nervous System Effects**

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

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

### 335 **5.13 Reduction in Bone Mineral Density**

336 Decreases in bone mineral density (BMD) have been observed with long-term  
337 administration of products containing inhaled corticosteroids. The clinical significance of small  
338 changes in BMD with regard to long-term consequences such as fracture is unknown. Patients  
339 with major risk factors for decreased bone mineral content, such as prolonged immobilization,  
340 family history of osteoporosis, post-menopausal status, tobacco use, advanced age, poor  
341 nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral  
342 corticosteroids) should be monitored and treated with established standards of care.

343 2-Year Fluticasone Propionate Study: A 2-year study of 160 patients (females aged  
344 18 to 40 years, males 18 to 50) with asthma receiving CFC-propelled fluticasone propionate  
345 inhalation aerosol 88 or 440 mcg twice daily demonstrated no statistically significant changes in  
346 BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by  
347 dual-energy x-ray absorptiometry at lumbar regions L1 through L4.

### 348 **5.14 Effect on Growth**

349 Orally inhaled corticosteroids may cause a reduction in growth velocity when  
350 administered to pediatric patients. Monitor the growth of pediatric patients receiving ADVAIR  
351 HFA routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled  
352 corticosteroids, including ADVAIR HFA, titrate each patient's dose to the lowest dosage that  
353 effectively controls his/her symptoms [*see Use in Specific Populations (8.4)*].

### 354 **5.15 Glaucoma and Cataracts**

355 Glaucoma, increased intraocular pressure, and cataracts have been reported in patients  
356 with asthma following the long-term administration of inhaled corticosteroids, including  
357 fluticasone propionate, a component of ADVAIR HFA. Therefore, close monitoring is warranted  
358 in patients with a change in vision or with a history of increased intraocular pressure, glaucoma,  
359 and/or cataracts.

### 360 **5.16 Eosinophilic Conditions and Churg-Strauss Syndrome**

361 In rare cases, patients on inhaled fluticasone propionate, a component of ADVAIR HFA,  
362 may present with systemic eosinophilic conditions. Some of these patients have clinical features  
363 of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with  
364 systemic corticosteroid therapy. These events usually, but not always, have been associated with

365 the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of  
366 fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with  
367 other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia,  
368 vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy  
369 presenting in their patients. A causal relationship between fluticasone propionate and these  
370 underlying conditions has not been established.

### 371 **5.17 Coexisting Conditions**

372 ADVAIR HFA, like all medications containing sympathomimetic amines, should be used  
373 with caution in patients with convulsive disorders or thyrotoxicosis and in those who are  
374 unusually responsive to sympathomimetic amines. Doses of the related beta<sub>2</sub>-adrenoceptor  
375 agonist albuterol, when administered intravenously, have been reported to aggravate preexisting  
376 diabetes mellitus and ketoacidosis.

### 377 **5.18 Hypokalemia and Hyperglycemia**

378 Beta-adrenergic agonist medications may produce significant hypokalemia in some  
379 patients, possibly through intracellular shunting, which has the potential to produce adverse  
380 cardiovascular effects [*see Clinical Pharmacology (12.2)*]. The decrease in serum potassium is  
381 usually transient, not requiring supplementation. Clinically significant changes in blood glucose  
382 and/or serum potassium were seen infrequently during clinical studies with ADVAIR HFA at  
383 recommended doses.

## 384 **6 ADVERSE REACTIONS**

385 **LABAs, such as salmeterol, one of the active ingredients in ADVAIR HFA, increase**  
386 **the risk of asthma-related death. Data from a large placebo-controlled US study that**  
387 **compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to**  
388 **usual asthma therapy showed an increase in asthma-related deaths in patients receiving**  
389 **salmeterol [*see Warnings and Precautions (5.1)*]. Currently available data are inadequate to**  
390 **determine whether concurrent use of inhaled corticosteroids or other long-term asthma**  
391 **control drugs mitigates the increased risk of asthma-related death from LABAs. Available**  
392 **data from controlled clinical trials suggest that LABAs increase the risk of asthma-related**  
393 **hospitalization in pediatric and adolescent patients.**

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

- 395 • *Candida albicans* infection [*see Warnings and Precautions (5.4)*]
- 396 • Pneumonia in patients with COPD [*see Warnings and Precautions (5.5)*]
- 397 • Immunosuppression [*see Warnings and Precautions (5.6)*]
- 398 • Hypercorticism and adrenal suppression [*see Warnings and Precautions (5.8)*]
- 399 • Growth effects [*see Warnings and Precautions (5.14)*]
- 400 • Glaucoma and cataracts [*see Warnings and Precautions (5.15)*]

### 401 **6.1 Clinical Trials Experience**

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

405 **Adult and Adolescent Patients Aged 12 Years and Older:** The incidence of adverse  
 406 reactions associated with ADVAIR HFA in Table 2 is based upon 2 placebo-controlled 12-week  
 407 US clinical studies (Studies 1 and 3) and 1 active-controlled 12-week US clinical study (Study  
 408 2). A total of 1,008 adult and adolescent patients with asthma (556 females and 452 males)  
 409 previously treated with albuterol alone, salmeterol, or inhaled corticosteroids were treated twice  
 410 daily with 2 inhalations of ADVAIR HFA 45/21 or ADVAIR HFA 115/21, fluticasone  
 411 propionate chlorofluorocarbon (CFC) inhalation aerosol (44- or 110-mcg doses), salmeterol CFC  
 412 inhalation aerosol 21 mcg, or placebo HFA inhalation aerosol. The average duration of exposure  
 413 was 71 to 81 days in the active treatment groups compared with 51 days in the placebo group.  
 414

415 **Table 2. Adverse Reactions With  $\geq 3\%$  Incidence With ADVAIR HFA Inhalation Aerosol**  
 416 **in Adult and Adolescent Patients With Asthma**

Adverse Event	ADVAIR HFA Inhalation Aerosol		Fluticasone Propionate CFC Inhalation Aerosol		Salmeterol CFC Inhalation Aerosol	Placebo HFA Inhalation Aerosol
	45/21 (n = 187) %	115/21 (n = 94) %	44 mcg (n = 186) %	110 mcg (n = 91) %	21 mcg (n = 274) %	(n = 176) %
Ear, nose, & throat						
Upper respiratory tract infection	16	24	13	15	17	13
Throat irritation	9	7	12	13	9	7
Upper respiratory inflammation	4	4	3	7	5	3
Hoarseness/dysphonia	3	1	2	0	1	0
Lower respiratory						
Viral respiratory infection	3	5	4	5	3	4
Neurology						
Headache	21	15	24	16	20	11
Dizziness	4	1	1	0	<1	0
Gastrointestinal						
Nausea & vomiting	5	3	4	2	2	3
Viral gastrointestinal infection	4	2	2	0	1	2

Gastrointestinal signs & symptoms	3	2	2	1	1	1
Musculoskeletal						
Musculoskeletal pain	5	7	8	2	4	4
Muscle pain	4	1	1	1	3	<1

417

418           The incidence of common adverse reactions reported in Study 4, a 12-week non-US  
419 clinical study of 509 patients previously treated with inhaled corticosteroids who were treated  
420 twice daily with 2 inhalations of ADVAIR HFA 230/21, fluticasone propionate CFC inhalation  
421 aerosol 220 mcg, or 1 inhalation of ADVAIR DISKUS 500/50 was similar to the incidences  
422 reported in Table 2.

423           Additional Adverse Reactions: Other adverse reactions not previously listed, whether  
424 considered drug-related or not by the investigators, that occurred in the groups receiving  
425 ADVAIR HFA with an incidence of 1% to 3% and that occurred at a greater incidence than with  
426 placebo include the following: tachycardia, arrhythmias, myocardial infarction, postoperative  
427 complications, wounds and lacerations, soft tissue injuries, ear signs and symptoms,  
428 rhinorrhea/postnasal drip, epistaxis, nasal congestion/blockage, laryngitis, unspecified  
429 oropharyngeal plaques, dryness of nose, weight gain, allergic eye disorders, eye edema and  
430 swelling, gastrointestinal discomfort and pain, dental discomfort and pain, candidiasis  
431 mouth/throat, hyposalivation, gastrointestinal infections, disorders of hard tissue of teeth,  
432 abdominal discomfort and pain, oral abnormalities, arthralgia and articular rheumatism, muscle  
433 cramps and spasms, musculoskeletal inflammation, bone and skeletal pain, muscle injuries, sleep  
434 disorders, migraines, allergies and allergic reactions, viral infections, bacterial infections,  
435 candidiasis unspecified site, congestion, inflammation, bacterial reproductive infections, lower  
436 respiratory signs and symptoms, lower respiratory infections, lower respiratory hemorrhage,  
437 eczema, dermatitis and dermatosis, urinary infections.

438           Laboratory Test Abnormalities: In Study 3, there were more reports of hyperglycemia  
439 among adults and adolescents receiving ADVAIR HFA, but this was not seen in Studies 1 and 2.

## 440 **6.2 Postmarketing Experience**

441           In addition to adverse reactions reported from clinical trials, the following adverse  
442 reactions have been identified during postmarketing use of any formulation of ADVAIR,  
443 fluticasone propionate, and/or salmeterol regardless of indication. Because these reactions are  
444 reported voluntarily from a population of uncertain size, it is not always possible to reliably  
445 estimate their frequency or establish a causal relationship to drug exposure. These events have  
446 been chosen for inclusion due to either their seriousness, frequency of reporting, or causal  
447 connection to ADVAIR, fluticasone propionate, and/or salmeterol or a combination of these  
448 factors.

449           Cardiovascular: Arrhythmias (including atrial fibrillation, extrasystoles,  
450 supraventricular tachycardia), hypertension, ventricular tachycardia.

451 Ear, Nose, and Throat: Aponia, earache, facial and oropharyngeal edema, paranasal  
452 sinus pain, rhinitis, throat soreness, tonsillitis.

453 Endocrine and Metabolic: Cushing's syndrome, Cushingoid features, growth velocity  
454 reduction in children/adolescents, hypercorticism, osteoporosis.

455 Eye: Cataracts, glaucoma.

456 Gastrointestinal: Dyspepsia, xerostomia.

457 Hepatobiliary Tract and Pancreas: Abnormal liver function tests.

458 Immune System: Immediate and delayed hypersensitivity reactions, including rash and  
459 rare events of angioedema, bronchospasm, and anaphylaxis.

460 Musculoskeletal: Back pain, myositis.

461 Neurology: Paresthesia, restlessness.

462 Non-Site Specific: Fever, pallor.

463 Psychiatry: Agitation, aggression, anxiety, depression. Behavioral changes, including  
464 hyperactivity and irritability, have been reported very rarely and primarily in children.

465 Respiratory: Asthma; asthma exacerbation; chest congestion; chest tightness; cough;  
466 dyspnea; immediate bronchospasm; influenza; paradoxical bronchospasm; tracheitis; wheezing;  
467 pneumonia; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling  
468 such as stridor or choking.

469 Skin: Contact dermatitis, contusions, ecchymoses, photodermatitis, pruritus.

470 Urogenital: Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease,  
471 vaginal candidiasis, vaginitis, vulvovaginitis.

## 472 **7 DRUG INTERACTIONS**

473 ADVAIR HFA has been used concomitantly with other drugs, including short-acting  
474 beta<sub>2</sub>-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with  
475 asthma, without adverse drug reactions [see *Clinical Pharmacology (12.2)*]. No formal drug  
476 interaction studies have been performed with ADVAIR HFA.

### 477 **7.1 Inhibitors of Cytochrome P450 3A4**

478 Fluticasone propionate and salmeterol, the individual components of ADVAIR HFA, are  
479 substrates of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir,  
480 clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole,  
481 telithromycin) with ADVAIR HFA is not recommended because increased systemic  
482 corticosteroid and increased cardiovascular adverse effects may occur.

483 Ritonavir: Fluticasone Propionate: A drug interaction study with fluticasone  
484 propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4  
485 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in  
486 significantly reduced serum cortisol concentrations [see *Clinical Pharmacology (12.3)*]. During  
487 postmarketing use, there have been reports of clinically significant drug interactions in patients  
488 receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects  
489 including Cushing's syndrome and adrenal suppression.

490 Ketoconazole: Fluticasone Propionate: Coadministration of orally inhaled fluticasone  
491 propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased plasma  
492 fluticasone propionate exposure and reduced plasma cortisol area under the curve (AUC), but  
493 had no effect on urinary excretion of cortisol.

494 Salmeterol: In a drug interaction study in 20 healthy subjects, coadministration of  
495 inhaled salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days  
496 resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C<sub>max</sub> increased  
497 1.4-fold). Three (3) subjects were withdrawn due to beta<sub>2</sub>-agonist side effects (2 with prolonged  
498 QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on  
499 the mean QTc, coadministration of salmeterol and ketoconazole was associated with more  
500 frequent increases in QTc duration compared with salmeterol and placebo administration.

## 501 **7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants**

502 ADVAIR HFA should be administered with extreme caution to patients being treated  
503 with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of  
504 discontinuation of such agents, because the action of salmeterol, a component of ADVAIR HFA,  
505 on the vascular system may be potentiated by these agents.

## 506 **7.3 Beta-Adrenergic Receptor Blocking Agents**

507 Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a  
508 component of ADVAIR HFA, but may produce severe bronchospasm in patients with reversible  
509 obstructive airways disease. Therefore, patients with asthma should not normally be treated with  
510 beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to  
511 the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could  
512 be considered, although they should be administered with caution.

## 513 **7.4 Diuretics**

514 The ECG changes and/or hypokalemia that may result from the administration of  
515 nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by  
516 beta-agonists such as salmeterol, a component of ADVAIR HFA, especially when the  
517 recommended dose of the beta-agonist is exceeded. Although the clinical relevance of these  
518 effects is not known, caution is advised in the coadministration of ADVAIR HFA with  
519 nonpotassium-sparing diuretics.

# 520 **8 USE IN SPECIFIC POPULATIONS**

## 521 **8.1 Pregnancy**

522 Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled  
523 studies with ADVAIR HFA in pregnant women. The combination of fluticasone propionate and  
524 salmeterol was teratogenic in mice and rats. Fluticasone propionate alone was teratogenic in  
525 mice, rats, and rabbits, and salmeterol alone was teratogenic in rabbits and not in rats. From the  
526 reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using  
527 combinations of fluticasone propionate and salmeterol when compared with toxicity data from  
528 the components administered separately.

529 ADVAIR HFA should be used during pregnancy only if the potential benefit justifies the  
530 potential risk to the fetus.

531 *Combination of Fluticasone Propionate and Salmeterol:* In the mouse  
532 reproduction assay, fluticasone propionate by the subcutaneous route at a dose approximately  
533 equivalent to the maximum recommended human daily inhalation dose (MRHD) (on a mcg/m<sup>2</sup>  
534 basis at a maternal dose of 150 mcg/kg) combined with oral salmeterol at a dose approximately  
535 580 times the MRHD (on a mg/m<sup>2</sup> basis at a maternal dose of 10 mg/kg) produced cleft palate,  
536 fetal death, increased implantation loss, and delayed ossification. These observations are  
537 characteristic of glucocorticoids. No developmental toxicity was observed at combination doses  
538 of fluticasone propionate subcutaneously up to approximately 1/5 the MRHD (on a mcg/m<sup>2</sup> basis  
539 at a maternal dose of 40 mcg/kg) and oral doses of salmeterol up to approximately 80 times the  
540 MRHD (on a mg/m<sup>2</sup> basis at a maternal dose of 1.4 mg/kg). In rats, combining fluticasone  
541 propionate subcutaneously at a dose equivalent to the MRHD (on a mcg/m<sup>2</sup> basis at a maternal  
542 dose of 100 mcg/kg) and an oral dose of salmeterol at approximately 1,200 times the MRHD (on  
543 a mg/m<sup>2</sup> basis at a maternal dose of 10 mg/kg) produced decreased fetal weight, umbilical  
544 hernia, delayed ossification, and changes in the occipital bone. No such effects were seen when  
545 combining fluticasone propionate subcutaneously at a dose less than the MRHD (on a mcg/m<sup>2</sup>  
546 basis at a maternal dose of 30 mcg/kg) and an oral dose of salmeterol at approximately 120 times  
547 the MRHD (on a mg/m<sup>2</sup> basis at a maternal dose of 1 mg/kg).

548 *Fluticasone Propionate:* Subcutaneous studies in mice at a dose less than the MRHD  
549 (on a mcg/m<sup>2</sup> basis at a maternal dose of 45 mcg/kg) and in rats at a dose equivalent to the  
550 MRHD (on a mcg/m<sup>2</sup> basis at a maternal dose of 100 mcg/kg) revealed fetal toxicity  
551 characteristic of potent corticosteroid compounds, including embryonic growth retardation,  
552 omphalocele, cleft palate, and retarded cranial ossification. No teratogenicity was seen in rats at  
553 inhalation doses approximately equivalent to the MRHD (on a mcg/m<sup>2</sup> basis at maternal doses up  
554 to 68.7 mg/kg).

555 In rabbits, fetal weight reduction and cleft palate were observed at a subcutaneous dose  
556 less than the MRHD (on a mcg/m<sup>2</sup> basis at a maternal dose of 4 mcg/kg). However, no  
557 teratogenic effects were reported at oral doses up to approximately 6 times the MRHD (on a  
558 mcg/m<sup>2</sup> basis at maternal doses up to 300 mcg/kg). No fluticasone propionate was detected in the  
559 plasma in this study, consistent with the established low bioavailability following oral  
560 administration [*see Clinical Pharmacology (12.3)*].

561 Fluticasone propionate crossed the placenta following subcutaneous administration to  
562 mice and rats and oral administration to rabbits.

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

568 *Salmeterol*: No teratogenic effects occurred in rats at oral doses approximately 230  
569 times the MRHD (on a mg/m<sup>2</sup> basis at maternal doses up to 2 mg/kg). In Dutch rabbits  
570 administered oral doses approximately 25 times the MRHD (on an AUC basis at maternal doses  
571 of 1 mg/kg and higher), salmeterol exhibited fetal toxic effects characteristically resulting from  
572 beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate,  
573 sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones.  
574 No such effects occurred at an oral dose approximately 10 times the MRHD (on an AUC basis at  
575 a maternal dose of 0.6 mg/kg).

576 New Zealand White rabbits were less sensitive since only delayed ossification of the  
577 frontal cranial bones was seen at an oral dose approximately 2,300 times the MRHD (on a mg/m<sup>2</sup>  
578 basis at a maternal dose of 10 mg/kg). Extensive use of other beta-agonists has provided no  
579 evidence that these class effects in animals are relevant to their use in humans.

580 Salmeterol xinafoate crossed the placenta following oral administration to mice and rats.

## 581 **8.2 Labor and Delivery**

582 There are no well-controlled human studies that have investigated effects of ADVAIR  
583 HFA on preterm labor or labor at term. Because of the potential for beta-agonist interference  
584 with uterine contractility, use of ADVAIR HFA during labor should be restricted to those  
585 patients in whom the benefits clearly outweigh the risks.

## 586 **8.3 Nursing Mothers**

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

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

## 595 **8.4 Pediatric Use**

596 Thirty-eight (38) patients aged 12 to 17 years were treated with ADVAIR HFA in US  
597 pivotal clinical trials. Patients in this age-group demonstrated efficacy results similar to those  
598 observed in patients aged 18 years and older. There were no obvious differences in the type or  
599 frequency of adverse events reported in this age-group compared with patients aged 18 years and  
600 older.

601 In a 12-week study, the safety of ADVAIR HFA 45/21 given as 2 inhalations twice daily  
602 was compared with that of fluticasone propionate 44 mcg HFA (FLOVENT<sup>®</sup> HFA) 2 inhalations  
603 twice daily in 350 subjects aged 4 to 11 years with persistent asthma currently being treated with  
604 inhaled corticosteroids. No new safety concerns were observed in children aged 5 to 11 years  
605 treated for 12 weeks with ADVAIR HFA 45/21 compared with adults and adolescents aged 12  
606 years and older. Common adverse reactions ( $\geq 3\%$ ) seen in children aged 5 to 11 years treated  
607 with ADVAIR HFA 45/21 but not reported in the adult and adolescent clinical trials of ADVAIR

608 HFA include: pyrexia, cough, pharyngolaryngeal pain, rhinitis, and sinusitis [*see Adverse*  
609 *Reactions (6.1)*]. This study was not designed to assess the effect of salmeterol, a component of  
610 ADVAIR HFA, on asthma hospitalizations and death in patients aged 4 to 11 years.

611 The pharmacokinetics and pharmacodynamic effect on serum cortisol of 21 days of  
612 treatment with ADVAIR HFA 45/21 (2 inhalations twice daily with or without a spacer) or  
613 ADVAIR DISKUS 100/50 (1 inhalation twice daily) was evaluated in a study of 31 children  
614 aged 4 to 11 years with mild asthma. Systemic exposure to salmeterol xinafoate was similar for  
615 ADVAIR HFA, ADVAIR HFA delivered with a spacer, and ADVAIR DISKUS while the  
616 systemic exposure to fluticasone propionate was lower with ADVAIR HFA compared with that  
617 of ADVAIR HFA delivered with a spacer or ADVAIR DISKUS. There were reductions in serum  
618 cortisol from baseline in all treatment groups (14%, 22%, and 13% for ADVAIR HFA, ADVAIR  
619 HFA delivered with a spacer, and ADVAIR DISKUS, respectively) [*see Clinical Pharmacology*  
620 *(12.2, 12.3)*].

621 The safety and effectiveness of ADVAIR HFA in children less than 12 years have not  
622 been established.

623 **Effects on Growth:** Inhaled corticosteroids, including fluticasone propionate, a  
624 component of ADVAIR HFA, may cause a reduction in growth velocity in children and  
625 adolescents [*see Warnings and Precautions (5.14)*]. The growth of pediatric patients receiving  
626 orally inhaled corticosteroids, including ADVAIR HFA, should be monitored.

627 A 52-week placebo-controlled study to assess the potential growth effects of fluticasone  
628 propionate inhalation powder (FLOVENT<sup>®</sup> ROTADISK<sup>®</sup>) at 50 and 100 mcg twice daily was  
629 conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to 11  
630 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were  
631 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and  
632 5.66 cm/year in the 100-mcg group (n = 89). An imbalance in the proportion of children entering  
633 puberty between groups and a higher dropout rate in the placebo group due to poorly controlled  
634 asthma may be confounding factors in interpreting these data. A separate subset analysis of  
635 children who remained prepubertal during the study revealed growth rates at 52 weeks of  
636 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and  
637 5.67 cm/year in the 100-mcg group (n = 79). In children aged 8.5 years, the mean age of children  
638 in this study, the range for expected growth velocity is: boys – 3<sup>rd</sup> percentile = 3.8 cm/year, 50<sup>th</sup>  
639 percentile = 5.4 cm/year, and 97<sup>th</sup> percentile = 7.0 cm/year; girls – 3<sup>rd</sup> percentile = 4.2 cm/year,  
640 50<sup>th</sup> percentile = 5.7 cm/year, and 97<sup>th</sup> percentile = 7.3 cm/year. The clinical relevance of these  
641 growth data is not certain.

642 If a child or adolescent on any corticosteroid appears to have growth suppression, the  
643 possibility that he/she is particularly sensitive to this effect of corticosteroids should be  
644 considered. The potential growth effects of prolonged treatment should be weighed against the  
645 clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids,  
646 including ADVAIR HFA, each patient should be titrated to the lowest strength that effectively  
647 controls his/her asthma.

648 **8.5 Geriatric Use**

649 Clinical studies of ADVAIR HFA did not include sufficient numbers of patients aged 65  
650 years and older to determine whether older patients respond differently than younger patients. In  
651 general, dose selection for an elderly patient should be cautious, usually starting at the low end of  
652 the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function,  
653 and of concomitant disease or other drug therapy. In addition, as with other products containing  
654 beta<sub>2</sub>-agonists, special caution should be observed when using ADVAIR HFA in geriatric  
655 patients who have concomitant cardiovascular disease that could be adversely affected by  
656 beta<sub>2</sub>-agonists.

657 **8.6 Hepatic Impairment**

658 Formal pharmacokinetic studies using ADVAIR HFA have not been conducted in  
659 patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are  
660 predominantly cleared by hepatic metabolism, impairment of liver function may lead to  
661 accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with  
662 hepatic disease should be closely monitored.

663 **8.7 Renal Impairment**

664 Formal pharmacokinetic studies using ADVAIR HFA have not been conducted in  
665 patients with renal impairment.

666 **10 OVERDOSAGE**

667 Fluticasone Propionate: Chronic overdosage with fluticasone propionate may result in  
668 signs/symptoms of hypercorticism [*see Warnings and Precautions (5.7)*]. Inhalation by healthy  
669 volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single  
670 doses of 1,760 or 3,520 mcg of fluticasone propionate CFC inhalation aerosol was well tolerated.  
671 Fluticasone propionate given by inhalation aerosol at dosages of 1,320 mcg twice daily for 7 to  
672 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily  
673 for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients  
674 were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were  
675 similar in active and placebo treatment groups.

676 Salmeterol: The expected signs and symptoms with overdosage of salmeterol are those  
677 of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the  
678 following: seizures, angina, hypertension or hypotension, tachycardia with rates up to  
679 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth,  
680 palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with salmeterol can  
681 lead to clinically significant prolongation of the QTc interval, which can produce ventricular  
682 arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

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

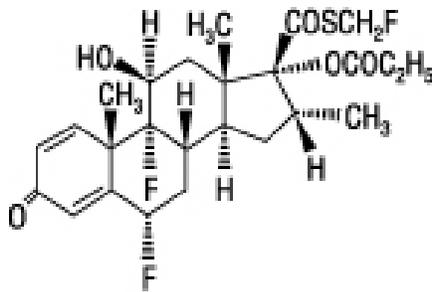
685 Treatment consists of discontinuation of salmeterol together with appropriate  
686 symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be

687 considered, bearing in mind that such medication can produce bronchospasm. There is  
688 insufficient evidence to determine if dialysis is beneficial for overdosage of salmeterol. Cardiac  
689 monitoring is recommended in cases of overdosage.

## 690 11 DESCRIPTION

691 ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR HFA 115/21 Inhalation Aerosol, and  
692 ADVAIR HFA 230/21 Inhalation Aerosol are combinations of fluticasone propionate and  
693 salmeterol xinafoate.

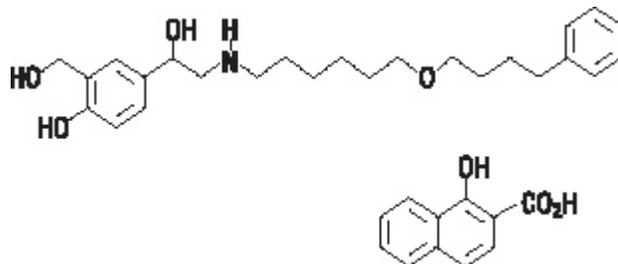
694 One active component of ADVAIR HFA is fluticasone propionate, a corticosteroid  
695 having the chemical name *S*-(fluoromethyl) 6 $\alpha$ ,9-difluoro-11 $\beta$ ,17-dihydroxy-16 $\alpha$ -methyl-3-  
696 oxoandrosta-1,4-diene-17 $\beta$ -carbothioate, 17-propionate and the following chemical structure:  
697



698  
699

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

703 The other active component of ADVAIR HFA is salmeterol xinafoate, a beta<sub>2</sub>-adrenergic  
704 bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt  
705 of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy- $\alpha$ <sup>1</sup>-[[[6-(4-  
706 phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-  
707 naphthalenecarboxylate, and it has the following chemical structure:  
708



709  
710

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

714 ADVAIR HFA 45/21 Inhalation Aerosol, ADVAIR HFA 115/21 Inhalation Aerosol, and  
715 ADVAIR HFA 230/21 Inhalation Aerosol are pressurized metered-dose aerosol units fitted with  
716 a counter. ADVAIR HFA is intended for oral inhalation only. Each unit contains a  
717 microcrystalline suspension of fluticasone propionate (micronized) and salmeterol xinafoate  
718 (micronized) in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

719 After priming, each actuation of the inhaler delivers 50, 125, or 250 mcg of fluticasone  
720 propionate and 25 mcg of salmeterol in 75 mg of suspension from the valve. Each actuation  
721 delivers 45, 115, or 230 mcg of fluticasone propionate and 21 mcg of salmeterol from the  
722 actuator. Twenty-one micrograms (21 mcg) of salmeterol base is equivalent to 30.45 mcg of  
723 salmeterol xinafoate. The actual amount of drug delivered to the lung may depend on patient  
724 factors, such as the coordination between the actuation of the device and inspiration through the  
725 delivery system.

726 Each 8-g canister contains 60 inhalations. Each 12-g canister provides 120 inhalations.

727 ADVAIR HFA should be primed before using for the first time by releasing 4 test sprays  
728 into the air away from the face, shaking well for 5 seconds before each spray. In cases where the  
729 inhaler has not been used for more than 4 weeks or when it has been dropped, prime the inhaler  
730 again by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before  
731 each spray.

## 732 **12 CLINICAL PHARMACOLOGY**

### 733 **12.1 Mechanism of Action**

734 ADVAIR HFA: Since ADVAIR HFA contains both fluticasone propionate and  
735 salmeterol, the mechanisms of action described below for the individual components apply to  
736 ADVAIR HFA. These drugs represent 2 classes of medications (a synthetic corticosteroid and a  
737 selective LABA) that have different effects on clinical, physiologic, and inflammatory indices of  
738 asthma.

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

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

751 Salmeterol Xinafoate: Salmeterol is a selective LABA. In vitro studies show salmeterol  
752 to be at least 50 times more selective for beta<sub>2</sub>-adrenoceptors than albuterol. Although

753 beta<sub>2</sub>-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and  
754 beta<sub>1</sub>-adrenoceptors are the predominant receptors in the heart, there are also  
755 beta<sub>2</sub>-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors.  
756 The precise function of these receptors has not been established, but their presence raises the  
757 possibility that even selective beta<sub>2</sub>-agonists may have cardiac effects.

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

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

## 770 **12.2 Pharmacodynamics**

771 ADVAIR HFA: Healthy Subjects: Cardiovascular Effects: Since systemic  
772 pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher  
773 doses were used to produce measurable effects. Four (4) placebo-controlled crossover studies  
774 were conducted in healthy subjects: (1) a cumulative-dose study using 42 to 336 mcg of  
775 salmeterol CFC inhalation aerosol given alone or as ADVAIR HFA 115/21, (2) a single-dose  
776 study using 4 inhalations of ADVAIR HFA 230/21, salmeterol CFC inhalation aerosol 21 mcg,  
777 or fluticasone propionate CFC inhalation aerosol 220 mcg, (3) a single-dose study using  
778 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, or ADVAIR HFA 230/21, and (4)  
779 a single-dose study using 4 inhalations of ADVAIR HFA 230/21; 2 inhalations of ADVAIR  
780 DISKUS 500/50; 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg; or  
781 1,010 mcg of fluticasone propionate given intravenously. In these studies pulse rate, blood  
782 pressure, QTc interval, glucose, and/or potassium were measured. Comparable or lower effects  
783 were observed for ADVAIR HFA compared with ADVAIR DISKUS or salmeterol alone. The  
784 effect of salmeterol on pulse rate and potassium was not altered by the presence of different  
785 amounts of fluticasone propionate in ADVAIR HFA.

786 Hypothalamic-Pituitary-Adrenal Axis Effects: The potential effect of salmeterol  
787 on the effects of fluticasone propionate on the HPA axis was also evaluated in 3 of these studies.  
788 Compared with fluticasone propionate CFC inhalation aerosol, ADVAIR HFA had less effect on  
789 24-hour urinary cortisol excretion and less or comparable effect on 24-hour serum cortisol. In  
790 these crossover studies in healthy subjects, ADVAIR HFA and ADVAIR DISKUS had similar  
791 effects on urinary and serum cortisol.

792 *Patients With Asthma: Cardiovascular Effects:* In clinical studies with  
793 ADVAIR HFA in adult and adolescent patients aged 12 years and older with asthma, systemic  
794 pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and  
795 glucose) were similar to or slightly lower in patients treated with ADVAIR HFA compared with  
796 patients treated with salmeterol CFC inhalation aerosol 21 mcg. In 61 adult and adolescent  
797 patients with asthma given ADVAIR HFA (45/21 or 115/21 mcg), continuous 24-hour  
798 electrocardiographic monitoring was performed after the first dose and after 12 weeks of  
799 twice-daily therapy, and no clinically significant dysrhythmias were noted.

800 The effect of 21 days of treatment with ADVAIR HFA 45/21 (2 inhalations twice daily  
801 with or without a spacer) or ADVAIR DISKUS 100/50 (1 inhalation twice daily) was evaluated  
802 in 31 children aged 4 to 11 years with mild asthma. There were no notable changes from baseline  
803 for QTc, heart rate, or systolic and diastolic blood pressure.

804 *Hypothalamic-Pituitary-Adrenal Axis Effects:* A 4-way crossover study in 13  
805 patients with asthma compared pharmacodynamics at steady state following 4 weeks of  
806 twice-daily treatment with 2 inhalations of ADVAIR HFA 115/21, 1 inhalation of ADVAIR  
807 DISKUS 250/50 mcg, 2 inhalations of fluticasone propionate HFA inhalation aerosol 110 mcg,  
808 and placebo. No significant differences in serum cortisol AUC were observed between active  
809 treatments and placebo. Mean 12-hour serum cortisol AUC ratios comparing active treatment  
810 with placebo ranged from 0.9 to 1.2. No statistically or clinically significant increases in heart  
811 rate or QTc interval were observed for any active treatment compared with placebo.

812 In a 12-week study in adult and adolescent patients with asthma, ADVAIR HFA 115/21  
813 was compared with the individual components, fluticasone propionate CFC inhalation aerosol  
814 110 mcg and salmeterol CFC inhalation aerosol 21 mcg, and placebo [see *Clinical Studies*  
815 (14.1)]. All treatments were administered as 2 inhalations twice daily. After 12 weeks of  
816 treatment with these therapeutic doses, the geometric mean ratio of urinary cortisol excretion  
817 compared with baseline was 0.9 for ADVAIR HFA and fluticasone propionate and 1.0 for  
818 placebo and salmeterol. In addition, the ability to increase cortisol production in response to  
819 stress, as assessed by 30-minute cosyntropin stimulation in 23 to 32 patients per treatment group,  
820 remained intact for the majority of patients and was similar across treatments. Three patients  
821 who received ADVAIR HFA 115/21 had an abnormal response (peak serum cortisol  
822 <18 mcg/dL) after dosing, compared with 1 patient who received placebo, 2 patients who  
823 received fluticasone propionate 110 mcg, and 1 patient who received salmeterol.

824 In another 12-week study in adult and adolescent patients with asthma, ADVAIR HFA  
825 230/21 (2 inhalations twice daily) was compared with ADVAIR DISKUS 500/50 (1 inhalation  
826 twice daily) and fluticasone propionate CFC inhalation aerosol 220 mcg (2 inhalations twice  
827 daily) [see *Clinical Studies* (14.1)]. The geometric mean ratio of 24-hour urinary cortisol  
828 excretion at week 12 compared with baseline was 0.9 for all 3 treatment groups.

829 The effect of 21 days of treatment with ADVAIR HFA 45/21 (2 inhalations twice daily  
830 with or without a spacer) or ADVAIR DISKUS 100/50 (1 inhalation twice daily) on serum  
831 cortisol was evaluated in 31 children aged 4 to 11 years with mild asthma. There were reductions

832 in serum cortisol from baseline in all treatment groups (14%, 22%, and 13% for ADVAIR HFA,  
833 ADVAIR HFA with spacer, and ADVAIR DISKUS, respectively).

834 **Other Fluticasone Propionate Products: Patients With Asthma: Hypothalamic-**  
835 **Pituitary-Adrenal Axis Effects:** In clinical trials with fluticasone propionate inhalation powder  
836 using dosages up to and including 250 mcg twice daily, occasional abnormal short cosyntropin  
837 tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted both in  
838 patients receiving fluticasone propionate and in patients receiving placebo. The incidence of  
839 abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out  
840 with the DISKHALER<sup>®</sup> inhalation device in 64 patients with mild, persistent asthma (mean  
841 FEV<sub>1</sub> 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo,  
842 no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin  
843 infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1  
844 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing  
845 at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had  
846 an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

847 **Other Salmeterol Xinafoate Products: Patients With Asthma: Cardiovascular**  
848 **Effects:** Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related  
849 cardiovascular effects and effects on blood glucose and/or serum potassium [*see Warnings and*  
850 *Precautions (5.12, 5.18)*]. The cardiovascular effects (heart rate, blood pressure) associated with  
851 salmeterol occur with similar frequency, and are of similar type and severity, as those noted  
852 following albuterol administration.

853 The effects of rising inhaled doses of salmeterol and standard inhaled doses of albuterol  
854 were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg  
855 administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the  
856 same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). In 2 double-blind  
857 asthma studies, patients receiving either 42 mcg of salmeterol inhalation aerosol twice daily  
858 (n = 81) or 180 mcg of albuterol inhalation aerosol 4 times daily (n = 80) underwent continuous  
859 electrocardiographic monitoring during four 24-hour periods; no clinically significant  
860 dysrhythmias were noted.

861 **Concomitant Use of ADVAIR HFA With Other Respiratory Medications:**  
862 **Short-Acting Beta<sub>2</sub>-Agonists:** In three 12-week US clinical trials, the mean daily need for  
863 additional beta<sub>2</sub>-agonist use in 277 patients receiving ADVAIR HFA was approximately  
864 1.2 inhalations/day and ranged from 0 to 9 inhalations/day. Two percent (2%) of patients  
865 receiving ADVAIR HFA in these trials averaged 6 or more inhalations per day over the course of  
866 the 12-week trials. No increase in frequency of cardiovascular adverse reactions was observed  
867 among patients who averaged 6 or more inhalations per day.

868 **Methylxanthines:** The concurrent use of intravenously or orally administered  
869 methylxanthines (e.g., aminophylline, theophylline) by patients receiving ADVAIR HFA has not  
870 been completely evaluated. In five 12-week clinical trials (3 US and 2 non-US), 45 patients  
871 receiving ADVAIR HFA 45/21, 115/21, or 230/21 twice daily concurrently with a theophylline

872 product had adverse event rates similar to those in 577 patients receiving ADVAIR HFA without  
873 theophylline.

874 *Fluticasone Propionate Nasal Spray*: In patients receiving ADVAIR HFA in three  
875 12-week US clinical trials, no difference in the profile of adverse events or HPA axis effects was  
876 noted between patients receiving FLONASE® (fluticasone propionate) Nasal Spray, 50 mcg  
877 concurrently (n = 89) and those who were not (n = 192).

### 878 **12.3 Pharmacokinetics**

879 Absorption: Fluticasone Propionate: Healthy Subjects: Fluticasone propionate acts  
880 locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral  
881 dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of  
882 fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and  
883 presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone  
884 propionate delivered to the lung is systemically absorbed.

885 Three single-dose placebo-controlled crossover studies were conducted in healthy  
886 subjects: (1) a study using 4 inhalations of ADVAIR HFA 230/21, salmeterol CFC inhalation  
887 aerosol 21 mcg, or fluticasone propionate CFC inhalation aerosol 220 mcg, (2) a study using  
888 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, or ADVAIR HFA 230/21, and (3)  
889 a study using 4 inhalations of ADVAIR HFA 230/21; 2 inhalations of ADVAIR DISKUS  
890 500/50; 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg; or 1,010 mcg of  
891 fluticasone propionate given intravenously. Peak plasma concentrations of fluticasone propionate  
892 were achieved in 0.33 to 1.5 hours and those of salmeterol were achieved in 5 to 10 minutes.

893 Peak plasma concentrations of fluticasone propionate (N = 20 subjects) following  
894 8 inhalations of ADVAIR HFA 45/21, ADVAIR HFA 115/21, and ADVAIR HFA 230/21  
895 averaged 41, 108, and 173 pg/mL, respectively.

896 Systemic exposure (N = 20 subjects) from 4 inhalations of ADVAIR HFA 230/21 was  
897 53% of the value from the individual inhaler for fluticasone propionate CFC inhalation aerosol  
898 and 42% of the value from the individual inhaler for salmeterol CFC inhalation aerosol. Peak  
899 plasma concentrations from ADVAIR HFA for fluticasone propionate (86 versus 120 pg/mL)  
900 and salmeterol (170 versus 510 pg/mL) were significantly lower compared with individual  
901 inhalers.

902 In 15 healthy subjects, systemic exposure (AUC) to fluticasone propionate from 4  
903 inhalations of ADVAIR HFA 230/21 (920/84 mcg) and 2 inhalations of ADVAIR DISKUS  
904 500/50 (1,000/100 mcg) were similar between the 2 inhalers (i.e., 799 versus 832 pg•hr/mL,  
905 respectively) but approximately half the systemic exposure from 4 inhalations of fluticasone  
906 propionate CFC inhalation aerosol 220 mcg (880 mcg, AUC = 1,543 pg•hr/mL). Similar results  
907 were observed for peak fluticasone propionate plasma concentrations (186 and 182 pg/mL from  
908 ADVAIR HFA and ADVAIR DISKUS, respectively, and 307 pg/mL from the fluticasone  
909 propionate CFC inhalation aerosol). Absolute bioavailability of fluticasone propionate was 5.3%  
910 and 5.5% following administration of ADVAIR HFA and ADVAIR DISKUS, respectively.

911 *Patients With Asthma:* A double-blind crossover study was conducted in 13 adult  
912 patients with asthma to evaluate the steady-state pharmacokinetics of fluticasone propionate and  
913 salmeterol following administration of 2 inhalations of ADVAIR HFA 115/21 twice daily or 1  
914 inhalation of ADVAIR DISKUS 250/50 twice daily for 4 weeks. Systemic exposure (AUC) to  
915 fluticasone propionate was similar for ADVAIR HFA (274 pg•hr/mL [95% CI: 150, 502]) and  
916 ADVAIR DISKUS (338 pg•hr/mL [95% CI: 197, 581]).

917 The effect of 21 days of treatment with ADVAIR HFA 45/21 (2 inhalations twice daily  
918 with or without a spacer) or ADVAIR DISKUS 100/50 (1 inhalation twice daily) was evaluated  
919 in a study of 31 children aged 4 to 11 years with mild asthma. Systemic exposure to fluticasone  
920 propionate was similar with ADVAIR DISKUS and ADVAIR HFA with a spacer  
921 (138 pg•hr/mL [95% CI: 69, 273] and 107 pg•hr/mL [95% CI: 46, 252], respectively) and lower  
922 with ADVAIR HFA without a spacer (24 pg•hr/mL [95% CI: 10, 60]).

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

927 Peak plasma concentrations of salmeterol (N = 20 subjects) following 8 inhalations of  
928 ADVAIR HFA 45/21, ADVAIR HFA 115/21, and ADVAIR HFA 230/21 ranged from 220 to  
929 470 pg/mL.

930 In 15 healthy subjects receiving ADVAIR HFA 230/21 (920/84 mcg) and ADVAIR  
931 DISKUS 500/50 (1,000/100 mcg), systemic exposure to salmeterol was higher (317 versus  
932 169 pg•hr/mL) and peak salmeterol concentrations were lower (196 versus 223 pg/mL)  
933 following ADVAIR HFA compared with ADVAIR DISKUS, although pharmacodynamic results  
934 were comparable.

935 *Patients With Asthma:* Because of the small therapeutic dose, systemic levels of  
936 salmeterol are low or undetectable after inhalation of recommended dosages (42 mcg of  
937 salmeterol inhalation aerosol twice daily). Following chronic administration of an inhaled dosage  
938 of 42 mcg of salmeterol inhalation aerosol twice daily, salmeterol was detected in plasma within  
939 5 to 10 minutes in 6 patients with asthma; plasma concentrations were very low, with mean peak  
940 concentrations of 150 pg/mL at 20 minutes and no accumulation with repeated doses.

941 A double-blind crossover study was conducted in 13 adult patients with asthma to  
942 evaluate the steady-state pharmacokinetics of fluticasone propionate and salmeterol following  
943 administration of 2 inhalations of ADVAIR HFA 115/21 twice daily or 1 inhalation of ADVAIR  
944 DISKUS 250/50 twice daily for 4 weeks. Systemic exposure to salmeterol was similar for  
945 ADVAIR HFA (53 pg•hr/mL [95% CI: 17, 164]) and ADVAIR DISKUS (70 pg•hr/mL [95%  
946 CI: 19, 254]).

947 The effect of 21 days of treatment with ADVAIR HFA 45/21 (2 inhalations twice daily  
948 with or without a spacer) or ADVAIR DISKUS 100/50 (1 inhalation twice daily) was evaluated  
949 in 31 children aged 4 to 11 years with mild asthma. Systemic exposure to salmeterol was similar  
950 for ADVAIR HFA, ADVAIR HFA with spacer, and ADVAIR DISKUS (126 pg•hr/mL [95%

951 CI: 70, 225], 103 pg•hr/mL [95% CI: 54, 200], and 110 pg•hr/mL [95% CI: 55, 219],  
952 respectively).

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

956 The percentage of fluticasone propionate bound to human plasma proteins averages 99%.  
957 Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly  
958 bound to human transcortin.

959 **Salmeterol:** The percentage of salmeterol bound to human plasma proteins averages  
960 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much  
961 higher concentrations than those achieved following therapeutic doses of salmeterol.

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

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

972 An in vitro study using human liver microsomes showed that salmeterol is extensively  
973 metabolized to  $\alpha$ -hydroxysalmeterol (aliphatic oxidation) by CYP3A4. Ketoconazole, a strong  
974 inhibitor of CYP3A4, essentially completely inhibited the formation of  $\alpha$ -hydroxysalmeterol in  
975 vitro.

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

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

986 The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is  
987 highly protein bound (>99%) and has a long elimination half-life of 11 days. No terminal  
988 half-life estimates were calculated for salmeterol following administration of ADVAIR HFA.

989 **Special Populations:** A population pharmacokinetic analysis was performed for  
990 fluticasone propionate and salmeterol utilizing data from 9 controlled clinical trials that included

991 350 patients with asthma aged 4 to 77 years who received treatment with ADVAIR DISKUS,  
992 ADVAIR HFA, fluticasone propionate inhalation powder (FLOVENT<sup>®</sup> DISKUS<sup>®</sup>),  
993 HFA-propelled fluticasone propionate inhalation aerosol (FLOVENT HFA), or CFC-propelled  
994 fluticasone propionate inhalation aerosol. The population pharmacokinetic analyses for  
995 fluticasone propionate and salmeterol showed no clinically relevant effects of age, gender, race,  
996 body weight, body mass index, or percent of predicted FEV<sub>1</sub> on apparent clearance and apparent  
997 volume of distribution.

998 **Hepatic and Renal Impairment:** Formal pharmacokinetic studies using ADVAIR  
999 HFA have not been conducted in patients with hepatic or renal impairment. However, since both  
1000 fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism,  
1001 impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol  
1002 in plasma. Therefore, patients with hepatic disease should be closely monitored.

1003 **Drug Interactions:** In the repeat- and single-dose studies, there was no evidence of  
1004 significant drug interaction in systemic exposure between fluticasone propionate and salmeterol  
1005 when given alone or in combination via the DISKUS. Similar definitive studies have not been  
1006 performed with ADVAIR HFA. The population pharmacokinetic analysis from 9 controlled  
1007 clinical trials in 350 patients with asthma showed no significant effects on fluticasone propionate  
1008 or salmeterol pharmacokinetics following co-administration with beta<sub>2</sub>-agonists, corticosteroids,  
1009 antihistamines, or theophyllines.

1010 **Inhibitors of Cytochrome P450 3A4: Ritonavir: Fluticasone Propionate:**  
1011 Fluticasone propionate is a substrate of CYP3A4. Coadministration of fluticasone propionate and  
1012 the strong CYP3A4 inhibitor ritonavir is not recommended based upon a multiple-dose crossover  
1013 drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray  
1014 (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma  
1015 fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone  
1016 were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable peak  
1017 levels (C<sub>max</sub>) averaged 11.9 pg/mL (range: 10.8 to 14.1 pg/mL) and AUC<sub>(0-τ)</sub> averaged  
1018 8.43 pg•hr/mL (range: 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C<sub>max</sub> and AUC<sub>(0-τ)</sub>  
1019 increased to 318 pg/mL (range: 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range: 1,207.1 to  
1020 5,662.0 pg•hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate  
1021 aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted  
1022 in a significant decrease (86%) in serum cortisol AUC.

1023 **Ketoconazole: Fluticasone Propionate:** In a placebo-controlled crossover study  
1024 in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone  
1025 propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in  
1026 increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no  
1027 effect on urinary excretion of cortisol.

1028 **Salmeterol:** In a placebo-controlled crossover drug interaction study in  
1029 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the  
1030 strong CYP3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant

1031 increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with  
1032 and without ketoconazole 15.76 [90% CI: 10.66, 23.31]) mainly due to increased bioavailability  
1033 of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by  
1034 1.4-fold (90% CI: 1.23, 1.68). Three (3) out of 20 subjects (15%) were withdrawn from  
1035 salmeterol and ketoconazole coadministration due to beta-agonist-mediated systemic effects (2  
1036 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of  
1037 salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate,  
1038 mean blood potassium, or mean blood glucose. Although there was no statistical effect on the  
1039 mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent  
1040 increases in QTc duration compared with salmeterol and placebo administration.

1041 *Erythromycin: Fluticasone Propionate:* In a multiple-dose drug interaction study,  
1042 coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and  
1043 erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

1044 *Salmeterol:* In a repeat-dose study in 13 healthy subjects, concomitant  
1045 administration of erythromycin (a moderate CYP3A4 inhibitor) and salmeterol inhalation aerosol  
1046 resulted in a 40% increase in salmeterol  $C_{max}$  at steady state (ratio with and without erythromycin  
1047 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],  
1048  $p < 0.04$ ), a 5.8-msec increase in QTc interval ([95% CI: -6.14, 17.77],  $p = 0.34$ ), and no change  
1049 in plasma potassium.

## 1050 **13 NONCLINICAL TOXICOLOGY**

### 1051 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

1052 Fluticasone Propionate: Fluticasone propionate demonstrated no tumorigenic potential  
1053 in mice at oral doses up to 1,000 mcg/kg (approximately 5 times the MRHD on a mcg/m<sup>2</sup> basis)  
1054 for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than the MRHD on a mcg/m<sup>2</sup>  
1055 basis) for 104 weeks.

1056 Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in  
1057 vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in  
1058 vitro or in the in vivo mouse micronucleus test.

1059 No evidence of impairment of fertility was observed in reproductive studies conducted in  
1060 rats at subcutaneous doses up to 50 mcg/kg (less than the MRHD on a mcg/m<sup>2</sup> basis). Prostate  
1061 weight was significantly reduced.

1062 Salmeterol: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses  
1063 of 1.4 mg/kg and above (approximately 10 times the MRHD based on comparison of the plasma  
1064 AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic  
1065 glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were seen at  
1066 0.2 mg/kg (approximately 2 times the MRHD for adults based on comparison of the AUCs).

1067 In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats,  
1068 salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and  
1069 ovarian cysts at doses of 0.68 mg/kg and above (approximately 80 times the MRHD on a mg/m<sup>2</sup>

1070 basis). No tumors were seen at 0.21 mg/kg (approximately 25 times the MRHD on a mg/m<sup>2</sup>  
1071 basis). These findings in rodents are similar to those reported previously for other  
1072 beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

1073 Salmeterol produced no detectable or reproducible increases in microbial and mammalian  
1074 gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo  
1075 in a rat micronucleus test. No effects on fertility were identified in rats treated with salmeterol at  
1076 oral doses up to 2 mg/kg (approximately 230 times the MRHD on a mg/m<sup>2</sup> basis).

### 1077 **13.2 Animal Toxicology and/or Pharmacology**

1078 Preclinical: Studies in laboratory animals (minipigs, rodents, and dogs) have  
1079 demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence  
1080 of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently.  
1081 The clinical relevance of these findings is unknown.

1082 Propellant HFA-134a: In animals and humans, propellant HFA-134a was found to be  
1083 rapidly absorbed and rapidly eliminated, with an elimination half-life of 3 to 27 minutes in  
1084 animals and 5 to 7 minutes in humans. Time to maximum plasma concentration (T<sub>max</sub>) and mean  
1085 residence time are both extremely short, leading to a transient appearance of HFA-134a in the  
1086 blood with no evidence of accumulation.

1087 Propellant HFA-134a is devoid of pharmacological activity except at very high doses in  
1088 animals (i.e., 380 to 1,300 times the maximum human exposure based on comparisons of area  
1089 under the plasma concentration versus time curve [AUC] values), primarily producing ataxia,  
1090 tremors, dyspnea, or salivation. These events are similar to effects produced by the structurally  
1091 related CFCs, which have been used extensively in metered-dose inhalers. In drug interaction  
1092 studies in male and female dogs, there was a slight increase in the salmeterol-related effect on  
1093 heart rate (a known effect of beta<sub>2</sub>-agonists) when given in combination with high doses of  
1094 fluticasone propionate. This effect was not observed in clinical studies.

## 1095 **14 CLINICAL STUDIES**

1096 ADVAIR HFA has been studied in patients with asthma aged 12 years and older.  
1097 ADVAIR HFA has not been studied in patients less than 12 years of age or in patients with  
1098 COPD. In clinical trials comparing ADVAIR HFA Inhalation Aerosol with its individual  
1099 components, improvements in most efficacy endpoints were greater with ADVAIR HFA than  
1100 with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials  
1101 showed comparable results between ADVAIR HFA and ADVAIR DISKUS.

### 1102 **14.1 Studies Comparing ADVAIR HFA With Fluticasone Propionate Alone or** 1103 **Salmeterol Alone**

1104 Four (4) double-blind parallel-group clinical trials were conducted with ADVAIR HFA  
1105 in 1,517 adult and adolescent patients (≥12 years, mean baseline FEV<sub>1</sub> 65% to 75% of predicted  
1106 normal) with asthma that was not optimally controlled on their current therapy. All metered-dose  
1107 inhaler treatments were inhalation aerosols given as 2 inhalations twice daily, and other  
1108 maintenance therapies were discontinued.

1109 **Study 1: Clinical Trial With ADVAIR HFA 45/21 Inhalation Aerosol:** This placebo-  
 1110 controlled 12-week US study compared ADVAIR HFA 45/21 with fluticasone propionate CFC  
 1111 inhalation aerosol 44 mcg or salmeterol CFC inhalation aerosol 21 mcg, each given as  
 1112 2 inhalations twice daily. The primary efficacy endpoints were predose FEV<sub>1</sub> and withdrawals  
 1113 due to worsening asthma. This study was stratified according to baseline asthma therapy: patients  
 1114 using beta-agonists (albuterol alone [n = 142], salmeterol [n = 84], or inhaled corticosteroids  
 1115 [n = 134] [daily doses of beclomethasone dipropionate 252 to 336 mcg; budesonide 400 to  
 1116 600 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol 176 mcg; fluticasone  
 1117 propionate inhalation powder 200 mcg; or triamcinolone acetonide 600 to 800 mcg]). Baseline  
 1118 FEV<sub>1</sub> measurements were similar across treatments: ADVAIR HFA 45/21, 2.29 L; fluticasone  
 1119 propionate 44 mcg, 2.20 L; salmeterol, 2.33 L; and placebo, 2.27 L.

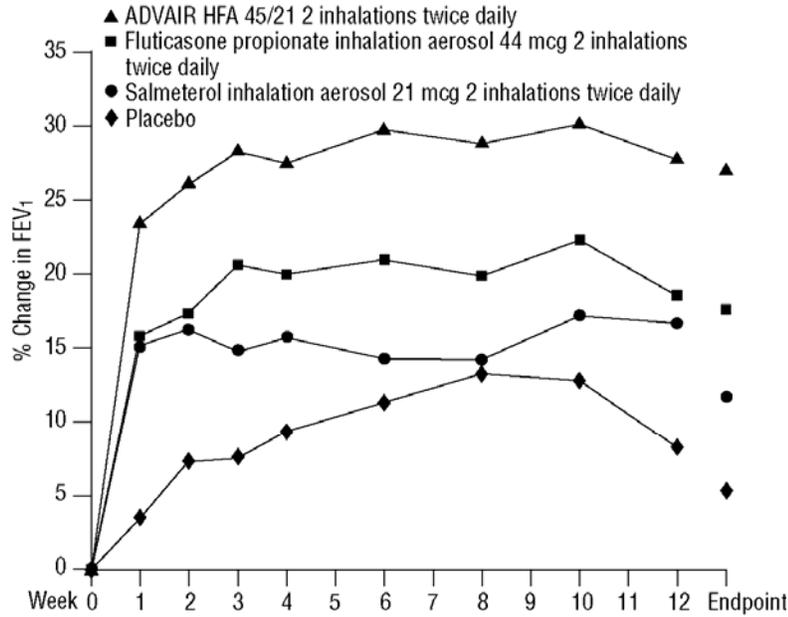
1120 Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma,  
 1121 were utilized for this placebo-controlled study. Worsening asthma was defined as a clinically  
 1122 important decrease in FEV<sub>1</sub> or PEF, increase in use of VENTOLIN<sup>®</sup> (albuterol, USP) Inhalation  
 1123 Aerosol, increase in night awakenings due to asthma, emergency intervention or hospitalization  
 1124 due to asthma, or requirement for asthma medication not allowed by the protocol. As shown in  
 1125 Table 4, statistically significantly fewer patients receiving ADVAIR HFA 45/21 were withdrawn  
 1126 due to worsening asthma compared with salmeterol and placebo. Fewer patients receiving  
 1127 ADVAIR HFA 45/21 were withdrawn due to worsening asthma compared with fluticasone  
 1128 propionate 44 mcg; however, the difference was not statistically significant.

1130 **Table 4. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously**  
 1131 **Treated With Beta<sub>2</sub>-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids**  
 1132 **(Study 1)**

ADVAIR HFA 45/21 Inhalation Aerosol (n = 92)	Fluticasone Propionate CFC Inhalation Aerosol 44 mcg (n = 89)	Salmeterol CFC Inhalation Aerosol 21 mcg (n = 92)	Placebo HFA Inhalation Aerosol (n = 87)
2%	8%	25%	28%

1133  
 1134 The FEV<sub>1</sub> results are displayed in Figure 2. Because this trial used predetermined criteria  
 1135 for worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV<sub>1</sub>  
 1136 results at Endpoint (last available FEV<sub>1</sub> result) are also provided. Patients receiving ADVAIR  
 1137 HFA 45/21 had significantly greater improvements in FEV<sub>1</sub> (0.58 L, 27%) compared with  
 1138 fluticasone propionate 44 mcg (0.36 L, 18%), salmeterol (0.25 L, 12%), and placebo (0.14 L,  
 1139 5%). These improvements in FEV<sub>1</sub> with ADVAIR HFA 45/21 were achieved regardless of  
 1140 baseline asthma therapy (albuterol alone, salmeterol, or inhaled corticosteroids).

1142 **Figure 2. Mean Percent Change From Baseline in FEV<sub>1</sub> in Patients**  
 1143 **Previously Treated With Either Beta<sub>2</sub>-Agonists (Albuterol or**  
 1144 **Salmeterol) or Inhaled Corticosteroids (Study 1)**  
 1145



	Week 0	Week 6	Week 12
ADVAIR HFA 45/21	N 92	N 88	N 85
Fluticasone propionate inhalation aerosol 44 mcg	89	84	76
Salmeterol inhalation aerosol 21 mcg	92	72	65
Placebo	87	63	58

1146  
 1147  
 1148 The effect of ADVAIR HFA 45/21 on the secondary efficacy parameters, including  
 1149 morning and evening PEF, usage of VENTOLIN Inhalation Aerosol, and asthma symptoms over  
 1150 24 hours on a scale of 0 to 5 is shown in Table 5.  
 1151

1152 **Table 5. Secondary Efficacy Variable Results for Patients Previously Treated With**  
 1153 **Beta<sub>2</sub>-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)**

Efficacy Variable <sup>a</sup>	ADVAIR HFA 45/21 Inhalation Aerosol (n = 92)	Fluticasone Propionate CFC Inhalation Aerosol 44 mcg (n = 89)	Salmeterol CFC Inhalation Aerosol 21 mcg (n = 92)	Placebo HFA Inhalation Aerosol (n = 87)
AM PEF (L/min)				
Baseline	377	369	381	382
Change from baseline	58	27	25	1
PM PEF (L/min)				
Baseline	397	387	402	407
Change from baseline	48	20	16	3
Use of VENTOLIN Inhalation Aerosol (inhalations/day)				
Baseline	3.1	2.4	2.7	2.7
Change from baseline	-2.1	-0.4	-0.8	0.2
Asthma symptom score/day				
Baseline	1.8	1.6	1.7	1.7
Change from baseline	-1.0	-0.3	-0.4	0

1154 <sup>a</sup> Change from baseline = change from baseline at Endpoint (last available data).  
 1155

1156 The subjective impact of asthma on patients' perceptions of health was evaluated through  
 1157 use of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a  
 1158 7-point scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR HFA  
 1159 45/21 had clinically meaningful improvements in overall asthma-specific quality of life as  
 1160 defined by a difference between groups of  $\geq 0.5$  points in change from baseline AQLQ scores  
 1161 (difference in AQLQ score of 1.14 [95% CI: 0.85, 1.44] compared with placebo).

1162 **Study 2: Clinical Trial With ADVAIR HFA 45/21 Inhalation Aerosol:** This active-  
 1163 controlled 12-week US study compared ADVAIR HFA 45/21 with fluticasone propionate CFC  
 1164 inhalation aerosol 44 mcg and salmeterol CFC inhalation aerosol 21 mcg, each given as 2  
 1165 inhalations twice daily, in 283 patients using as-needed albuterol alone. The primary efficacy  
 1166 endpoint was predose FEV<sub>1</sub>. Baseline FEV<sub>1</sub> measurements were similar across treatments:  
 1167 ADVAIR HFA 45/21, 2.37 L; fluticasone propionate 44 mcg, 2.31 L; and salmeterol, 2.34 L.

1168 Efficacy results in this study were similar to those observed in Study 1. Patients receiving  
 1169 ADVAIR HFA 45/21 had significantly greater improvements in FEV<sub>1</sub> (0.69 L, 33%) compared  
 1170 with fluticasone propionate 44 mcg (0.51 L, 25%) and salmeterol (0.47 L, 22%).

1171 Study 3: Clinical Trial With ADVAIR HFA 115/21 Inhalation Aerosol: This placebo-  
1172 controlled 12-week US study compared ADVAIR HFA 115/21 with fluticasone propionate CFC  
1173 inhalation aerosol 110 mcg or salmeterol CFC inhalation aerosol 21 mcg, each given as 2  
1174 inhalations twice daily, in 365 patients using inhaled corticosteroids (daily doses of  
1175 beclomethasone dipropionate 378 to 840 mcg; budesonide 800 to 1,200 mcg; flunisolide 1,250 to  
1176 2,000 mcg; fluticasone propionate inhalation aerosol 440 to 660 mcg; fluticasone propionate  
1177 inhalation powder 400 to 600 mcg; or triamcinolone acetonide 900 to 1,600 mcg). The primary  
1178 efficacy endpoints were predose FEV<sub>1</sub> and withdrawals due to worsening asthma. Baseline FEV<sub>1</sub>  
1179 measurements were similar across treatments: ADVAIR HFA 115/21, 2.23 L; fluticasone  
1180 propionate 110 mcg, 2.18 L; salmeterol, 2.22 L; and placebo, 2.17 L.

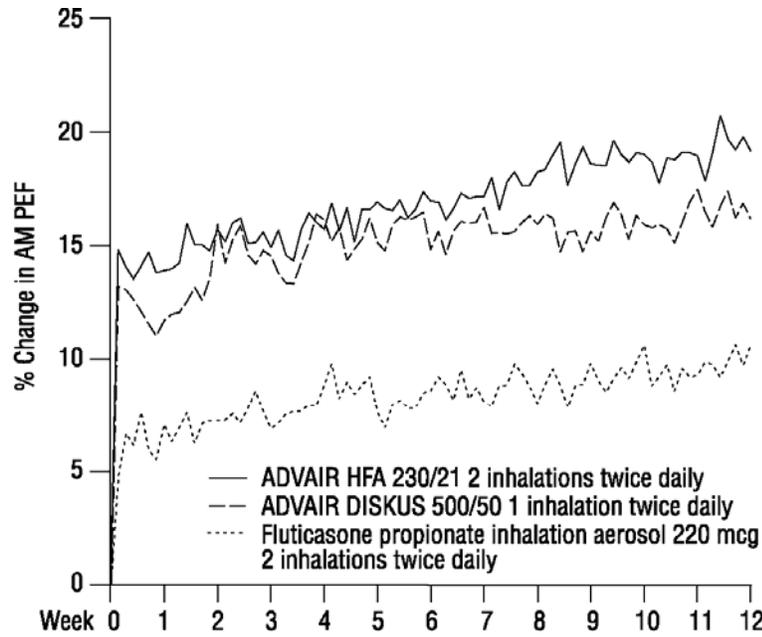
1181 Efficacy results in this study were similar to those observed in Studies 1 and 2. Patients  
1182 receiving ADVAIR HFA 115/21 had significantly greater improvements in FEV<sub>1</sub> (0.41 L, 20%)  
1183 compared with fluticasone propionate 110 mcg (0.19 L, 9%), salmeterol (0.15 L, 8%), and  
1184 placebo (-0.12 L, -6%). Significantly fewer patients receiving ADVAIR HFA 115/21 were  
1185 withdrawn from this study for worsening asthma (7%) compared with salmeterol (24%) and  
1186 placebo (54%). Fewer patients receiving ADVAIR HFA 115/21 were withdrawn due to  
1187 worsening asthma (7%) compared with fluticasone propionate 110 mcg (11%); however, the  
1188 difference was not statistically significant.

1189 Study 4: Clinical Trial With ADVAIR HFA 230/21 Inhalation Aerosol: This  
1190 active-controlled 12-week non-US study compared ADVAIR HFA 230/21 with fluticasone  
1191 propionate CFC inhalation aerosol 220 mcg, each given as 2 inhalations twice daily, and with  
1192 ADVAIR DISKUS 500/50 given as 1 inhalation twice daily in 509 patients using inhaled  
1193 corticosteroids (daily doses of beclomethasone dipropionate CFC inhalation aerosol 1,500 to  
1194 2,000 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; fluticasone  
1195 propionate inhalation aerosol 660 to 880 mcg; or fluticasone propionate inhalation powder 750 to  
1196 1,000 mcg). The primary efficacy endpoint was morning PEF.

1197 Baseline morning PEF measurements were similar across treatments: ADVAIR HFA  
1198 230/21, 327 L/min; ADVAIR DISKUS 500/50, 341 L/min; and fluticasone propionate 220 mcg,  
1199 345 L/min. As shown in Figure 3, morning PEF improved significantly with ADVAIR HFA  
1200 230/21 compared with fluticasone propionate 220 mcg over the 12-week treatment period.  
1201 Improvements in morning PEF observed with ADVAIR HFA 230/21 were similar to  
1202 improvements observed with ADVAIR DISKUS 500/50.

1203

1204 **Figure 3. Mean Percent Change From Baseline in Morning Peak**  
 1205 **Expiratory Flow in Patients Previously Treated With Inhaled**  
 1206 **Corticosteroids (Study 4)**  
 1207



	Week 0 N	Week 6 N	Week 12 N
ADVAIR HFA 230/21	176	159	130
ADVAIR DISKUS 500/50	161	147	119
Fluticasone propionate inhalation aerosol 220 mcg	172	155	133

1208  
1209

## 14.2 One-Year Safety Study

### Clinical Trial With ADVAIR HFA 45/21, 115/21, and 230/21 Inhalation Aerosol:

1212 This 1-year open-label non-US study evaluated the safety of ADVAIR HFA 45/21, 115/21, and  
 1213 230/21 given as 2 inhalations twice daily in 325 patients. This study was stratified into 3 groups  
 1214 according to baseline asthma therapy: patients using short-acting beta<sub>2</sub>-agonists alone (n = 42),  
 1215 salmeterol (n = 91), or inhaled corticosteroids (n = 277). Patients treated with short-acting  
 1216 beta<sub>2</sub>-agonists alone, salmeterol, or low doses of inhaled corticosteroids with or without  
 1217 concurrent salmeterol received ADVAIR HFA 45/21. Patients treated with moderate doses of  
 1218 inhaled corticosteroids with or without concurrent salmeterol received ADVAIR HFA 115/21.  
 1219 Patients treated with high doses of inhaled corticosteroids with or without concurrent salmeterol  
 1220 received ADVAIR HFA 230/21. Baseline FEV<sub>1</sub> measurements ranged from 2.3 to 2.6 L.

1221 Improvements in FEV<sub>1</sub> (0.17 to 0.35 L at 4 weeks) were seen across all 3 treatments and  
 1222 were sustained throughout the 52-week treatment period. Few patients (3%) were withdrawn due  
 1223 to worsening asthma over 1 year.

## 1224 14.3 Onset of Action and Progression of Improvement in Control

1225 The onset of action and progression of improvement in asthma control were evaluated in  
 1226 2 placebo-controlled US trials and 1 active-controlled US trial. Following the first dose, the  
 1227 median time to onset of clinically significant bronchodilatation ( $\geq 15\%$  improvement in FEV<sub>1</sub>) in  
 1228 most patients was seen within 30 to 60 minutes. Maximum improvement in FEV<sub>1</sub> occurred  
 1229 within 4 hours, and clinically significant improvement was maintained for 12 hours (see Figure  
 1230 4).

1231 Following the initial dose, predose FEV<sub>1</sub> relative to Day 1 baseline improved markedly  
 1232 over the first week of treatment and continued to improve over the 12 weeks of treatment in all  
 1233 3 studies.

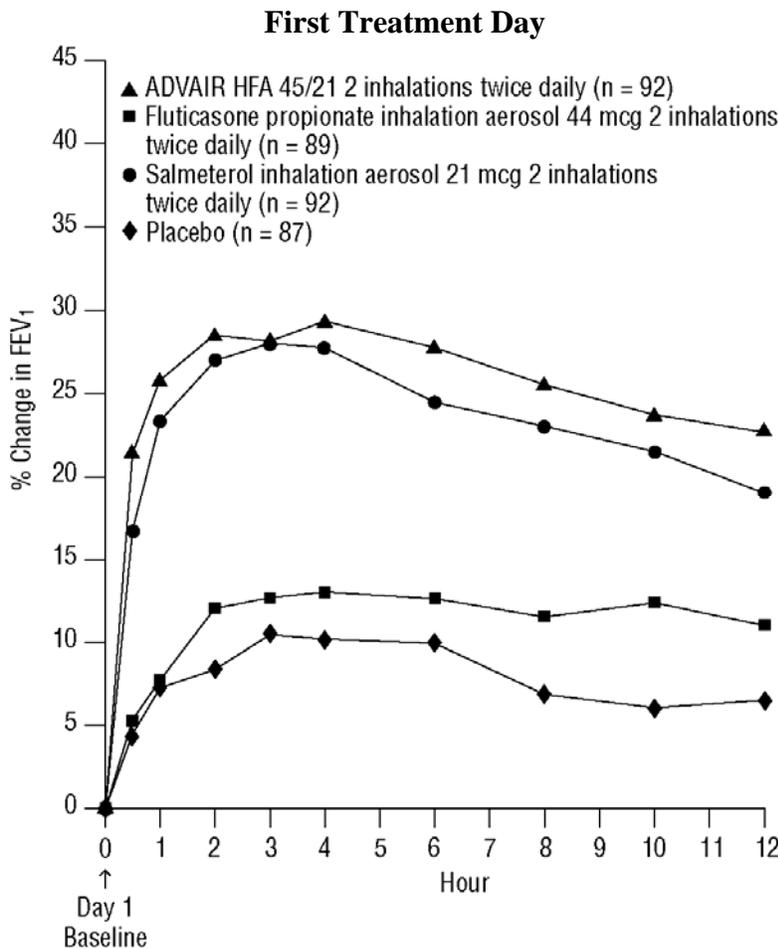
1234 No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR  
 1235 HFA 45/21 (Figures 4 and 5) or ADVAIR HFA 230/21 as assessed by FEV<sub>1</sub> following 12 weeks  
 1236 of therapy.

1237

1238 **Figure 4. Percent Change in Serial 12-Hour FEV<sub>1</sub> in**  
 1239 **Patients Previously Using Either Beta<sub>2</sub>-Agonists (Albuterol**  
 1240 **or Salmeterol) or Inhaled Corticosteroids (Study 1)**

1241

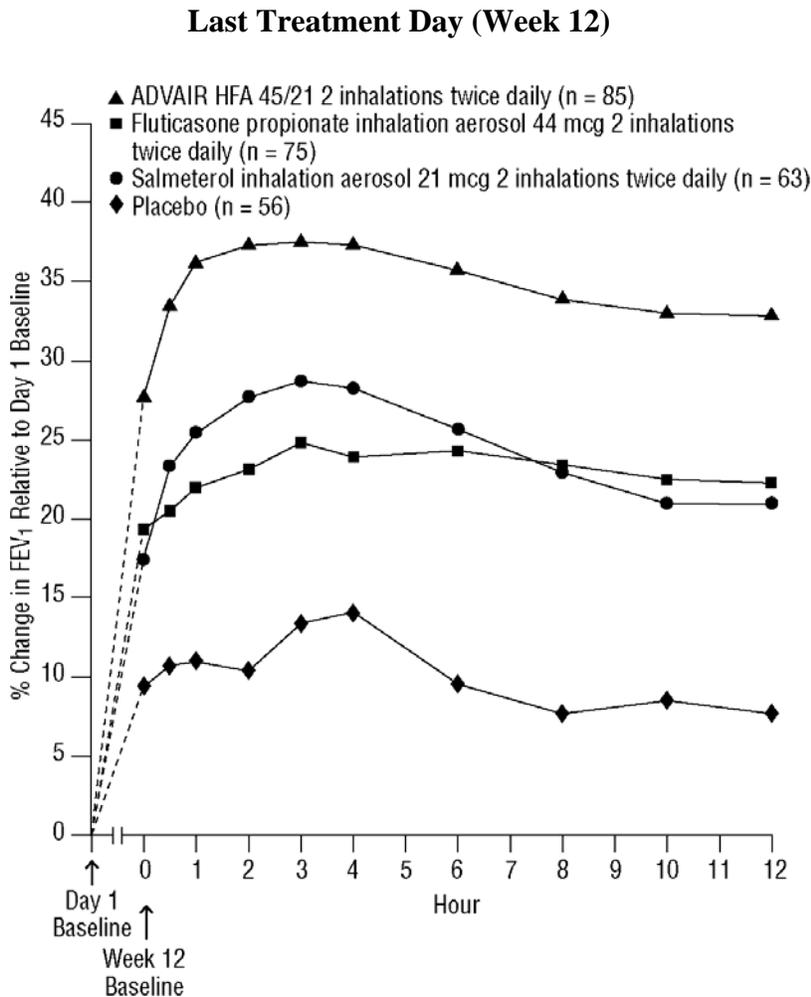
1242



1243

1244  
1245  
1246  
1247  
1248  
1249  
1250

**Figure 5. Percent Change in Serial 12-Hour FEV<sub>1</sub> in Patients Previously Using Either Beta<sub>2</sub>-Agonists (Albuterol or Salmeterol) or Inhaled Corticosteroids (Study 1)**



1251  
1252  
1253  
1254  
1255

Reduction in asthma symptoms and use of rescue VENTOLIN Inhalation Aerosol and improvement in morning and evening PEF also occurred within the first day of treatment with ADVAIR HFA, and continued to improve over the 12 weeks of therapy in all 3 studies.

1256 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1257 ADVAIR HFA 45/21 Inhalation Aerosol is supplied in 12-g pressurized aluminum  
1258 canisters containing 120 metered actuations in boxes of 1 (NDC 0173-0715-20) and 8-g  
1259 pressurized aluminum canisters containing 60 metered actuations in institutional pack boxes of 1  
1260 (NDC 0173-0715-22).

1261 ADVAIR HFA 115/21 Inhalation Aerosol is supplied in 12-g pressurized aluminum  
1262 canisters containing 120 metered actuations in boxes of 1 (NDC 0173-0716-20) and 8-g

1263 pressurized aluminum canisters containing 60 metered actuations in institutional pack boxes of 1  
1264 (NDC 0173-0716-22).

1265         ADVAIR HFA 230/21 Inhalation Aerosol is supplied in 12-g pressurized aluminum  
1266 canisters containing 120 metered actuations in boxes of 1 (NDC 0173-0717-20) and 8-g  
1267 pressurized aluminum canisters containing 60 metered actuations in institutional pack boxes of 1  
1268 (NDC 0173-0717-22).

1269         Each canister is fitted with a counter, supplied with a purple actuator with a light purple  
1270 strapcap, and sealed in a plastic-coated, moisture-protective foil pouch with a desiccant that  
1271 should be discarded when the pouch is opened. Each canister is packaged with a Medication  
1272 Guide leaflet.

1273         The purple actuator supplied with ADVAIR HFA Inhalation Aerosol should not be used  
1274 with any other product canisters, and actuators from other products should not be used with an  
1275 ADVAIR HFA Inhalation Aerosol canister.

1276         The correct amount of medication in each actuation cannot be assured after the counter  
1277 reads 000, even though the canister is not completely empty and will continue to operate. The  
1278 inhaler should be discarded when the counter reads 000.

1279         Keep out of reach of children. Avoid spraying in eyes.

1280         Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame.  
1281 Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or  
1282 incinerator.

1283         Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Store the inhaler with  
1284 the mouthpiece down. For best results, the inhaler should be at room temperature before use.  
1285 SHAKE WELL FOR 5 SECONDS BEFORE USING.

## 1286 **17 PATIENT COUNSELING INFORMATION**

1287         *See FDA-approved patient labeling (Medication Guide).*

### 1288 **17.1 Asthma-Related Death**

1289         **Patients should be informed that salmeterol, one of the active ingredients in**  
1290 **ADVAIR HFA, increases the risk of asthma-related death and may increase the risk of**  
1291 **asthma-related hospitalization in pediatric and adolescent patients. They should also be**  
1292 **informed that currently available data are inadequate to determine whether concurrent**  
1293 **use of inhaled corticosteroids or other long-term asthma control drugs mitigates the**  
1294 **increased risk of asthma-related death from LABAs.**

### 1295 **17.2 Not for Acute Symptoms**

1296         ADVAIR HFA is not meant to relieve acute asthma symptoms, and extra doses should  
1297 not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting  
1298 beta<sub>2</sub>-agonist such as albuterol. The healthcare provider should provide the patient with such  
1299 medication and instruct the patient in how it should be used.

1300         Patients should be instructed to seek medical attention immediately if they experience  
1301 any of the following:

- 1302 • Decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonists  
1303 • Need for more inhalations than usual of inhaled, short-acting beta<sub>2</sub>-agonists  
1304 • Significant decrease in lung function as outlined by the physician  
1305 Patients should not stop therapy with ADVAIR HFA without physician/provider  
1306 guidance since symptoms may recur after discontinuation.

1307 **17.3 Do Not Use Additional Long-Acting Beta<sub>2</sub>-Agonists**

1308 When patients are prescribed ADVAIR HFA, other LABAs for asthma should not be  
1309 used.

1310 **17.4 Risks Associated With Corticosteroid Therapy**

1311 Local Effects: Patients should be advised that localized infections with *Candida albicans*  
1312 occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it  
1313 should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still  
1314 continuing therapy with ADVAIR HFA, but at times therapy with ADVAIR HFA may need to  
1315 be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is  
1316 advised.

1317 Pneumonia: Patients with COPD have a higher risk of pneumonia and should be  
1318 instructed to contact their healthcare provider if they develop symptoms of pneumonia.

1319 Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids  
1320 should be warned to avoid exposure to chickenpox or measles and if they are exposed to consult  
1321 their physicians without delay. Patients should be informed of potential worsening of existing  
1322 tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

1323 Hypercorticism and Adrenal Suppression: Patients should be advised that ADVAIR  
1324 HFA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression.  
1325 Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred  
1326 during and after transfer from systemic corticosteroids. Patients should taper slowly from  
1327 systemic corticosteroids if transferring to ADVAIR HFA.

1328 Reduction in Bone Mineral Density: Patients who are at an increased risk for  
1329 decreased BMD should be advised that the use of corticosteroids may pose an additional risk.

1330 Reduced Growth Velocity: Patients should be informed that orally inhaled  
1331 corticosteroids, including fluticasone propionate, may cause a reduction in growth velocity when  
1332 administered to pediatric patients. Physicians should closely follow the growth of children and  
1333 adolescents taking corticosteroids by any route.

1334 Ocular Effects: Long-term use of inhaled corticosteroids may increase the risk of some  
1335 eye problems (cataracts or glaucoma); regular eye examinations should be considered.

1336 **17.5 Risks Associated With Beta-Agonist Therapy**

1337 Patients should be informed of adverse effects associated with beta<sub>2</sub>-agonists, such as  
1338 palpitations, chest pain, rapid heart rate, tremor, or nervousness.

1339  
1340 ADVAIR, ADVAIR DISKUS, DISKUS, FLOVENT, FLONASE, ROTADISK, SEREVENT,  
1341 and VENTOLIN are registered trademarks of GlaxoSmithKline.

1342 The other brands listed are trademarks of their respective owners and are not trademarks of  
1343 GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse  
1344 GlaxoSmithKline or its products.

1345  
1346



1347  
1348 GlaxoSmithKline  
1349 Research Triangle Park, NC 27709

1350  
1351 ©2012, GlaxoSmithKline. All rights reserved.

1352  
1353 December 2012  
1354 ADH:XPI

1355

---

**PHARMACIST—DETACH HERE AND GIVE MEDICATION GUIDE TO PATIENT**

---

1356

-----  
**MEDICATION GUIDE**

1357

**ADVAIR<sup>®</sup> HFA [*ad' vair*] 45/21 Inhalation Aerosol  
(fluticasone propionate 45 mcg and salmeterol 21 mcg)**

1358

1359

**ADVAIR<sup>®</sup> HFA 115/21 Inhalation Aerosol  
(fluticasone propionate 115 mcg and salmeterol 21 mcg)**

1360

1361

**ADVAIR<sup>®</sup> HFA 230/21 Inhalation Aerosol  
(fluticasone propionate 230 mcg and salmeterol 21 mcg)**

1362

1363

1364

1365 Read the Medication Guide that comes with ADVAIR HFA Inhalation Aerosol before  
1366 you start using it and each time you get a refill. There may be new information.  
1367 This Medication Guide does not take the place of talking to your healthcare provider  
1368 about your medical condition or treatment.

1369

1370 **What is the most important information I should know about ADVAIR HFA?**

1371

**ADVAIR HFA can cause serious side effects, including:**

- 1372 1. **People with asthma who take long-acting beta<sub>2</sub>-adrenergic agonist**  
1373 **(LABA) medicines, such as salmeterol (one of the medicines in ADVAIR**  
1374 **HFA), have an increased risk of death from asthma problems.** It is not  
1375 known whether fluticasone propionate, the other medicine in ADVAIR HFA,  
1376 reduces the risk of death from asthma problems seen with salmeterol.

- 1377 • **Call your healthcare provider if breathing problems worsen over time**  
1378 **while using ADVAIR HFA.** You may need different treatment.
- 1379 • **Get emergency medical care if:**  
1380 • breathing problems worsen quickly and  
1381 • you use your rescue inhaler medicine, but it does not relieve your  
1382 breathing problems.
- 1383 2. ADVAIR HFA should be used only if your healthcare provider decides that your  
1384 asthma is not well controlled with a long-term asthma control medicine, such as  
1385 inhaled corticosteroids.
- 1386 3. When your asthma is well controlled, your healthcare provider may tell you to  
1387 stop taking ADVAIR HFA. Your healthcare provider will decide if you can stop  
1388 ADVAIR HFA without loss of asthma control. Your healthcare provider may  
1389 prescribe a different long-term asthma control medicine for you, such as an  
1390 inhaled corticosteroid.
- 1391 4. Children and adolescents who take LABA medicines may have an increased risk  
1392 of being hospitalized for asthma problems.

1393

#### 1394 **What is ADVAIR HFA?**

- 1395 • ADVAIR HFA combines an inhaled corticosteroid medicine, fluticasone propionate  
1396 (the same medicine found in FLOVENT<sup>®</sup>), and a LABA medicine, salmeterol (the  
1397 same medicine found in SEREVENT<sup>®</sup>).
- 1398 • Inhaled corticosteroids help to decrease inflammation in the lungs.  
1399 Inflammation in the lungs can lead to asthma symptoms.
- 1400 • LABA medicines are used in people with asthma and chronic obstructive  
1401 pulmonary disease (COPD). LABA medicines help the muscles around the  
1402 airways in your lungs stay relaxed to prevent symptoms, such as wheezing  
1403 and shortness of breath. These symptoms can happen when the muscles  
1404 around the airways tighten. This makes it hard to breathe. In severe cases,  
1405 wheezing can stop your breathing and cause death if not treated right away.
- 1406 • ADVAIR HFA is used to control symptoms of asthma and to prevent symptoms  
1407 such as wheezing in adults and adolescents aged 12 years and older.
- 1408 • ADVAIR HFA should not be used as a rescue inhaler.
- 1409 • ADVAIR HFA contains salmeterol (the same medicine found in SEREVENT). LABA  
1410 medicines, such as salmeterol, increase the risk of death from asthma problems.

1411 ADVAIR HFA is not for adults and adolescents with asthma who are well controlled  
1412 with an asthma control medicine, such as a low to medium dose of an inhaled  
1413 corticosteroid medicine.

1414

#### 1415 **Who should not use ADVAIR HFA?**

1416 Do not use ADVAIR HFA:

- 1417 • to treat sudden, severe symptoms of asthma and
- 1418 • if you are allergic to any of the ingredients in ADVAIR HFA. See the end of this  
1419 Medication Guide for a list of ingredients in ADVAIR HFA.

1420

#### 1421 **What should I tell my healthcare provider before using ADVAIR HFA?**

1422 **Tell your healthcare provider about all of your health conditions, including**  
1423 **if you:**

- 1424 • **have heart problems**
- 1425 • **have high blood pressure**
- 1426 • **have seizures**
- 1427 • **have thyroid problems**
- 1428 • **have diabetes**
- 1429 • **have liver problems**
- 1430 • **have osteoporosis**
- 1431 • **have an immune system problem**
- 1432 • **have eye problems such as increased pressure in the eye (glaucoma) or**  
1433 **cataracts**
- 1434 • **are pregnant or planning to become pregnant.** It is not known if ADVAIR  
1435 HFA may harm your unborn baby.
- 1436 • **are breastfeeding.** It is not known if ADVAIR HFA passes into your milk and if  
1437 it can harm your baby.
- 1438 • **are allergic to ADVAIR HFA or any other medicines**
- 1439 • **are exposed to chickenpox or measles**

1440 Tell your healthcare provider about all the medicines you take including prescription  
1441 and non-prescription medicines, vitamins, and herbal supplements. ADVAIR HFA  
1442 and certain other medicines may interact with each other. This may cause serious  
1443 side effects. Especially, tell your healthcare provider if you take ritonavir. The anti-  
1444 HIV medicines NORVIR<sup>®</sup> (ritonavir capsules) Soft Gelatin, NORVIR (ritonavir oral  
1445 solution), and KALETRA<sup>®</sup> (lopinavir/ritonavir) Tablets contain ritonavir.

1446 Know the medicines you take. Keep a list and show it to your healthcare provider  
1447 and pharmacist each time you get a new medicine.

1448

1449 **How do I use ADVAIR HFA?**

1450 **See the step-by-step instructions for using ADVAIR HFA at the end of this**  
1451 **Medication Guide.** Do not use ADVAIR HFA unless your healthcare provider has  
1452 taught you and you understand everything. Ask your healthcare provider or  
1453 pharmacist if you have any questions.

- 1454 • Use ADVAIR HFA exactly as prescribed. **Do not use ADVAIR HFA more often**  
1455 **than prescribed.** ADVAIR HFA comes in 3 strengths. Your healthcare provider  
1456 has prescribed the one that is best for your condition.
- 1457 • The usual dosage of ADVAIR HFA is 2 inhalations 2 times each day (morning and  
1458 evening). The 2 doses should be about 12 hours apart. Rinse your mouth with  
1459 water after using ADVAIR HFA.
- 1460 • If you take more ADVAIR HFA than your doctor has prescribed, get medical help  
1461 right away if you have any unusual symptom, such as worsening shortness of  
1462 breath, chest pain, increased heart rate, or shakiness.
- 1463 • If you miss a dose of ADVAIR HFA, just skip that dose. Take your next dose at  
1464 your usual time. Do not take 2 doses at one time.
- 1465 • **While you are using ADVAIR HFA 2 times each day, do not use other**  
1466 **medicines that contain a LABA for any reason.** Ask your healthcare provider  
1467 or pharmacist if any of your other medicines are LABA medicines.
- 1468 • Do not stop using ADVAIR HFA or other asthma medicines unless told to do so  
1469 by your healthcare provider because your symptoms might get worse. Your  
1470 healthcare provider will change your medicines as needed.
- 1471 • ADVAIR HFA does not relieve sudden symptoms. Always have a rescue inhaler  
1472 medicine with you to treat sudden symptoms. If you do not have a short-acting  
1473 bronchodilator rescue inhaler, call your healthcare provider to have one  
1474 prescribed for you.
- 1475 • Call your healthcare provider or get medical care right away if:
  - 1476 • your breathing problems worsen with ADVAIR HFA
  - 1477 • you need to use your rescue inhaler medicine more often than usual
  - 1478 • your rescue inhaler medicine does not work as well for you at relieving  
1479 symptoms
  - 1480 • you need to use 4 or more inhalations of your rescue inhaler medicine for 2  
1481 or more days in a row
  - 1482 • you use 1 whole canister of your rescue inhaler medicine in 8 weeks' time
  - 1483 • your peak flow meter results decrease. Your healthcare provider will tell you  
1484 the numbers that are right for you.

- 1485 • your asthma symptoms do not improve after using ADVAIR HFA regularly for  
1486 1 week

1487

1488 **What are the possible side effects with ADVAIR HFA?**

1489 **ADVAIR HFA can cause serious side effects, including:**

- 1490 • **See “What is the most important information I should know about**  
1491 **ADVAIR HFA?”**

- 1492 • **serious allergic reactions.** Call your healthcare provider or get emergency  
1493 medical care if you get any of the following symptoms of a serious allergic  
1494 reaction:

- 1495 • rash
- 1496 • hives
- 1497 • swelling of the face, mouth, and tongue
- 1498 • breathing problems

- 1499 • **sudden breathing problems immediately after inhaling your medicine**

- 1500 • **effects on heart**

- 1501 • increased blood pressure
- 1502 • a fast and irregular heartbeat
- 1503 • chest pain

- 1504 • **effects on nervous system**

- 1505 • tremor
- 1506 • nervousness

- 1507 • **reduced adrenal function (may result in loss of energy)**

- 1508 • **changes in blood (sugar, potassium, certain types of white blood cells)**

- 1509 • **weakened immune system and a higher chance of infections**

- 1510 • **lower bone mineral density.** This may be a problem for people who already  
1511 have a higher chance of low bone density (osteoporosis).

- 1512 • **eye problems including glaucoma and cataracts.** You should have regular  
1513 eye exams while using ADVAIR HFA.

- 1514 • **slowed growth in children.** A child’s growth should be checked often.

- 1515 • **throat tightness**

- 1516 • **pneumonia.** ADVAIR HFA contains the same medicine found in ADVAIR  
1517 DISKUS<sup>®</sup>. ADVAIR DISKUS is used to treat people with asthma and people with  
1518 chronic obstructive pulmonary disease (COPD). People with COPD have a higher  
1519 chance of getting pneumonia. ADVAIR DISKUS may increase the chance of

1520 getting pneumonia. ADVAIR HFA has not been studied in people with COPD. Call  
1521 your healthcare provider if you notice any of the following symptoms:  
1522 • increase in mucus (sputum) production  
1523 • change in mucus color  
1524 • fever  
1525 • chills  
1526 • increased cough  
1527 • increased breathing problems

1528 **Common side effects of ADVAIR HFA include:**

- 1529 • upper respiratory tract infection
- 1530 • throat irritation
- 1531 • hoarseness and voice changes
- 1532 • headache
- 1533 • dizziness
- 1534 • nausea and vomiting

1535 Tell your healthcare provider about any side effect that bothers you or that does  
1536 not go away.

1537 These are not all the side effects with ADVAIR HFA. Ask your healthcare provider or  
1538 pharmacist for more information.

1539 Call your doctor for medical advice about side effects. You may report side effects  
1540 to FDA at 1-800-FDA-1088.

1541

1542 **How do I store ADVAIR HFA?**

- 1543 • Store ADVAIR HFA at room temperature between 59°F to 86°F (15°C to 30°C),  
1544 with the mouthpiece down.
- 1545 • **Contents Under Pressure:** Do not puncture. Do not use or store near heat or  
1546 open flame. Exposure to temperatures above 120°F may cause bursting.
- 1547 • Do not throw into fire or an incinerator.
- 1548 • Keep ADVAIR HFA and all medicines out of the reach of children.

1549

1550 **General Information about ADVAIR HFA**

1551 Medicines are sometimes prescribed for purposes not mentioned in a Medication  
1552 Guide. Do not use ADVAIR HFA for a condition for which it was not prescribed. Do  
1553 not give your ADVAIR HFA to other people, even if they have the same condition  
1554 that you have. It may harm them.

1555 This Medication Guide summarizes the most important information about ADVAIR  
1556 HFA. If you would like more information, talk with your healthcare provider or  
1557 pharmacist. You can ask your healthcare provider or pharmacist for information  
1558 about ADVAIR HFA that was written for healthcare professionals. You can also  
1559 contact the company that makes ADVAIR HFA (toll free) at 1-888-825-5249 or at  
1560 www.advair.com.

1561

## 1562 **What are the ingredients in ADVAIR HFA?**

1563 Active ingredients: fluticasone propionate, salmeterol xinafoate

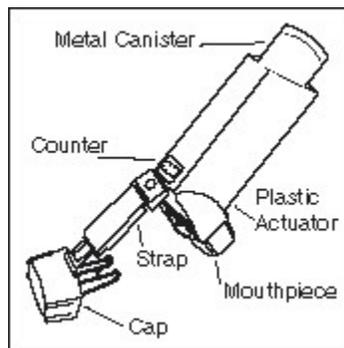
1564 Inactive ingredient: propellant HFA-134a

1565

## 1566 **Instructions for using your ADVAIR HFA**

### 1567 **The parts of your ADVAIR HFA**

1568



1569

1570

**Figure 1**

1571 There are 2 main parts to your ADVAIR HFA  
1572 inhaler—the metal canister that holds the medicine  
1573 and the purple plastic actuator that sprays the  
1574 medicine from the canister (see Figure 1).

1575 The canister has a counter to show how many  
1576 sprays of medicine you have left. The number  
1577 shows through a window in the back of the  
1578 actuator. The counter starts at 124, or at 064 if  
1579 you have a sample or institutional canister. The  
1580 number will count down by 1 each time you spray  
1581 the inhaler. The counter will stop counting at 000.

1582 **Never try to change the numbers or take the counter off the metal**  
1583 **canister.** The counter cannot be reset, and it is permanently attached to the  
1584 canister.

1585 The mouthpiece of the actuator is covered by a cap. The strap on the cap keeps  
1586 it attached to the actuator.

1587 **Do not use the actuator with a canister of medicine from any other**  
1588 **inhaler. Do not use an ADVAIR HFA canister with an actuator from any**  
1589 **other inhaler.**

### 1590 **Using your ADVAIR HFA**

1591 • The inhaler should be at room temperature before you use it.

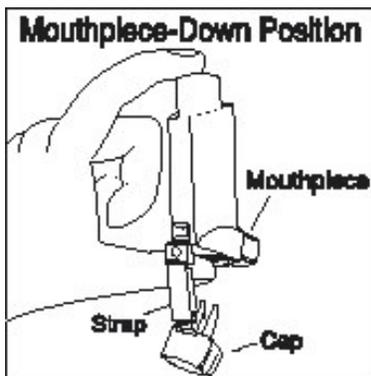
- 1592 • Take your ADVAIR HFA inhaler out of the moisture-protective pouch just before  
1593 you use it for the first time. Safely throw away the foil pouch and the drying  
1594 packet that comes inside the pouch.

1595 **Priming your ADVAIR HFA**

1596 **Before you use ADVAIR HFA for the first time, you must prime the**  
1597 **inhaler so that you will get the right amount of medicine when you use it.**  
1598 To prime the inhaler, take the cap off the mouthpiece and shake the inhaler well for  
1599 5 seconds. Then spray the inhaler 1 time into the air away from your face. **Avoid**  
1600 **spraying in eyes.** Shake and spray the inhaler like this 3 more times to finish  
1601 priming it. The counter should now read 120, or 060 if you have a sample or  
1602 institutional canister.

1603 You must prime your inhaler again if you have not used it in more than 4 weeks  
1604 or if you drop it. Take the cap off the mouthpiece, shake the inhaler well for 5  
1605 seconds. Then spray it into the air away from your face. Shake and spray the  
1606 inhaler like this 1 more time to finish priming it.

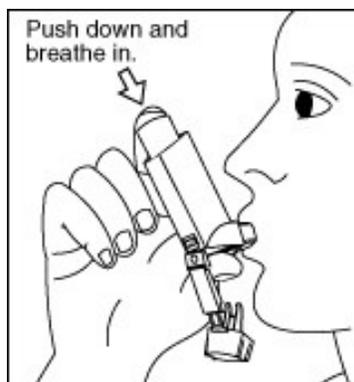
1607 Read the following 7 steps before using ADVAIR HFA and follow them at each  
1608 use. If you have any questions, ask your doctor or pharmacist.



1609  
1610

**Figure 2**

- 1611 1. **Take the cap off the mouthpiece of the**  
1612 **actuator** (see Figure 2).  
1613 Look inside the mouthpiece for foreign objects,  
1614 and take out any you see.  
1615 Make sure the canister fits firmly in the actuator.  
1616 **Shake the inhaler well** for 5 seconds.  
1617 2. Hold the inhaler with the mouthpiece down (see  
1618 Figure 2).  
1619 **Breathe out through your mouth** and push as  
1620 much air from your lungs as you can. Put the  
1621 mouthpiece in your mouth and close your lips  
1622 around it.



**Figure 3**

- 1625 3. **Push the top of the canister all the way**  
 1626 **down while you breathe in deeply and**  
 1627 **slowly through your mouth** (see Figure 3).

1628 Right after the spray comes out, take your finger  
 1629 off the canister. After you have breathed in all  
 1630 the way, take the inhaler out of your mouth and  
 1631 close your mouth.

- 1632 4. **Hold your breath as long as you can**, up to  
 1633 10 seconds, then breathe normally.

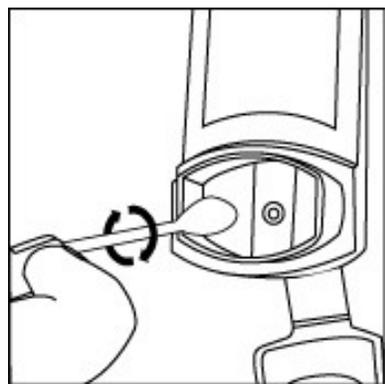
- 1634 5. **Wait about 30 seconds and shake the inhaler** well for 5 seconds. Repeat  
 1635 steps 2 through 4.

1636 6. After you finish taking this medicine, rinse your mouth with water. Spit out the  
 1637 water. Do not swallow it.

1638 7. Put the cap back on the mouthpiece after every time you use the inhaler. Make  
 1639 sure it snaps firmly into place.

### **Cleaning your ADVAIR HFA**

1640 Clean your inhaler at least 1 time each week after your evening dose. It is  
 1641 important to keep the canister and plastic actuator clean so the medicine will not  
 1642 build-up and block the spray.  
 1643



**Figure 4**

- 1646 1. Take the cap off the mouthpiece. The strap on  
 1647 the cap will stay attached to the actuator. Do not  
 1648 take the canister out of the plastic actuator.

1649 2. Use a dry cotton swab to clean the small circular  
 1650 opening where the medicine sprays out of the  
 1651 canister. Carefully twist the swab in a circular  
 1652 motion to take off any medicine (see Figure 4).

1653 3. Wipe the inside of the mouthpiece with a clean  
 1654 tissue dampened with water. Let the actuator  
 1655 air-dry overnight.

1656 4. Put the cap back on the mouthpiece after the  
 1657 actuator has dried.

### **Replacing your ADVAIR HFA**

- 1660 • **When the counter reads 020**, you should refill your prescription or ask your  
 1661 doctor if you need another prescription for ADVAIR HFA.

- 1662 • **When the counter reads 000, throw the inhaler away.** You should not keep  
1663 using the inhaler when the counter reads 000 because you will not receive the  
1664 right amount of medicine.  
1665 • **Do not use the inhaler** after the expiration date, which is on the packaging it  
1666 comes in.

1667  
1668 **This Medication Guide has been approved by the U.S. Food and Drug**  
1669 **Administration.**

1670  
1671 ADAIR, ADAIR DISKUS, FLOVENT, and SEREVENT are registered trademarks of  
1672 GlaxoSmithKline. The other brands listed are trademarks of their respective owners  
1673 and are not trademarks of GlaxoSmithKline. The makers of these brands are not  
1674 affiliated with and do not endorse GlaxoSmithKline or its products.

1675  
1676



1677  
1678 GlaxoSmithKline  
1679 Research Triangle Park, NC 27709

1680  
1681 ©2012, GlaxoSmithKline. All rights reserved.

1682  
1683 December 2012  
1684 ADH: XMG