

PRESCRIBING INFORMATION

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2 **FLOVENT<sup>®</sup> HFA 44 mcg**  
3 **(fluticasone propionate 44 mcg)**  
4 **Inhalation Aerosol**

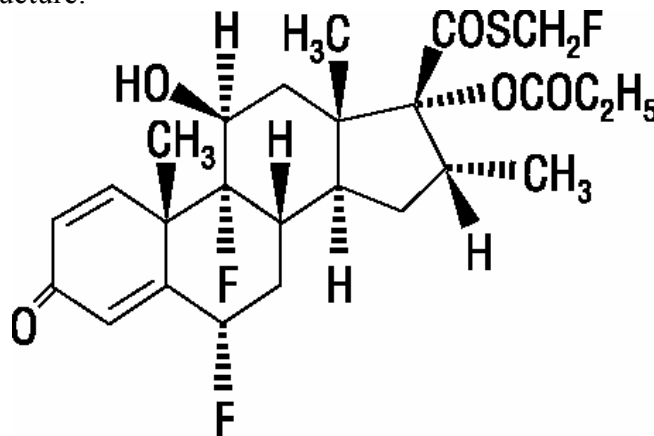
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6 **FLOVENT<sup>®</sup> HFA 110 mcg**  
7 **(fluticasone propionate 110 mcg)**  
8 **Inhalation Aerosol**

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10 **FLOVENT<sup>®</sup> HFA 220 mcg**  
11 **(fluticasone propionate 220 mcg)**  
12 **Inhalation Aerosol**

13  
14 **For Oral Inhalation Only**

15 **DESCRIPTION**

16 The active component of FLOVENT HFA 44 mcg Inhalation Aerosol, FLOVENT HFA  
17 110 mcg Inhalation Aerosol, and FLOVENT HFA 220 mcg Inhalation Aerosol is fluticasone  
18 propionate, a corticosteroid having the chemical name *S*-(fluoromethyl) 6 $\alpha$ ,9-difluoro-11 $\beta$ ,17-  
19 dihydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioate, 17-propionate and the  
20 following chemical structure:



21  
22  
23 Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and  
24 the empirical formula is C<sub>25</sub>H<sub>31</sub>F<sub>3</sub>O<sub>5</sub>S. It is practically insoluble in water, freely soluble in  
25 dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

26 FLOVENT HFA 44 mcg Inhalation Aerosol, FLOVENT HFA 110 mcg Inhalation Aerosol,  
27 and FLOVENT HFA 220 mcg Inhalation Aerosol are pressurized metered-dose aerosol units  
28 fitted with a counter. FLOVENT HFA is intended for oral inhalation only. Each unit contains a

29 microcrystalline suspension of fluticasone propionate (micronized) in propellant HFA-134a  
30 (1,1,1,2-tetrafluoroethane). It contains no other excipients.

31 After priming, each actuation of the inhaler delivers 50, 125, or 250 mcg of fluticasone  
32 propionate in 60 mg of suspension (for the 44-mcg product) or in 75 mg of suspension (for the  
33 110- and 220-mcg products) from the valve. Each actuation delivers 44, 110, or 220 mcg of  
34 fluticasone propionate from the actuator. The actual amount of drug delivered to the lung may  
35 depend on patient factors, such as the coordination between the actuation of the device and  
36 inspiration through the delivery system.

37 Each 10.6-g canister (44 mcg) and each 12-g canister (110 and 220 mcg) provides  
38 120 inhalations.

39 FLOVENT HFA should be primed before using for the first time by releasing 4 test sprays  
40 into the air away from the face, shaking well for 5 seconds before each spray. In cases where the  
41 inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler  
42 again by shaking well for 5 seconds before each spray and releasing 1 test spray into the air away  
43 from the face.

44 This product does not contain any chlorofluorocarbon (CFC) as the propellant.

## 45 **CLINICAL PHARMACOLOGY**

46 **Mechanism of Action:** Fluticasone propionate is a synthetic trifluorinated corticosteroid with  
47 potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have  
48 established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18  
49 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate  
50 (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of  
51 budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these  
52 results. The clinical significance of these findings is unknown.

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

58 Though effective for the treatment of asthma, corticosteroids do not affect asthma symptoms  
59 immediately. Individual patients will experience a variable time to onset and degree of symptom  
60 relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment.  
61 When corticosteroids are discontinued, asthma stability may persist for several days or longer.

62 Studies in patients with asthma have shown a favorable ratio between topical  
63 anti-inflammatory activity and systemic corticosteroid effects with recommended doses of orally  
64 inhaled fluticasone propionate. This is explained by a combination of a relatively high local  
65 anti-inflammatory effect, negligible oral systemic bioavailability (<1%), and the minimal  
66 pharmacological activity of the only metabolite detected in man.

67 **Preclinical:** In animals and humans, propellant HFA-134a was found to be rapidly absorbed and  
68 rapidly eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to 7 minutes  
69 in humans. Time to maximum plasma concentration ( $T_{max}$ ) and mean residence time are both  
70 extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of  
71 accumulation.

72 Propellant HFA-134a is devoid of pharmacological activity except at very high doses in  
73 animals (i.e., 380 to 1,300 times the maximum human exposure based on comparisons of area  
74 under the plasma concentration versus time curve [AUC] values), primarily producing ataxia,  
75 tremors, dyspnea, or salivation. These events are similar to effects produced by the structurally  
76 related CFCs, which have been used extensively in metered-dose inhalers.

77 **Pharmacokinetics: Absorption:** Fluticasone propionate acts locally in the lung; therefore,  
78 plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and  
79 unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate  
80 is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the  
81 gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is  
82 systemically absorbed. Systemic exposure as measured by AUC in healthy subjects (N = 24)  
83 who received 8 inhalations, as a single dose, of fluticasone propionate HFA using the 44-, 110-,  
84 and 220-mcg strengths increased proportionally with dose. The geometric means (95% CI) of  
85  $AUC_{0-24\text{ hr}}$  for the 44-, 110-, and 220-mcg strengths were 488 (362, 657); 1,284 (904; 1,822); and  
86 2,495 (1,945; 3,200)  $\text{pg}\cdot\text{hr}/\text{mL}$ , respectively, and the geometric means of  $C_{max}$  were 126 (108,  
87 148), 254 (202, 319), and 421 (338, 524)  $\text{pg}/\text{mL}$ , respectively. Systemic exposure from  
88 fluticasone propionate HFA 220 mcg was 30% lower than that from the fluticasone propionate  
89 CFC inhaler. Systemic exposure was measured in patients with asthma who received 2  
90 inhalations of fluticasone propionate HFA 44 mcg (n = 20), 110 mcg (n = 15), or 220 mcg  
91 (n = 17) twice daily for at least 4 weeks. The geometric means (95% CI) of  $AUC_{0-12\text{ hr}}$  for the  
92 44-, 110-, and 220-mcg strengths were 76 (33, 175), 298 (191, 464), and 601 (431, 838)  
93  $\text{pg}\cdot\text{hr}/\text{mL}$ , respectively.  $C_{max}$  occurred in about 1 hour, and the geometric means were 25 (18,  
94 36), 61 (46, 81), and 103 (73, 145)  $\text{pg}/\text{mL}$ , respectively.

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

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

101 **Metabolism:** The total clearance of fluticasone propionate is high (average, 1,093 mL/min),  
102 with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite  
103 detected in man is the  $17\beta$ -carboxylic acid derivative of fluticasone propionate, which is formed  
104 through the cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately  
105 1/2,000) than the parent drug for the corticosteroid receptor of human lung cytosol in vitro and

106 negligible pharmacological activity in animal studies. Other metabolites detected in vitro using  
107 cultured human hepatoma cells have not been detected in man.

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

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

116 **Pediatric:** Two pharmacokinetic studies evaluated the systemic exposure to fluticasone  
117 propionate at steady state in children with asthma aged 4 to 11 years following inhalation of  
118 fluticasone propionate HFA. In an open-label, multiple-dose, 2-period crossover study, 13  
119 children aged 4 to 11 years received 88 mcg of fluticasone propionate HFA twice daily for  
120 7.5 days in one period and 88 mcg of fluticasone propionate CFC twice daily for 7.5 days in the  
121 other period. The geometric means (95% CI) of  $AUC_{(last)}$  were 28 pg•hr/mL (10, 80) following  
122 fluticasone propionate HFA and 65 pg•hr/mL (27, 153) following fluticasone propionate CFC,  
123 indicating that systemic exposure was 55% lower using fluticasone propionate HFA. The  
124 geometric means (95% CI) of  $C_{max}$  were 15.1 pg/mL (8.5, 27) following fluticasone propionate  
125 HFA and 20.4 pg/mL (13, 32) following fluticasone propionate CFC; indicating that  $C_{max}$  was  
126 26% lower using fluticasone propionate HFA.  $T_{max}$  was similar for both treatments.  $AUC_{last}$  and  
127  $C_{max}$  in this pediatric population were 37% and 60%, respectively, of those in adult patients  
128 receiving the same dose.

129 In a second open-label, single-dose, 2-period crossover study, 21 children with asthma aged 5  
130 to 11 years received 264 mcg of fluticasone propionate HFA administered with and without an  
131 AeroChamber Plus™ Valved Holding Chamber (VHC). The geometric means (95% CI) of  
132  $AUC_{last}$  were 261 pg•hr/mL (252, 444) with the use of the VHC and 40 pg•hr/mL (16, 208)  
133 without the VHC. The geometric means (95% CI) of  $C_{max}$  were 52 pg/mL (46, 70) with the VHC  
134 and 19 pg/mL (17, 41) without the VHC. The median  $T_{max}$  was 1 hour with or without the VHC.  
135 Therefore, systemic exposure was higher with the VHC in these pediatric patients with asthma.

136 **Gender:** In 19 male and 33 female patients with asthma, systemic exposure was similar  
137 from 2 inhalations of fluticasone propionate CFC 44, 110, and 220 mcg twice daily.

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

140 **Drug Interactions:** Fluticasone propionate is a substrate of cytochrome P450 3A4.  
141 Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor  
142 ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18  
143 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was  
144 coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate  
145 concentrations following fluticasone propionate aqueous nasal spray alone were undetectable

146 (<10 pg/mL) in most subjects, and when concentrations were detectable, peak levels ( $C_{max}$ )  
147 averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and  $AUC_{(0-\tau)}$  averaged 8.43 pg•hr/mL (range,  
148 4.2 to 18.8 pg•hr/mL). Fluticasone propionate  $C_{max}$  and  $AUC_{(0-\tau)}$  increased to 318 pg/mL (range,  
149 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively,  
150 after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This  
151 significant increase in plasma fluticasone propionate exposure resulted in a significant decrease  
152 (86%) in serum cortisol AUC.

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

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

161 Similar definitive studies with fluticasone propionate HFA were not performed, but results  
162 should be independent of the formulation and drug delivery device.

163 **Pharmacodynamics:** Serum cortisol concentrations, urinary excretion of cortisol, and urine  
164 6- $\beta$ -hydroxycortisol excretion collected over 24 hours in 24 healthy subjects following  
165 8 inhalations of fluticasone propionate HFA 44, 110, and 220 mcg decreased with increasing  
166 dose. However, in patients with asthma treated with 2 inhalations of fluticasone propionate HFA  
167 44, 110, and 220 mcg twice daily for at least 4 weeks, differences in serum cortisol  $AUC_{(0-12\text{ hr})}$   
168 concentrations (n = 65) and 24-hour urinary excretion of cortisol (n = 47) compared with  
169 placebo were not related to dose and generally not significant. In the study with healthy  
170 volunteers, the effect of propellant was also evaluated by comparing results following the  
171 220-mcg strength inhaler containing HFA 134a propellant with the same strength of inhaler  
172 containing CFC 11/12 propellant. A lesser effect on the hypothalamic-pituitary-adrenal (HPA)  
173 axis with the HFA formulation was observed for serum cortisol, but not urine cortisol and  
174 6-betahydroxy cortisol excretion. In addition, in a crossover study of children with asthma aged  
175 4 to 11 years (N = 40), 24-hour urinary excretion of cortisol was not affected after a 4-week  
176 treatment period with 88 mcg of fluticasone propionate HFA twice daily compared with urinary  
177 excretion after the 2-week placebo period. The ratio (95% CI) of urinary excretion of cortisol  
178 over 24 hours following fluticasone propionate HFA versus placebo was 0.987 (0.796, 1.223).

179 The potential systemic effects of fluticasone propionate HFA on the HPA axis were also  
180 studied in patients with asthma. Fluticasone propionate given by inhalation aerosol at dosages of  
181 440 or 880 mcg twice daily was compared with placebo in oral corticosteroid-dependent patients  
182 with asthma (range of mean dose of prednisone at baseline, 13 to 14 mg/day) in a 16-week study.  
183 Consistent with maintenance treatment with oral corticosteroids, abnormal plasma cortisol  
184 responses to short cosyntropin stimulation (peak plasma cortisol <18 mcg/dL) were present at  
185 baseline in the majority of patients participating in this study (69% of patients later randomized

186 to placebo and 72% to 78% of patients later randomized to fluticasone propionate HFA). At  
187 week 16, 8 patients (73%) on placebo compared to 14 (54%) and 13 (68%) patients receiving  
188 fluticasone propionate HFA (440 and 880 mcg b.i.d., respectively) had post-stimulation cortisol  
189 levels of <18 mcg/dL.

190 To confirm that systemic absorption does not play a role in the clinical response to inhaled  
191 fluticasone propionate, a double-blind clinical study comparing inhaled fluticasone propionate  
192 powder and oral fluticasone propionate was conducted. Fluticasone propionate inhalation powder  
193 in dosages of 100 and 500 mcg twice daily was compared to oral fluticasone propionate  
194 20,000 mcg once daily and placebo for 6 weeks. Plasma levels of fluticasone propionate were  
195 detectable in all 3 active groups, but the mean values were highest in the oral group. Both  
196 dosages of inhaled fluticasone propionate were effective in maintaining asthma stability and  
197 improving lung function, while oral fluticasone propionate and placebo were ineffective. This  
198 demonstrates that the clinical effectiveness of inhaled fluticasone propionate is due to its direct  
199 local effect and not to an indirect effect through systemic absorption.

## 200 **CLINICAL TRIALS**

201 **Adolescent and Adult Patients:** Three randomized, double-blind, parallel-group,  
202 placebo-controlled clinical trials were conducted in the US in 980 adolescent and adult patients  
203 ( $\geq 12$  years of age) with asthma to assess the efficacy and safety of FLOVENT HFA in the  
204 treatment of asthma. Fixed dosages of 88, 220, and 440 mcg twice daily (each dose administered  
205 as 2 inhalations of the 44-, 110-, and 220-mcg strengths, respectively) and 880 mcg twice daily  
206 (administered as 4 inhalations of the 220-mcg strength) were compared with placebo to provide  
207 information about appropriate dosing to cover a range of asthma severity. Patients in these  
208 studies included those inadequately controlled with bronchodilators alone (Study 1), those  
209 already receiving inhaled corticosteroids (Study 2), and those requiring oral corticosteroid  
210 therapy (Study 3). In all 3 studies, patients (including placebo-treated patients) were allowed to  
211 use VENTOLIN<sup>®</sup> (albuterol, USP) Inhalation Aerosol as needed for relief of acute asthma  
212 symptoms. In Studies 1 and 2, other maintenance asthma therapies were discontinued.

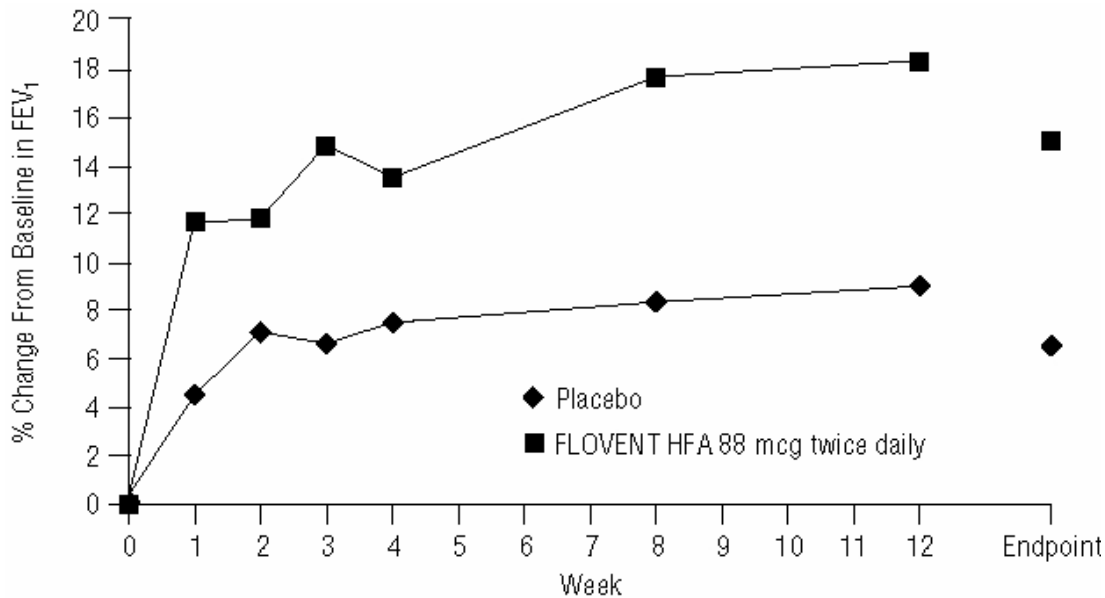
213 Study 1 enrolled 397 patients with asthma inadequately controlled on bronchodilators alone.  
214 FLOVENT HFA was evaluated at dosages of 88, 220, and 440 mcg twice daily for 12 weeks.  
215 Baseline FEV<sub>1</sub> values were similar across groups (mean 67% of predicted normal). All 3 dosages  
216 of FLOVENT HFA significantly improved asthma control as measured by improvement in AM  
217 pre-dose FEV<sub>1</sub> compared with placebo. Pulmonary function (AM pre-dose FEV<sub>1</sub>) improved  
218 significantly with FLOVENT HFA compared with placebo after the first week of treatment, and  
219 this improvement was maintained over the 12-week treatment period.

220 At Endpoint (last observation), mean change from baseline in AM pre-dose percent predicted  
221 FEV<sub>1</sub> was greater in all 3 groups treated with FLOVENT HFA (9.0% to 11.2%) compared with  
222 the placebo group (3.4%). The mean differences between the groups treated with  
223 FLOVENT HFA 88, 220, and 440 mcg and the placebo group were significant, and the

224 corresponding 95% confidence intervals were (2.2%, 9.2%), (2.8%, 9.9%), and (4.3%, 11.3%),  
225 respectively.

226 Figure 1 displays results of pulmonary function tests (mean percent change from baseline in  
227 FEV<sub>1</sub> prior to AM dose) for the recommended starting dosage of FLOVENT HFA (88 mcg twice  
228 daily) and placebo from Study 1. This trial used predetermined criteria for lack of efficacy  
229 (indicators of worsening asthma), resulting in withdrawal of more patients in the placebo group.  
230 Therefore, pulmonary function results at Endpoint (the last evaluable FEV<sub>1</sub> result, including  
231 most patients' lung function data) are also displayed.  
232

233 **Figure 1. A 12-Week Clinical Trial in Patients ≥12 Years of Age Inadequately**  
234 **Controlled on Bronchodilators Alone: Mean Percent Change From Baseline in**  
235 **FEV<sub>1</sub> Prior to AM Dose (Study 1)**  
236



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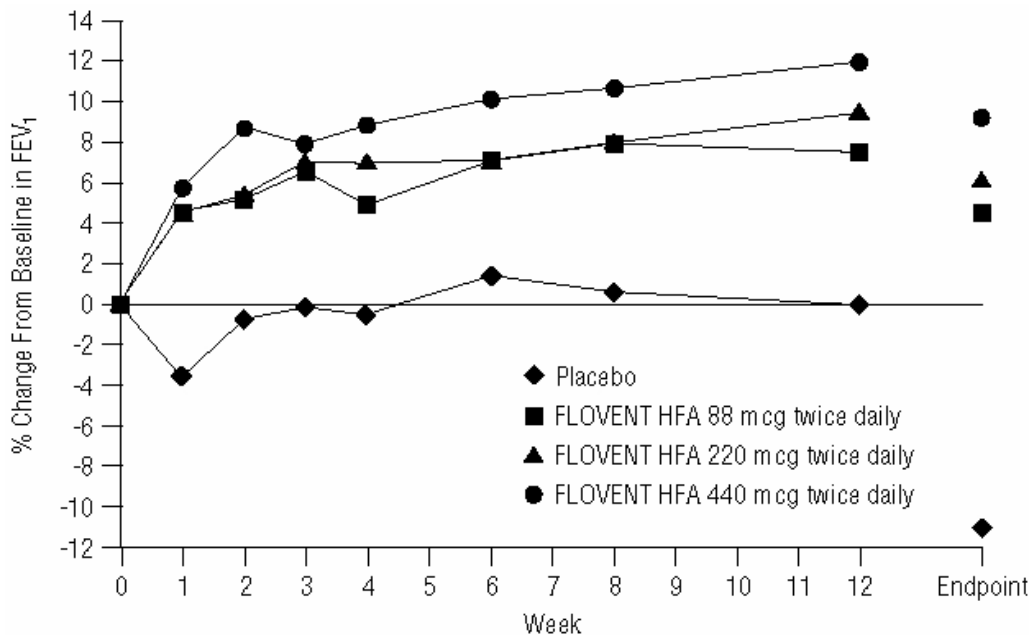
239 In Study 2, FLOVENT HFA at dosages of 88, 220, and 440 mcg twice daily was evaluated  
240 over 12 weeks of treatment in 415 patients with asthma who were already receiving an inhaled  
241 corticosteroid at a daily dose within its recommended dose range in addition to as-needed  
242 albuterol. Baseline FEV<sub>1</sub> values were similar across groups (mean 65% to 66% of predicted  
243 normal). All 3 dosages of FLOVENT HFA significantly improved asthma control (as measured  
244 by improvement in FEV<sub>1</sub>), compared with placebo. Discontinuations from the study for lack of  
245 efficacy (defined by a pre-specified decrease in FEV<sub>1</sub> or peak expiratory flow [PEF], or an  
246 increase in use of VENTOLIN or nighttime awakenings requiring treatment with VENTOLIN)  
247 were lower in the groups treated with FLOVENT HFA (6% to 11%) compared to placebo (50%).  
248 Pulmonary function (AM pre-dose FEV<sub>1</sub>) improved significantly with FLOVENT HFA  
249 compared with placebo after the first week of treatment, and the improvement was maintained  
250 over the 12-week treatment period.

251 At Endpoint (last observation), mean change from baseline in AM pre-dose percent predicted  
 252 FEV<sub>1</sub> was greater in all 3 groups treated with FLOVENT HFA (2.2% to 4.6%) compared with  
 253 the placebo group (-8.3%). The mean differences between the groups treated with  
 254 FLOVENT HFA 88, 220, and 440 mcg and the placebo group were significant, and the  
 255 corresponding 95% confidence intervals were (7.1%, 13.8%), (8.2%, 14.9%), and (9.6%,  
 256 16.4%), respectively.

257 Figure 2 displays the mean percent change from baseline in FEV<sub>1</sub> from Week 1 through Week  
 258 12. This study also used predetermined criteria for lack of efficacy, resulting in withdrawal of  
 259 more patients in the placebo group; therefore, pulmonary function results at Endpoint are  
 260 displayed.

261

262 **Figure 2. A 12-Week Clinical Trial in Patients ≥12 Years of Age Already**  
 263 **Receiving Daily Inhaled Corticosteroids: Mean Percent Change From**  
 264 **Baseline in FEV<sub>1</sub> Prior to AM Dose (Study 2)**  
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266  
 267

268 In both studies, use of VENTOLIN, AM and PM PEF, and asthma symptom scores showed  
 269 numerical improvement with FLOVENT HFA compared to placebo.

270 Study 3 enrolled 168 patients with asthma requiring oral prednisone therapy (average baseline  
 271 daily prednisone dose ranged from 13 to 14 mg). FLOVENT HFA at dosages of 440 and  
 272 880 mcg twice daily was evaluated over a 16-week treatment period. Baseline FEV<sub>1</sub> values were  
 273 similar across groups (mean 59% to 62% of predicted normal). Over the course of the study,  
 274 patients treated with either dosage of FLOVENT HFA required a significantly lower mean daily  
 275 oral prednisone dose (6 mg) compared with placebo-treated patients (15 mg). Both dosages of  
 276 FLOVENT HFA enabled a larger percentage of patients (59% and 56% in the groups treated

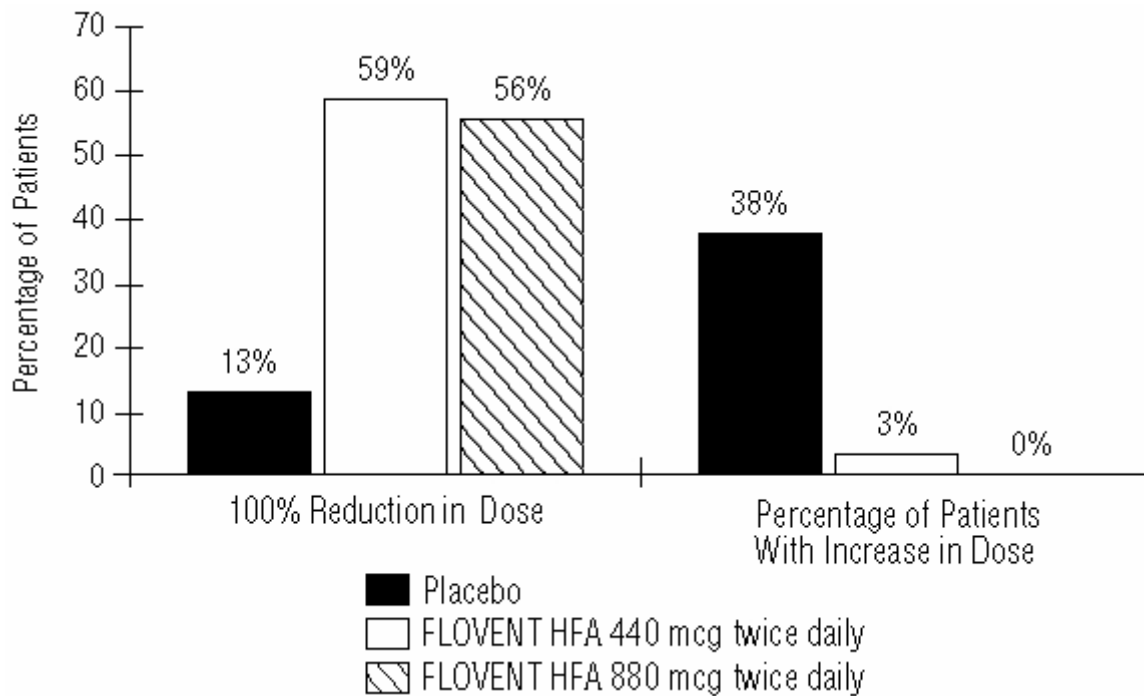


277 with FLOVENT HFA 440 and 880 mcg, respectively, twice daily) to eliminate oral prednisone  
 278 as compared with placebo (13%) (see Figure 3). There was no efficacy advantage of FLOVENT  
 279 HFA 880 mcg twice daily compared to 440 mcg twice daily. Accompanying the reduction in oral  
 280 corticosteroid use, patients treated with either dosage of FLOVENT HFA had significantly  
 281 improved lung function, fewer asthma symptoms, and less use of VENTOLIN Inhalation  
 282 Aerosol compared with the placebo-treated patients.

283

284 **Figure 3. A 16-Week Clinical Trial in Patients  $\geq 12$  Years of Age Requiring Chronic**  
 285 **Oral Prednisone Therapy: Change in Maintenance Prednisone Dose**

286



287

288

289 Two long-term safety studies (Study 4 and Study 5) of  $\geq 6$  months' duration were conducted in  
 290 507 adolescent and adult patients with asthma. Study 4 was designed to monitor the safety of  
 291 2 doses of FLOVENT HFA, while Study 5 compared fluticasone propionate HFA and  
 292 fluticasone propionate CFC. Study 4 enrolled 182 patients who were treated daily with low to  
 293 high doses of inhaled corticosteroids, beta-agonists (short-acting [as needed or regularly  
 294 scheduled] or long-acting), theophylline, inhaled cromolyn or nedocromil sodium, leukotriene  
 295 receptor antagonists, or 5-lipoxygenase inhibitors at baseline. FLOVENT HFA at dosages of 220  
 296 and 440 mcg twice daily was evaluated over a 26-week treatment period in 89 and 93 patients,  
 297 respectively. Study 5 enrolled 325 patients who were treated daily with moderate to high doses  
 298 of inhaled corticosteroids, with or without concurrent use of salmeterol or albuterol, at baseline.  
 299 Fluticasone propionate HFA at a dosage of 440 mcg twice daily and fluticasone propionate CFC  
 300 at a dosage of 440 mcg twice daily were evaluated over a 52-week treatment period in 163 and  
 301 162 patients, respectively. Baseline FEV<sub>1</sub> values were similar across groups (mean 81% to 84%

302 of predicted normal). Throughout the 52-week treatment period, asthma control was maintained  
303 with both formulations of fluticasone propionate compared to baseline. In both studies, none of  
304 the patients were withdrawn due to lack of efficacy.

305 **Pediatric Patients:** A 12-week clinical trial conducted in 241 patients aged 4 to 11 years with  
306 asthma was supportive of efficacy but inconclusive due to measurable levels of fluticasone  
307 propionate in 6/48 (13%) of the plasma samples from patients randomized to placebo. Efficacy  
308 in patients 4 to 11 years of age is extrapolated from adult data with FLOVENT HFA and other  
309 supporting data (see PRECAUTIONS: Pediatric Use).

## 310 **INDICATIONS AND USAGE**

311 FLOVENT HFA Inhalation Aerosol is indicated for the maintenance treatment of asthma as  
312 prophylactic therapy in patients 4 years of age and older. It is also indicated for patients requiring  
313 oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate  
314 their requirement for oral corticosteroids over time.

315 FLOVENT HFA Inhalation Aerosol is NOT indicated for the relief of acute bronchospasm.

## 316 **CONTRAINDICATIONS**

317 FLOVENT HFA Inhalation Aerosol is contraindicated in the primary treatment of status  
318 asthmaticus or other acute episodes of asthma where intensive measures are required.

319 Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see  
320 DESCRIPTION).

## 321 **WARNINGS**

322 1. Transferring patients from systemic corticosteroid therapy. Particular care is needed for  
323 patients who have been transferred from systemically active corticosteroids to inhaled  
324 corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma  
325 during and after transfer from systemic corticosteroids to less systemically available inhaled  
326 corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required  
327 for recovery of HPA function.

328 Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid  
329 use after transferring to FLOVENT HFA. In a clinical trial of 168 patients, prednisone reduction  
330 was successfully accomplished by reducing the daily prednisone dose on a weekly basis  
331 following initiation of treatment with FLOVENT HFA. Successive reduction of prednisone dose  
332 was allowed only when lung function; symptoms; and as-needed, short-acting beta-agonist use  
333 were better than or comparable to that seen before initiation of prednisone dose reduction. Lung  
334 function (FEV<sub>1</sub> or AM PEF), beta-agonist use, and asthma symptoms should be carefully  
335 monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and  
336 symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as  
337 fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

338 Patients who have been previously maintained on 20 mg or more per day of prednisone (or its  
339 equivalent) may be most susceptible, particularly when their systemic corticosteroids have been

340 almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs  
341 and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection  
342 (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although  
343 inhaled corticosteroids may provide control of asthma symptoms during these episodes, in  
344 recommended doses they supply less than normal physiological amounts of glucocorticoid  
345 (cortisol) systemically and do NOT provide the mineralocorticoid activity that is necessary for  
346 coping with these emergencies.

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

352 Transfer of patients from systemic corticosteroid therapy to FLOVENT HFA may unmask  
353 conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis,  
354 conjunctivitis, eczema, arthritis, and eosinophilic conditions. Some patients may experience  
355 symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain,  
356 lassitude, and depression, despite maintenance or even improvement of respiratory function.

357 2. Bronchospasm. As with other inhaled medications, bronchospasm may occur with an  
358 immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with  
359 FLOVENT HFA, it should be treated immediately with a fast-acting inhaled bronchodilator.  
360 Treatment with FLOVENT HFA should be discontinued and alternative therapy instituted.

361 Patients should be instructed to contact their physicians immediately when episodes of asthma  
362 that are not responsive to bronchodilators occur during the course of treatment with  
363 FLOVENT HFA. During such episodes, patients may require therapy with oral corticosteroids.

364 3. Immunosuppression. Persons who are using drugs that suppress the immune system are more  
365 susceptible to infections than healthy individuals. Chickenpox and measles, for example, can  
366 have a more serious or even fatal course in susceptible children or adults using corticosteroids. In  
367 such children or adults who have not had these diseases or been properly immunized, particular  
368 care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid  
369 administration affect the risk of developing a disseminated infection is not known. The  
370 contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not  
371 known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG)  
372 may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin  
373 (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing  
374 information.) If chickenpox develops, treatment with antiviral agents may be considered.

375 4. Drug interaction with ritonavir. A drug interaction study in healthy subjects has shown that  
376 ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase systemic  
377 fluticasone propionate exposure (AUC), resulting in significantly reduced serum cortisol  
378 concentrations (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Drug Interactions* and  
379 PRECAUTIONS: Drug Interactions: *Inhibitors of Cytochrome P450*). During postmarketing

380 use, there have been reports of clinically significant drug interactions in patients receiving  
381 fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including  
382 Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone  
383 propionate and ritonavir is not recommended unless the potential benefit to the patient  
384 outweighs the risk of systemic corticosteroid side effects.  
385 5. FLOVENT HFA should not be used to treat acute symptoms. FLOVENT HFA is not to be  
386 regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

## 387 **PRECAUTIONS**

388 **General:** Orally inhaled corticosteroids may cause a reduction in growth velocity when  
389 administered to pediatric patients (see PRECAUTIONS: Pediatric Use).

390 Fluticasone propionate will often help control asthma symptoms with less suppression of HPA  
391 function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is  
392 absorbed into the circulation and can be systemically active at higher doses, the beneficial effects  
393 of FLOVENT HFA in minimizing HPA dysfunction may be expected only when recommended  
394 dosages are not exceeded and individual patients are titrated to the lowest effective dose. A  
395 relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated  
396 cortisol production has been shown after 4 weeks of treatment with fluticasone propionate  
397 inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians  
398 should consider this information when prescribing FLOVENT HFA.

399 Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated  
400 with FLOVENT HFA should be observed carefully for any evidence of systemic corticosteroid  
401 effects. Particular care should be taken in observing patients postoperatively or during periods of  
402 stress for evidence of inadequate adrenal response.

403 It is possible that systemic corticosteroid effects such as hypercorticism and adrenal  
404 suppression (including adrenal crisis) may appear in a small number of patients, particularly  
405 when FLOVENT HFA is administered at higher than recommended doses over prolonged  
406 periods of time. If such effects occur, the dosage of FLOVENT HFA should be reduced slowly,  
407 consistent with accepted procedures for reducing systemic corticosteroids and for management  
408 of asthma.

409 The long-term effects of FLOVENT HFA in human subjects are not fully known. In  
410 particular, the effects resulting from chronic use of fluticasone propionate on developmental or  
411 immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients  
412 have received inhaled fluticasone propionate on a continuous basis in a clinical study for up to 4  
413 years. In clinical studies with patients treated for 2 years with inhaled fluticasone propionate, no  
414 apparent differences in the type or severity of adverse reactions were observed after long- versus  
415 short-term treatment.

416 Glaucoma, increased intraocular pressure, and cataracts have been reported in patients  
417 following the long-term administration of inhaled corticosteroids, including fluticasone  
418 propionate.

419 In clinical studies with inhaled fluticasone propionate, the development of localized infections  
420 of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should  
421 be treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on  
422 treatment with FLOVENT HFA, but at times therapy with FLOVENT HFA may need to be  
423 interrupted.

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

427 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate may  
428 present with systemic eosinophilic conditions, with some patients presenting with clinical  
429 features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated  
430 with systemic corticosteroid therapy. These events usually, but not always, have been associated  
431 with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of  
432 fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with  
433 other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia,  
434 vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy  
435 presenting in their patients. A causal relationship between fluticasone propionate and these  
436 underlying conditions has not been established (see ADVERSE REACTIONS: Observed During  
437 Clinical Practice: *Eosinophilic Conditions*).

438 **Information for Patients:** Patients being treated with FLOVENT HFA should receive the  
439 following information and instructions. This information is intended to aid them in the safe and  
440 effective use of this medication. It is not a disclosure of all possible adverse or intended effects.  
441 It is important that patients understand how to use FLOVENT HFA in relation to other asthma  
442 medications they are taking.

- 443 1. Patients should use FLOVENT HFA at regular intervals as directed. Individual patients will  
444 experience a variable time to onset and degree of symptom relief and the full benefit may not  
445 be achieved until treatment has been administered for 1 to 2 weeks or longer. The patient  
446 should not increase the prescribed dosage but should contact the physician if symptoms do  
447 not improve or if the condition worsens.
- 448 2. Patients who are pregnant or nursing should contact their physicians about the use of  
449 FLOVENT HFA.
- 450 3. Patients should be warned to avoid exposure to chickenpox or measles and if they are  
451 exposed to consult their physicians without delay.
- 452 4. In general, the technique for administering FLOVENT HFA to children is similar to that for  
453 adults. Children should use FLOVENT HFA under adult supervision, as instructed by the  
454 patient's physician. (See Patient's Instructions for Use leaflet accompanying the product.)
- 455 5. Prime the inhaler before using for the first time by releasing 4 test sprays into the air away  
456 from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has  
457 not been used for more than 7 days or when it has been dropped, prime the inhaler again by

- 458 shaking well for 5 seconds before each spray and releasing 1 test spray into the air away from  
459 the face.
- 460 6. After inhalation, rinse the mouth with water and spit out. Do not swallow.
  - 461 7. Clean the inhaler at least once a week after the evening dose. Keeping the canister and plastic  
462 actuator clean is important to prevent medicine buildup. (See Patient's Instructions for Use  
463 leaflet accompanying the product.)
  - 464 8. Use FLOVENT HFA only with the actuator supplied with the product. When the counter  
465 reads 020, contact the pharmacist for a refill of medication or consult the physician to  
466 determine whether a prescription refill is needed. Discard the inhaler when the counter reads  
467 000. Never try to alter the numbers or remove the counter from the metal canister.
  - 468 9. Patients should never immerse the canister into water to determine the amount remaining in  
469 the canister ("float test").
  - 470 10. For the proper use of FLOVENT HFA and to attain maximum improvement, the patient  
471 should read and carefully follow the Patient's Instructions for Use leaflet accompanying the  
472 product.

473 **Drug Interactions: *Inhibitors of Cytochrome P450:*** Fluticasone propionate is a substrate  
474 of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal  
475 spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4  
476 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in  
477 significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY:  
478 Pharmacokinetics: *Drug Interactions*). During postmarketing use, there have been reports of  
479 clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir,  
480 resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression.  
481 Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless  
482 the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

483 In a placebo-controlled crossover study in 8 healthy adult volunteers, coadministration of a  
484 single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of  
485 ketoconazole (200 mg) to steady state resulted in increased systemic fluticasone propionate  
486 exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.  
487 Caution should be exercised when FLOVENT HFA is coadministered with ketoconazole and  
488 other known potent cytochrome P450 3A4 inhibitors.

489 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Fluticasone propionate  
490 demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately  
491 2 and 10 times the maximum recommended human daily inhalation dose in adults and children,  
492 respectively, on a mcg/m<sup>2</sup> basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less  
493 than and equivalent to the maximum recommended human daily inhalation dose in adults and  
494 children, respectively, on a mcg/m<sup>2</sup> basis) for 104 weeks.

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

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

502 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Subcutaneous studies in the  
503 mouse and rat at 45 and 100 mcg/kg, respectively (less than the maximum recommended human  
504 daily inhalation dose on a mcg/m<sup>2</sup> basis), revealed fetal toxicity characteristic of potent  
505 corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate,  
506 and retarded cranial ossification. No teratogenicity was seen in the rat at inhalation doses up to  
507 68.7 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup>  
508 basis).

509 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of  
510 4 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup>  
511 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg  
512 (approximately 3 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup>  
513 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this  
514 study, consistent with the established low bioavailability following oral administration (see  
515 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Absorption*).

516 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose  
517 of 100 mcg/kg to mice (less than the maximum recommended human daily inhalation dose on a  
518 mcg/m<sup>2</sup> basis), a subcutaneous or an oral dose of 100 mcg/kg to rats (less than the maximum  
519 recommended daily inhalation dose on a mcg/m<sup>2</sup> basis), and an oral dose of 300 mcg/kg to  
520 rabbits (approximately 3 times the maximum recommended human daily inhalation dose on a  
521 mcg/m<sup>2</sup> basis).

522 There are no adequate and well-controlled studies in pregnant women. FLOVENT HFA  
523 should be used during pregnancy only if the potential benefit justifies the potential risk to the  
524 fetus.

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

530 **Nursing Mothers:** It is not known whether fluticasone propionate is excreted in human breast  
531 milk. However, other corticosteroids have been detected in human milk. Subcutaneous  
532 administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the  
533 maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis) resulted in measurable  
534 radioactivity in milk.

535 Since there are no data from controlled trials on the use of FLOVENT HFA by nursing  
536 mothers, a decision should be made whether to discontinue nursing or to discontinue  
537 FLOVENT HFA, taking into account the importance of FLOVENT HFA to the mother.

538 Caution should be exercised when FLOVENT HFA is administered to a nursing woman.  
539 **Pediatric Use:** The safety and effectiveness of FLOVENT HFA in children 12 years of age and  
540 older have been established (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Special*  
541 *Populations: Pediatric*, CLINICAL TRIALS: Pediatric Patients, ADVERSE REACTIONS:  
542 Pediatric Patients). Use of FLOVENT HFA in patients 4 to 11 years of age is supported by  
543 evidence from adequate and well-controlled studies in adults and adolescents 12 years of age and  
544 older, pharmacokinetic studies in patients 4 to 11 years of age, established efficacy of fluticasone  
545 propionate formulated as FLOVENT<sup>®</sup> DISKUS<sup>®</sup> (fluticasone propionate inhalation powder) and  
546 FLOVENT<sup>®</sup> ROTADISK<sup>®</sup> (fluticasone propionate inhalation powder) in patients 4 to 11 years  
547 of age, and supportive findings with FLOVENT HFA in a study conducted in patients 4 to  
548 11 years of age. Types of adverse events in pediatric patients 4 to 11 years of age were generally  
549 similar to those observed in adults and adolescents (see CLINICAL TRIALS, CLINICAL  
550 PHARMACOLOGY: Pharmacokinetics, ADVERSE REACTIONS: Pediatric Patients). The  
551 safety and efficacy in children under 4 years of age have not been established.

552 Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to  
553 pediatric patients. A reduction of growth velocity in children or teenagers may occur as a result  
554 of poorly controlled asthma or from use of corticosteroids including inhaled corticosteroids. The  
555 effects of long-term treatment of children and adolescents with inhaled corticosteroids, including  
556 fluticasone propionate, on final adult height are not known.

557 Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in  
558 growth in pediatric patients. In these studies, the mean reduction in growth velocity was  
559 approximately 1 cm/year (range, 0.3 to 1.8 cm/year) and appears to depend upon dose and  
560 duration of exposure. This effect was observed in the absence of laboratory evidence of HPA  
561 axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic  
562 corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis  
563 function. The long-term effects of this reduction in growth velocity associated with orally  
564 inhaled corticosteroids, including the impact on final adult height, are unknown. The potential  
565 for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids  
566 has not been adequately studied. The effects on growth velocity of treatment with orally inhaled  
567 corticosteroids for over 1 year, including the impact on final adult height, are unknown. The  
568 growth of children and adolescents receiving orally inhaled corticosteroids, including  
569 FLOVENT HFA, should be monitored routinely (e.g., via stadiometry). The potential growth  
570 effects of prolonged treatment should be weighed against the clinical benefits obtained and the  
571 risks associated with alternative therapies. To minimize the systemic effects of orally inhaled  
572 corticosteroids, including FLOVENT HFA, each patient should be titrated to the lowest dose that  
573 effectively controls his/her symptoms.

574 Since a cross study comparison in adolescent and adult patients ( $\geq 12$  years of age) indicated  
575 that systemic exposure of inhaled fluticasone propionate from FLOVENT HFA would be higher  
576 than exposure from FLOVENT ROTADISK, results from a study to assess the potential growth  
577 effects of FLOVENT ROTADISK in pediatric patients (4 to 11 years of age) are provided.



578 A 52-week placebo-controlled study to assess the potential growth effects of fluticasone  
579 propionate inhalation powder (FLOVENT ROTADISK) at 50 and 100 mcg twice daily was  
580 conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to  
581 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were  
582 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and  
583 5.66 cm/year in the 100-mcg group (n = 89). An imbalance in the proportion of children entering  
584 puberty between groups and a higher dropout rate in the placebo group due to poorly controlled  
585 asthma may be confounding factors in interpreting these data. A separate subset analysis of  
586 children who remained prepubertal during the study revealed growth rates at 52 weeks of  
587 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and  
588 5.67 cm/year in the 100-mcg group (n = 79). In children 8.5 years of age, the mean age of  
589 children in this study, the range for expected growth velocity is: boys – 3<sup>rd</sup>  
590 percentile = 3.8 cm/year, 50<sup>th</sup> percentile = 5.4 cm/year, and 97<sup>th</sup> percentile = 7.0 cm/year; girls –  
591 3<sup>rd</sup> percentile = 4.2 cm/year, 50<sup>th</sup> percentile = 5.7 cm/year, and 97<sup>th</sup> percentile = 7.3 cm/year.

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

597 **Geriatric Use:** Of the total number of patients treated with FLOVENT HFA in US and non-US  
598 clinical trials, 173 were 65 years of age or older, 19 of which were 75 years of age or older. No  
599 apparent differences in safety or efficacy were observed between these patients and younger  
600 patients. No overall differences in safety were observed between these patients and younger  
601 patients, and other reported clinical experience has not identified differences in responses  
602 between the elderly and younger patients, but greater sensitivity of some older individuals cannot  
603 be ruled out. In general, dose selection for an elderly patient should be cautious, reflecting the  
604 greater frequency of decreased hepatic function and of concomitant disease or other drug  
605 therapy.

## 606 **ADVERSE REACTIONS**

607 **Adolescent and Adult Patients:** The incidence of common adverse events in Table 1 is  
608 based upon 2 placebo-controlled US clinical trials in which 812 adolescent and adult patients  
609 (457 females and 355 males) previously treated with as-needed bronchodilators and/or inhaled  
610 corticosteroids were treated twice daily for up to 12 weeks with 2 inhalations of FLOVENT HFA  
611 44 mcg Inhalation Aerosol, FLOVENT HFA 110 mcg Inhalation Aerosol, FLOVENT HFA  
612 220 mcg Inhalation Aerosol, (dosages of 88, 220, or 440 mcg twice daily) or placebo.

613

614 **Table 1. Overall Adverse Events With >3% Incidence in US Controlled Clinical Trials**  
615 **With FLOVENT HFA in Patients ≥12 Years of Age With Asthma Previously Receiving**  
616 **Bronchodilators and/or Inhaled Corticosteroids**

| Adverse Event                                   | FLOVENT HFA<br>88 mcg<br>twice daily<br>(n = 203)<br>% | FLOVENT HFA<br>220 mcg<br>twice daily<br>(n = 204)<br>% | FLOVENT HFA<br>440 mcg<br>twice daily<br>(n = 202)<br>% | Placebo<br>(n = 203)<br>% |
|---|--|---|---|---------------------------|
| Ear, nose, and throat                           |  |   |   |                           |
| Upper respiratory tract infection               | 18   | 16  | 16  | 14                        |
| Throat irritation                               | 8  | 8   | 10  | 5                         |
| Upper respiratory inflammation                  | 2  | 5   | 5   | 1                         |
| Sinusitis/sinus infection                       | 6  | 7   | 4   | 3                         |
| Hoarseness/dysphonia                            | 2  | 3   | 6   | <1                        |
| Gastrointestinal                                |  |   |   |                           |
| Candidiasis mouth/throat &<br>non-site specific | 4  | 2   | 5   | <1                        |
| Lower respiratory                               |  |   |   |                           |
| Cough   | 4  | 6   | 4   | 5                         |
| Bronchitis                                      | 2  | 2   | 6   | 5                         |
| Neurological                                    |  |   |   |                           |
| Headache  | 11   | 7   | 5   | 6                         |
| Average duration of exposure (days)             | 73   | 74  | 76  | 60                        |

617  
618 Table 1 includes all events (whether considered drug-related or nondrug-related by the  
619 investigator) that occurred at a rate of over 3% in any of the groups treated with FLOVENT HFA  
620 and were more common than in the placebo group. In considering these data, differences in  
621 average duration of exposure should be taken into account.

622 These adverse events were mostly mild to moderate in severity. Rare cases of immediate and  
623 delayed hypersensitivity reactions, including urticaria and rash, have been reported.

624 Other adverse events that occurred in the groups receiving FLOVENT HFA in these studies  
625 with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

626 **Ear, Nose, and Throat:** Sinusitis/sinus infection, rhinitis, pharyngitis/throat infection,  
627 rhinorrhea/post-nasal drip, nasal sinus disorders, laryngitis.

628 **Gastrointestinal:** Diarrhea, viral gastrointestinal infections, gastrointestinal signs and  
629 symptoms, dyspeptic symptoms, gastrointestinal discomfort and pain, hyposalivation.

630 **Musculoskeletal:** Musculoskeletal pain, muscle pain, muscle stiffness/tightness/rigidity.

631 **Neurological:** Dizziness, migraines.

632 **Non-Site Specific:** Fever, viral infections, pain, chest symptoms.

633 **Skin:** Viral skin infections.

634 **Trauma:** Muscle injuries, soft tissue injuries, injuries.

635 **Urogenital:** Urinary infections.

636 Fluticasone propionate inhalation aerosol (440 or 880 mcg twice daily) was administered for  
637 16 weeks to patients with asthma requiring oral corticosteroids (Study 3). Adverse events not  
638 included in Table 1, but reported by >3 patients in either group treated with FLOVENT HFA and  
639 more commonly than in the placebo group included rhinitis, nausea and vomiting, arthralgia and  
640 articular rheumatism, musculoskeletal pain, muscle pain, malaise and fatigue, and sleep  
641 disorders.

642 In 2 long-term studies (26 and 52 weeks), treatment with FLOVENT HFA at dosages up to  
643 440 mcg twice daily was well tolerated. The pattern of adverse events was similar to that  
644 observed in the 12-week studies. There were no new and/or unexpected adverse events with  
645 long-term treatment.

646 **Pediatric Patients:** FLOVENT HFA has been evaluated for safety in 56 pediatric patients  
647 aged 4 to 11 years who received 88 mcg twice daily for 4 weeks. Types of adverse events in  
648 these pediatric patients were generally similar to those observed in adults and adolescents.

649 **Observed During Clinical Practice:** In addition to adverse events reported from clinical  
650 trials, the following events have been identified during postapproval use of fluticasone  
651 propionate. Because they are reported voluntarily from a population of unknown size, estimates  
652 of frequency cannot be made. These events have been chosen for inclusion due to either their  
653 seriousness, frequency of reporting, or causal connection to fluticasone propionate or a  
654 combination of these factors.

655 **Ear, Nose, and Throat:** Aphonia, facial and oropharyngeal edema, including angioedema,  
656 and throat soreness and irritation.

657 **Endocrine and Metabolic:** Cushingoid features, growth velocity reduction in  
658 children/adolescents, hyperglycemia, osteoporosis, and weight gain.

659 **Eye:** Cataracts.

660 **Non-Site Specific:** Very rare anaphylactic reaction.

661 **Psychiatry:** Agitation, aggression, anxiety, depression, and restlessness. Behavioral  
662 changes, including hyperactivity and irritability, have been reported very rarely and primarily in  
663 children.

664 **Respiratory:** Asthma exacerbation, chest tightness, cough, dyspnea, immediate and delayed  
665 bronchospasm, paradoxical bronchospasm, pneumonia, and wheeze.

666 **Skin:** Contusions, cutaneous hypersensitivity reactions, ecchymoses, and pruritus.

667 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate may  
668 present with systemic eosinophilic conditions, with some patients presenting with clinical  
669 features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated  
670 with systemic corticosteroid therapy. These events usually, but not always, have been associated  
671 with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of  
672 fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with

673 other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia,  
674 vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy  
675 presenting in their patients. A causal relationship between fluticasone propionate and these  
676 underlying conditions has not been established (see PRECAUTIONS: Eosinophilic Conditions).

## 677 **OVERDOSAGE**

678 Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS:  
679 General). Inhalation by healthy volunteers of a single dose of 1,760 or 3,520 mcg of fluticasone  
680 propionate CFC inhalation aerosol was well tolerated. Doses of 1,320 mcg administered to  
681 healthy human volunteers twice daily for 7 to 15 days were also well tolerated. Repeat oral doses  
682 up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for  
683 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and  
684 incidences were similar in active and placebo treatment groups. The oral median lethal dose in  
685 mice was >1,000 mg/kg (approximately  $\geq 2,300$  and >11,000 times the maximum human daily  
686 inhalation dose in adults and children on a  $\text{mg}/\text{m}^2$  basis, respectively), and the subcutaneous  
687 median lethal dose in rats was >1,000 mg/kg (approximately >4,600 and >22,000 times the  
688 maximum human daily inhalation dose in adults and children on a  $\text{mg}/\text{m}^2$  basis, respectively).

## 689 **DOSAGE AND ADMINISTRATION**

690 FLOVENT HFA should be administered by the orally inhaled route only in patients 4 years of  
691 age and older. Individual patients will experience a variable time to onset and degree of symptom  
692 relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment.

693 After asthma stability has been achieved, it is always desirable to titrate to the lowest effective  
694 dosage to reduce the possibility of side effects. For patients who do not respond adequately to the  
695 starting dosage after 2 weeks of therapy, higher dosages may provide additional asthma control.  
696 The safety and efficacy of FLOVENT HFA when administered in excess of recommended  
697 dosages have not been established.

698 The recommended starting dosage and the highest recommended dosage of FLOVENT HFA,  
699 based on prior asthma therapy, are listed in Table 2.

700

701 **Table 2. Recommended Dosages of FLOVENT HFA**

702 **NOTE: In all patients, it is desirable to titrate to the lowest effective dosage once asthma**  
 703 **stability is achieved.**

| Previous Therapy                                      | Recommended Starting Dosage | Highest Recommended Dosage |
|---|-----------------------------|----------------------------|
| <b>Adolescent and adult patients (≥12 years)</b>      |                             |                            |
| Bronchodilators alone                                 | 88 mcg twice daily          | 440 mcg twice daily        |
| Inhaled corticosteroids                               | 88-220 mcg twice daily*     | 440 mcg twice daily        |
| Oral corticosteroids <sup>†</sup>                     | 440 mcg twice daily         | 880 mcg twice daily        |
| <b>Pediatric patients (4 to 11 years)<sup>‡</sup></b> | 88 mcg twice daily          | 88 mcg twice daily         |

704 \* **For Patients Currently Receiving Inhaled Corticosteroid Therapy:** Starting dosages above  
 705 88 mcg twice daily may be considered for patients with poorer asthma control or those who  
 706 have previously required doses of inhaled corticosteroids that are in the higher range for that  
 707 specific agent.

708 † **For Patients Currently Receiving Chronic Oral Corticosteroid Therapy:** Prednisone  
 709 should be reduced no faster than 2.5 to 5 mg/day on a weekly basis, beginning after at least  
 710 1 week of therapy with FLOVENT HFA. Patients should be carefully monitored for signs of  
 711 asthma instability, including serial objective measures of airflow, and for signs of adrenal  
 712 insufficiency (see WARNINGS). Once prednisone reduction is complete, the dosage of  
 713 fluticasone propionate HFA should be reduced to the lowest effective dosage.

714 ‡ Recommended pediatric dosage is 88 mcg twice daily regardless of prior therapy.

715  
 716 FLOVENT HFA should be primed before using for the first time by releasing 4 test sprays  
 717 into the air away from the face, shaking well before each spray. In cases where the inhaler has  
 718 not been used for more than 7 days or when it has been dropped, prime the inhaler again by  
 719 shaking well and releasing 1 test spray into the air away from the face.

720 **Geriatric Use:** In studies where geriatric patients (65 years of age or older, see  
 721 PRECAUTIONS: Geriatric Use) have been treated with fluticasone propionate inhalation  
 722 aerosol, efficacy and safety did not differ from that in younger patients. Based on available data  
 723 for FLOVENT HFA, no dosage adjustment is recommended.

724 **Directions for Use:** Illustrated Patient's Instructions for Use accompany each package of  
 725 FLOVENT HFA.

726 **HOW SUPPLIED**

727 FLOVENT HFA 44 mcg Inhalation Aerosol is supplied in 10.6-g pressurized aluminum  
 728 canisters containing 120 metered inhalations in boxes of 1 (NDC 0173-0718-20).

729 FLOVENT HFA 110 mcg Inhalation Aerosol is supplied in 12-g pressurized aluminum  
 730 canisters containing 120 metered inhalations in boxes of 1 (NDC 0173-0719-20).

731 FLOVENT HFA 220 mcg Inhalation Aerosol is supplied in 12-g pressurized aluminum  
732 canisters containing 120 metered inhalations in boxes of 1 (NDC 0173-0720-20).

733 Each canister is fitted with a dose counter and supplied with a dark orange oral actuator with a  
734 peach strapcap packaged within a plastic-coated, moisture-protective foil pouch and patient's  
735 instructions. The moisture-protective foil pouch also contains a desiccant that should be  
736 discarded when the pouch is opened.

737 **The dark orange actuator supplied with FLOVENT HFA should not be used with any**  
738 **other product canisters, and actuators from other products should not be used with a**  
739 **FLOVENT HFA canister.**

740 **The correct amount of medication in each inhalation cannot be assured after the counter**  
741 **reads 000, even though the canister is not completely empty and will continue to operate.**  
742 **The inhaler should be discarded when the counter reads 000. Never immerse the canister**  
743 **into water to determine the amount remaining in the canister ("float test").**

744 **Keep out of reach of children. Avoid spraying in eyes.**

745 **Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame.**  
746 **Exposure to temperatures above 120°F may cause bursting. Never throw into fire or**  
747 **incinerator.**

748 **Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Store the inhaler**  
749 **with the mouthpiece down. For best results, the inhaler should be at room temperature**  
750 **before use. SHAKE WELL BEFORE USING.**

751 FLOVENT HFA does not contain chlorofluorocarbons (CFCs) as the propellant.

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