

PRESCRIBING INFORMATION

FLOVENT[®] HFA 44 mcg
(fluticasone propionate 44 mcg)
Inhalation Aerosol

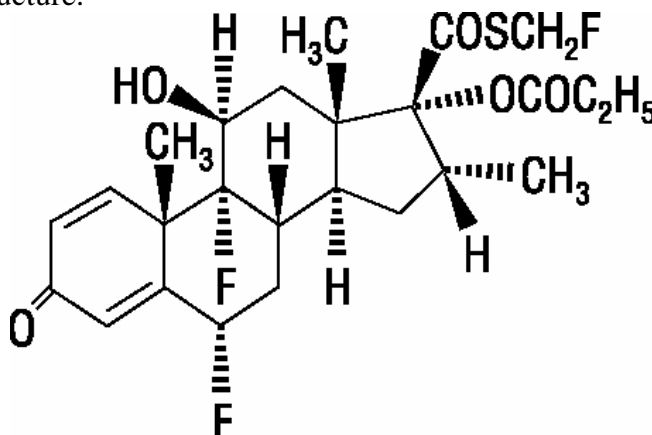
FLOVENT[®] HFA 110 mcg
(fluticasone propionate 110 mcg)
Inhalation Aerosol

FLOVENT[®] HFA 220 mcg
(fluticasone propionate 220 mcg)
Inhalation Aerosol

For Oral Inhalation Only

DESCRIPTION

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



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

FLOVENT HFA 44 mcg Inhalation Aerosol, FLOVENT HFA 110 mcg Inhalation Aerosol, and FLOVENT HFA 220 mcg Inhalation Aerosol are pressurized metered-dose aerosol units fitted with a counter. FLOVENT HFA is intended for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

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

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

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

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

43 **CLINICAL PHARMACOLOGY**

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

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

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

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

65 **Preclinical:** In animals and humans, propellant HFA-134a was found to be rapidly absorbed and
66 rapidly eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to 7 minutes
67 in humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both

68 extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of
69 accumulation.

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

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

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

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

99 **Metabolism:** The total clearance of fluticasone propionate is high (average, 1,093 mL/min),
100 with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite
101 detected in man is the 17β -carboxylic acid derivative of fluticasone propionate, which is formed
102 through the cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately
103 1/2,000) than the parent drug for the corticosteroid receptor of human lung cytosol in vitro and
104 negligible pharmacological activity in animal studies. Other metabolites detected in vitro using
105 cultured human hepatoma cells have not been detected in man.

106 **Elimination:** Following intravenous dosing, fluticasone propionate showed polyexponential
107 kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a

108 radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in
109 the feces as parent drug and metabolites.

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

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

127 In a second open-label, single-dose, 2-period crossover study, 21 children with asthma aged 5
128 to 11 years received 264 mcg of fluticasone propionate HFA administered with and without an
129 AeroChamber Plus® Valved Holding Chamber (VHC). The geometric means (95% CI) of
130 AUC_{last} were 261 pg•hr/mL (252, 444) with the use of the VHC and 40 pg•hr/mL (16, 208)
131 without the VHC. The geometric means (95% CI) of C_{max} were 52 pg/mL (46, 70) with the VHC
132 and 19 pg/mL (17, 41) without the VHC. The median T_{max} was 1 hour with or without the VHC.
133 Therefore, systemic exposure was higher with the VHC in these pediatric patients with asthma.
134 (See PRECAUTIONS: Pediatric Use for population pharmacokinetics information on children
135 aged 6 months to <4 years.)

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. (See
138 PRECAUTIONS: Pediatric Use for population pharmacokinetics information on children aged 1
139 to <4 years.)

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- β -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 (See PRECAUTIONS: Pediatric Use for pharmacodynamic information on children aged 6
180 months to <4 years.)

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

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

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

202 **CLINICAL TRIALS**

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

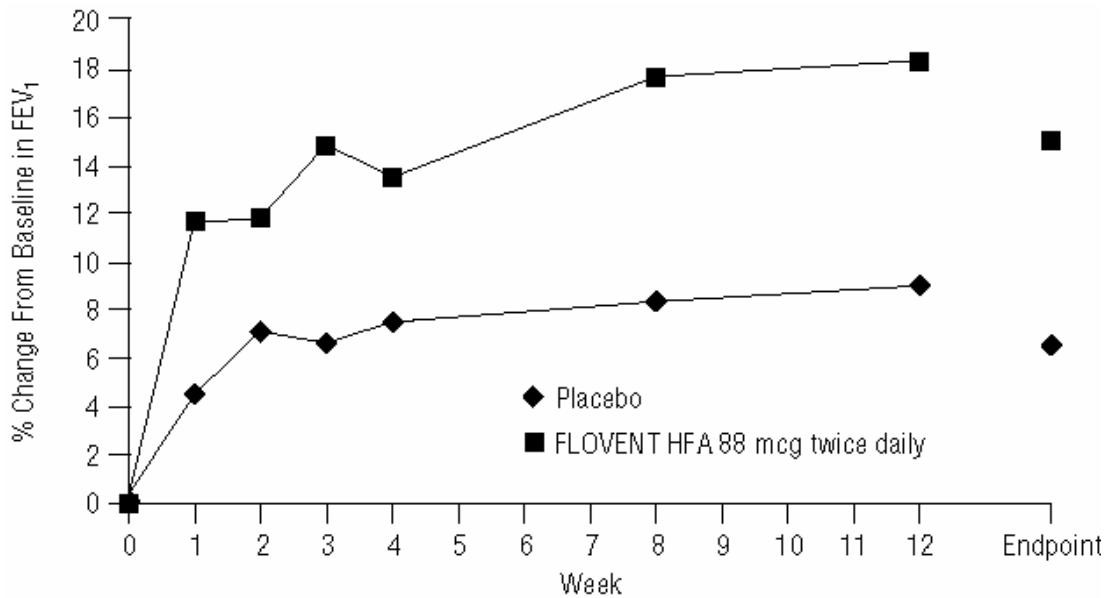
215 Study 1 enrolled 397 patients with asthma inadequately controlled on bronchodilators alone.
216 FLOVENT HFA was evaluated at dosages of 88, 220, and 440 mcg twice daily for 12 weeks.
217 Baseline FEV₁ values were similar across groups (mean 67% of predicted normal). All 3 dosages
218 of FLOVENT HFA significantly improved asthma control as measured by improvement in AM
219 pre-dose FEV₁ compared with placebo. Pulmonary function (AM pre-dose FEV₁) improved
220 significantly with FLOVENT HFA compared with placebo after the first week of treatment, and
221 this improvement was maintained over the 12-week treatment period.

222 At Endpoint (last observation), mean change from baseline in AM pre-dose percent predicted
223 FEV₁ was greater in all 3 groups treated with FLOVENT HFA (9.0% to 11.2%) compared with
224 the placebo group (3.4%). The mean differences between the groups treated with
225 FLOVENT HFA 88, 220, and 440 mcg and the placebo group were significant, and the

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

228 Figure 1 displays results of pulmonary function tests (mean percent change from baseline in
229 FEV₁ prior to AM dose) for the recommended starting dosage of FLOVENT HFA (88 mcg twice
230 daily) and placebo from Study 1. This trial used predetermined criteria for lack of efficacy
231 (indicators of worsening asthma), resulting in withdrawal of more patients in the placebo group.
232 Therefore, pulmonary function results at Endpoint (the last evaluable FEV₁ result, including
233 most patients' lung function data) are also displayed.
234

235 **Figure 1. A 12-Week Clinical Trial in Patients ≥12 Years of Age Inadequately**
236 **Controlled on Bronchodilators Alone: Mean Percent Change From Baseline in**
237 **FEV₁ Prior to AM Dose (Study 1)**
238



239
240

241 In Study 2, FLOVENT HFA at dosages of 88, 220, and 440 mcg twice daily was evaluated
242 over 12 weeks of treatment in 415 patients with asthma who were already receiving an inhaled
243 corticosteroid at a daily dose within its recommended dose range in addition to as-needed
244 albuterol. Baseline FEV₁ values were similar across groups (mean 65% to 66% of predicted
245 normal). All 3 dosages of FLOVENT HFA significantly improved asthma control (as measured
246 by improvement in FEV₁), compared with placebo. Discontinuations from the study for lack of
247 efficacy (defined by a pre-specified decrease in FEV₁ or peak expiratory flow [PEF], or an
248 increase in use of VENTOLIN or nighttime awakenings requiring treatment with VENTOLIN)
249 were lower in the groups treated with FLOVENT HFA (6% to 11%) compared to placebo (50%).
250 Pulmonary function (AM pre-dose FEV₁) improved significantly with FLOVENT HFA
251 compared with placebo after the first week of treatment, and the improvement was maintained
252 over the 12-week treatment period.

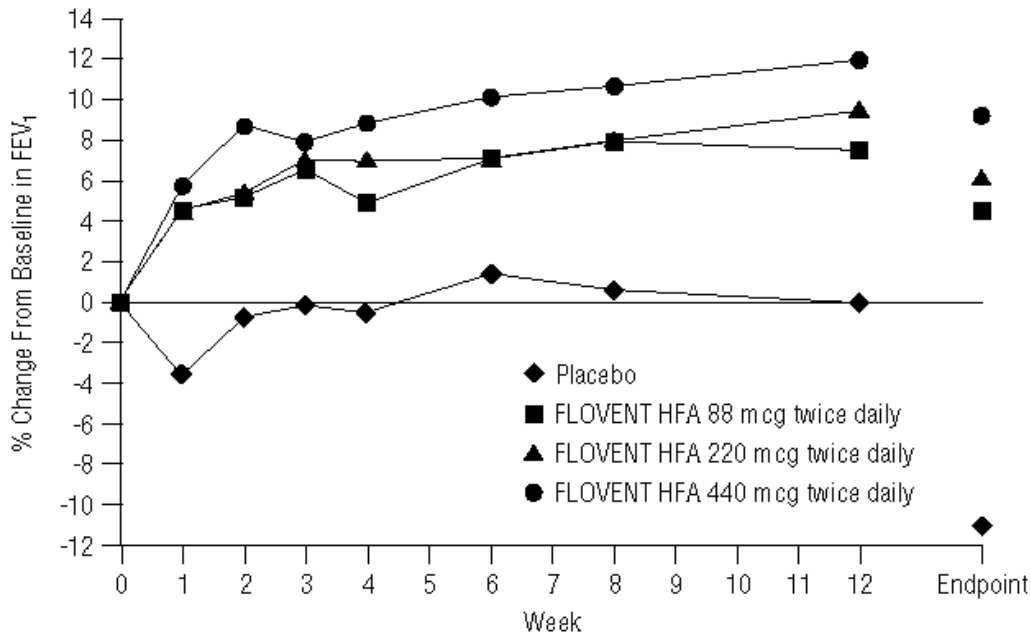
253 At Endpoint (last observation), mean change from baseline in AM pre-dose percent predicted
 254 FEV₁ was greater in all 3 groups treated with FLOVENT HFA (2.2% to 4.6%) compared with
 255 the placebo group (-8.3%). The mean differences between the groups treated with
 256 FLOVENT HFA 88, 220, and 440 mcg and the placebo group were significant, and the
 257 corresponding 95% confidence intervals were (7.1%, 13.8%), (8.2%, 14.9%), and (9.6%,
 258 16.4%), respectively.

259 Figure 2 displays the mean percent change from baseline in FEV₁ from Week 1 through Week
 260 12. This study also used predetermined criteria for lack of efficacy, resulting in withdrawal of
 261 more patients in the placebo group; therefore, pulmonary function results at Endpoint are
 262 displayed.

263

264 **Figure 2. A 12-Week Clinical Trial in Patients ≥12 Years of Age Already**
 265 **Receiving Daily Inhaled Corticosteroids: Mean Percent Change From**
 266 **Baseline in FEV₁ Prior to AM Dose (Study 2)**

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

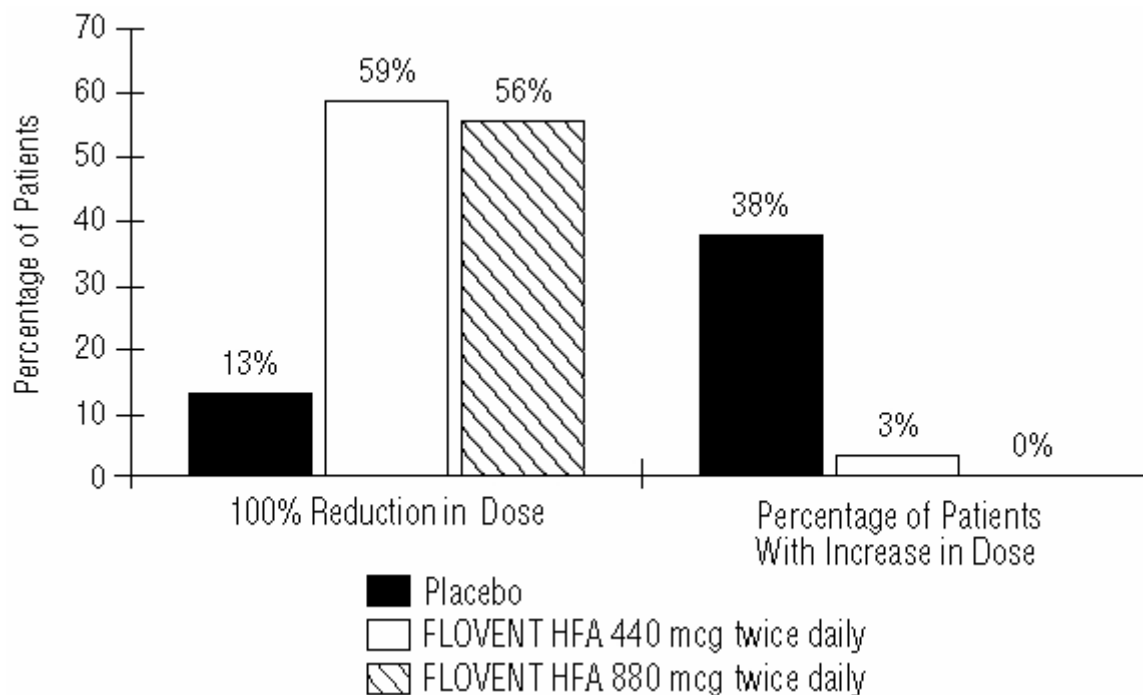
272 Study 3 enrolled 168 patients with asthma requiring oral prednisone therapy (average baseline
 273 daily prednisone dose ranged from 13 to 14 mg). FLOVENT HFA at dosages of 440 and
 274 880 mcg twice daily was evaluated over a 16-week treatment period. Baseline FEV₁ values were
 275 similar across groups (mean 59% to 62% of predicted normal). Over the course of the study,
 276 patients treated with either dosage of FLOVENT HFA required a significantly lower mean daily
 277 oral prednisone dose (6 mg) compared with placebo-treated patients (15 mg). Both dosages of
 278 FLOVENT HFA enabled a larger percentage of patients (59% and 56% in the groups treated

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

285

286 **Figure 3. A 16-Week Clinical Trial in Patients ≥ 12 Years of Age Requiring Chronic**
 287 **Oral Prednisone Therapy: Change in Maintenance Prednisone Dose**

288



289

290

291 Two long-term safety studies (Study 4 and Study 5) of ≥ 6 months' duration were conducted in
 292 507 adolescent and adult patients with asthma. Study 4 was designed to monitor the safety of
 293 2 doses of FLOVENT HFA, while Study 5 compared fluticasone propionate HFA and
 294 fluticasone propionate CFC. Study 4 enrolled 182 patients who were treated daily with low to
 295 high doses of inhaled corticosteroids, beta-agonists (short-acting [as needed or regularly
 296 scheduled] or long-acting), theophylline, inhaled cromolyn or nedocromil sodium, leukotriene
 297 receptor antagonists, or 5-lipoxygenase inhibitors at baseline. FLOVENT HFA at dosages of 220
 298 and 440 mcg twice daily was evaluated over a 26-week treatment period in 89 and 93 patients,
 299 respectively. Study 5 enrolled 325 patients who were treated daily with moderate to high doses
 300 of inhaled corticosteroids, with or without concurrent use of salmeterol or albuterol, at baseline.
 301 Fluticasone propionate HFA at a dosage of 440 mcg twice daily and fluticasone propionate CFC
 302 at a dosage of 440 mcg twice daily were evaluated over a 52-week treatment period in 163 and
 303 162 patients, respectively. Baseline FEV₁ values were similar across groups (mean 81% to 84%

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

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

312 **INDICATIONS AND USAGE**

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

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

318 **CONTRAINDICATIONS**

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

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

323 **WARNINGS**

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

330 Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid
331 use after transferring to FLOVENT HFA. In a clinical trial of 168 patients, prednisone reduction
332 was successfully accomplished by reducing the daily prednisone dose on a weekly basis
333 following initiation of treatment with FLOVENT HFA. Successive reduction of prednisone dose
334 was allowed only when lung function; symptoms; and as-needed, short-acting beta-agonist use
335 were better than or comparable to that seen before initiation of prednisone dose reduction. Lung
336 function (FEV₁ or AM PEF), beta-agonist use, and asthma symptoms should be carefully
337 monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and
338 symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as
339 fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

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

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

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

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

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

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

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

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

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

389 **PRECAUTIONS**

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

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

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

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

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

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

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

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

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

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

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

- 461 6. After inhalation, rinse the mouth with water and spit out. Do not swallow.
462 7. Clean the inhaler at least once a week after the evening dose. Keeping the canister and plastic
463 actuator clean is important to prevent medicine buildup. (See the cleaning instructions in the
464 Information for the Patient leaflet accompanying the product.)
465 8. Use FLOVENT HFA only with the actuator supplied with the product. When the counter
466 reads 020, contact the pharmacist for a refill of medication or consult the physician to
467 determine whether a prescription refill is needed. Discard the inhaler when the counter reads
468 000. Never try to alter the numbers or remove the counter from the metal canister.
469 9. For important summary information and instructions for the proper use of FLOVENT HFA,
470 the patient should carefully read and follow the Information for the Patient leaflet
471 accompanying the product.

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

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

488 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Fluticasone propionate
489 demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately
490 2 and 10 times the maximum recommended human daily inhalation dose in adults and children,
491 respectively, on a mcg/m² basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less
492 than and equivalent to the maximum recommended human daily inhalation dose in adults and
493 children, respectively, on a mcg/m² basis) for 104 weeks.

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

497 No evidence of impairment of fertility was observed in reproductive studies conducted in
498 male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum
499 recommended human daily inhalation dose on a mcg/m² basis). Prostate weight was significantly
500 reduced at a subcutaneous dose of 50 mcg/kg.

501 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Subcutaneous studies in the
502 mouse and rat at 45 and 100 mcg/kg, respectively (less than the maximum recommended human
503 daily inhalation dose on a mcg/m² basis), revealed fetal toxicity characteristic of potent
504 corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate,
505 and retarded cranial ossification. No teratogenicity was seen in the rat at inhalation doses up to
506 68.7 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m²
507 basis).

508 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of
509 4 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m²
510 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg
511 (approximately 3 times the maximum recommended human daily inhalation dose on a mcg/m²
512 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this
513 study, consistent with the established low bioavailability following oral administration (see
514 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Absorption*).

515 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose
516 of 100 mcg/kg to mice (less than the maximum recommended human daily inhalation dose on a
517 mcg/m² basis), a subcutaneous or an oral dose of 100 mcg/kg to rats (less than the maximum
518 recommended daily inhalation dose on a mcg/m² basis), and an oral dose of 300 mcg/kg to
519 rabbits (approximately 3 times the maximum recommended human daily inhalation dose on a
520 mcg/m² basis).

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

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

529 **Nursing Mothers:** It is not known whether fluticasone propionate is excreted in human breast
530 milk. However, other corticosteroids have been detected in human milk. Subcutaneous
531 administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (less than the
532 maximum recommended human daily inhalation dose on a mcg/m² basis) resulted in measurable
533 radioactivity in milk.

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

537 Caution should be exercised when FLOVENT HFA is administered to a nursing woman.

538 **Pediatric Use:** The safety and effectiveness of FLOVENT HFA in children 12 years of age and
539 older have been established (see CLINICAL PHARMACOLOGY: Pharmacokinetics: *Special*
540 *Populations: Pediatric*, CLINICAL TRIALS: Pediatric Patients, ADVERSE REACTIONS:

541 Pediatric Patients). Use of FLOVENT HFA in patients 4 to 11 years of age is supported by
542 evidence from adequate and well-controlled studies in adults and adolescents 12 years of age and
543 older, pharmacokinetic studies in patients 4 to 11 years of age, established efficacy of fluticasone
544 propionate formulated as FLOVENT[®] DISKUS[®] (fluticasone propionate inhalation powder) and
545 FLOVENT[®] ROTADISK[®] (fluticasone propionate inhalation powder) in patients 4 to 11 years
546 of age, and supportive findings with FLOVENT HFA in a study conducted in patients 4 to
547 11 years of age. Types of adverse events in pediatric patients 4 to 11 years of age were generally
548 similar to those observed in adults and adolescents.

549 **Children Less Than 4 Years of Age: Pharmacokinetics:** A 12-week, double-blind,
550 placebo-controlled, parallel-group study was conducted in children with asthma aged 1 to <4
551 years. Population pharmacokinetics analyses were conducted in 164 children treated with 88 mcg
552 of FLOVENT HFA administered twice daily with the AeroChamber Plus VHC with facemask.
553 The predicted AUC_{0-τ} and C_{max} ranged from 58.30 to 923.90 pg•hr/mL with a median of 129.05
554 pg•hr/mL and from 15.71 to 85.13 pg/mL with a median of 20.30 pg/mL, respectively. Predicted
555 geometric means for AUC_{0-τ} and C_{max} were 141 pg•hr/mL (95% CI: 127, 156) and 22 pg/mL
556 (95% CI: 21, 23), respectively, indicating higher levels of exposure in children aged 1 to <4
557 years compared to those in children aged 4 to 11 years (see CLINICAL PHARMACOLOGY:
558 Pharmacokinetics: *Special Populations: Pediatric*). Non-compartmental pharmacokinetic
559 analyses in children aged 4 to 11 years showed AUC_{0-τ} and C_{max} ranged from not calculable to
560 322 pg•hr/mL with a median of 30.20 pg•hr/mL and from below the limit of quantitation (BLQ)
561 to 87.4 pg/mL with median of 18.8 pg/mL, respectively when the same dosage of FLOVENT
562 HFA was administered without the VHC and facemask.

563 In a study in children 6 to <12 months of age with reactive airways disease, plasma
564 fluticasone propionate was measured over a 12-hour dosing period after 4 weeks of treatment
565 with 88 mcg of FLOVENT HFA twice daily with an AeroChamber Plus VHC with facemask.
566 The AUC_{0-τ} and C_{max} ranged from not calculable to 671.74 pg•hr/mL with a median of 104.2
567 pg•hr/mL and from BLQ to 106 pg/mL with a median of 32.0 pg/mL, respectively. The
568 geometric means for AUC_{0-τ} and C_{max} were 75 pg•hr/mL (95% CI: 34, 166; N = 16) and
569 25 pg/mL (95% CI: 13, 45; N = 17), respectively. The geometric mean AUC_{0-τ} and C_{max} values
570 in children 6 to <12 months of age were higher than those in children aged 4 to 11 years taking
571 the same dosage of FLOVENT HFA without the VHC and facemask (see CLINICAL
572 PHARMACOLOGY: Pharmacokinetics: *Special Populations: Pediatric*).

573 Population pharmacokinetic analysis of 102 male and 62 female subjects with asthma aged 1
574 to <4 years indicated that systemic exposure was not influenced by patient demographics,
575 including gender. No overall differences in fluticasone propionate pharmacokinetics were
576 observed between male and female patients with asthma.

577 **Pharmacodynamics:** A 12-week, double-blind, placebo-controlled, parallel-group study
578 was conducted in children with asthma aged 1 to <4 years. Twelve-hour overnight urinary
579 cortisol excretion after a 12-week treatment period with 88 mcg of FLOVENT HFA twice daily
580 (n = 73) and with placebo (n = 42) were calculated. The mean and median change from baseline

581 in urine cortisol over 12 hours were -0.7 and 0.0 mcg for FLOVENT HFA and 0.3 and -0.2 mcg
582 for placebo treatments, respectively.

583 In a 1-way crossover study in children 6 to <12 months of age with reactive airways disease
584 (N = 21), serum cortisol was measured over a 12-hour dosing period. Patients received placebo
585 treatment for a 2-week period followed by a 4-week treatment period with 88 mcg of FLOVENT
586 HFA twice daily with an AeroChamber Plus VHC with facemask. The geometric mean ratio of
587 serum cortisol over 12 hours ($AUC_{0-12\text{ hr}}$) following FLOVENT HFA (n = 16) versus placebo
588 (n = 18) was 0.95 (95% CI: 0.72, 1.27).

589 **Safety:** FLOVENT HFA administered as 88 mcg twice daily has been evaluated for safety
590 in 239 pediatric patients 1 to <4 years of age in a 12-week, double-blind, placebo-controlled
591 study. Treatments were administered with an AeroChamber Plus VHC with facemask. In
592 pediatric patients 1 to <4 years of age receiving FLOVENT HFA, the following events occurred
593 with a frequency >3% and more frequently than in pediatric patients who received placebo,
594 regardless of causality assessment: pyrexia, nasopharyngitis, upper respiratory tract infection,
595 vomiting, otitis media, diarrhea, bronchitis, pharyngitis, and viral infection.

596 FLOVENT HFA administered as 88 mcg twice daily has also been evaluated for safety in 23
597 pediatric patients 6 to 12 months of age in an open-label placebo-controlled study. Treatments
598 were administered with an AeroChamber Plus VHC with facemask for 2 weeks with placebo
599 followed by 4 weeks with active drug. Adverse events after placebo and active drug were similar
600 in kind and frequency.

601 **In Vitro Testing of Dose Delivery With Holding Chambers:** In vitro dose
602 characterization studies were performed to evaluate the delivery of FLOVENT HFA via holding
603 chambers with attached facemasks. The studies were conducted with 2 different holding
604 chambers (AeroChamber Plus VHC and AeroChamber Z-STAT Plus™ VHC) and facemasks
605 (small and medium size) at inspiratory flow rates of 4.9, 8.0, and 12.0 L/min in combination with
606 holding times of 0, 2, 5, and 10 seconds. The flow rates were selected to be representative of
607 inspiratory flow rates of children aged 6 to 12 months, 2 to 5 years, and over 5 years,
608 respectively. The mean delivered dose of fluticasone propionate through the holding chambers
609 with facemasks was lower than the 44 mcg of fluticasone propionate delivered directly from the
610 actuator mouthpiece. The results were similar through both holding chambers (see Table 1 for
611 data for the AeroChamber Plus VHC). The fine particle fraction (approximately 1 to 5 μm)
612 across the flow rates used in these studies was 70% to 84% of the delivered dose, consistent with
613 the removal of the coarser fraction by the holding chamber. In contrast, the fine particle fraction
614 for FLOVENT HFA delivered without a holding chamber typically represents 42% to 55% of the
615 delivered dose measured at the standard flow rate of 28.3 L/min. These data suggest that even at
616 low flow rates and extended holding times potentially experienced in realistic situations with
617 young children, an adequate amount of fluticasone propionate can be delivered to pediatric
618 patients via a holding chamber and facemask at the recommended doses.

619

620
621

Table 1: In Vitro Medication Delivery Through AeroChamber Plus® Valved Holding Chamber With a Facemask

Age	Facemask	Flow Rate (L/min)	Holding Time (seconds)	Mean Medication Delivery Through AeroChamber Plus VHC (mcg/actuation)	Body Weight 50 th Percentile (kg)*	Medication Delivered per Actuation (mcg/kg) [†]
6 to 12 Months	Small	4.9	0	8.3	7.5-9.9	0.8-1.1
			2	6.7		0.7-0.9
			5	7.5		0.8-1.0
			10	7.5		0.8-1.0
2 to 5 Years	Small	8.0	0	7.3	12.3-18.0	0.4-0.6
			2	6.8		0.4-0.6
			5	6.7		0.4-0.5
			10	7.7		0.4-0.6
2 to 5 Years	Medium	8.0	0	7.8	12.3-18.0	0.4-0.6
			2	7.7		0.4-0.6
			5	8.1		0.5-0.7
			10	9.0		0.5-0.7
>5 Years	Medium	12.0	0	12.3	18.0	0.7
			2	11.8		0.7
			5	12.0		0.7
			10	10.1		0.6

622 * Centers for Disease Control growth charts, developed by the National Center for Health
623 Statistics in collaboration with the National Center for Chronic Disease Prevention and Health
624 Promotion (2000). Ranges correspond to the average of the 50th percentile weight for boys
625 and girls at the ages indicated.

626 † A single inhalation of FLOVENT HFA in a 70-kg adult without use of a valved holding
627 chamber and facemask delivers approximately 44 mcg, or 0.6 mcg/kg.
628

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

634 Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in
635 growth in pediatric patients. In these studies, the mean reduction in growth velocity was
636 approximately 1 cm/year (range, 0.3 to 1.8 cm/year) and appears to depend upon dose and
637 duration of exposure. This effect was observed in the absence of laboratory evidence of HPA
638 axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic

639 corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis
640 function. The long-term effects of this reduction in growth velocity associated with orally
641 inhaled corticosteroids, including the impact on final adult height, are unknown. The potential
642 for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids
643 has not been adequately studied. The effects on growth velocity of treatment with orally inhaled
644 corticosteroids for over 1 year, including the impact on final adult height, are unknown. The
645 growth of children and adolescents receiving orally inhaled corticosteroids, including
646 FLOVENT HFA, should be monitored routinely (e.g., via stadiometry). The potential growth
647 effects of prolonged treatment should be weighed against the clinical benefits obtained and the
648 risks associated with alternative therapies. To minimize the systemic effects of orally inhaled
649 corticosteroids, including FLOVENT HFA, each patient should be titrated to the lowest dose that
650 effectively controls his/her symptoms.

651 Since a cross study comparison in adolescent and adult patients (≥ 12 years of age) indicated
652 that systemic exposure of inhaled fluticasone propionate from FLOVENT HFA would be higher
653 than exposure from FLOVENT ROTADISK, results from a study to assess the potential growth
654 effects of FLOVENT ROTADISK in pediatric patients (4 to 11 years of age) are provided.

655 A 52-week placebo-controlled study to assess the potential growth effects of fluticasone
656 propionate inhalation powder (FLOVENT ROTADISK) at 50 and 100 mcg twice daily was
657 conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to
658 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were
659 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and
660 5.66 cm/year in the 100-mcg group (n = 89). An imbalance in the proportion of children entering
661 puberty between groups and a higher dropout rate in the placebo group due to poorly controlled
662 asthma may be confounding factors in interpreting these data. A separate subset analysis of
663 children who remained prepubertal during the study revealed growth rates at 52 weeks of
664 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and
665 5.67 cm/year in the 100-mcg group (n = 79). In children 8.5 years of age, the mean age of
666 children in this study, the range for expected growth velocity is: boys – 3rd
667 percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls –
668 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year.

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

674 **Geriatric Use:** Of the total number of patients treated with FLOVENT HFA in US and non-US
675 clinical trials, 173 were 65 years of age or older, 19 of which were 75 years of age or older. No
676 apparent differences in safety or efficacy were observed between these patients and younger
677 patients. No overall differences in safety were observed between these patients and younger
678 patients, and other reported clinical experience has not identified differences in responses

679 between the elderly and younger patients, but greater sensitivity of some older individuals cannot
 680 be ruled out. In general, dose selection for an elderly patient should be cautious, reflecting the
 681 greater frequency of decreased hepatic function and of concomitant disease or other drug
 682 therapy.

683 **ADVERSE REACTIONS**

684 **Adolescent and Adult Patients:** The incidence of common adverse events in Table 2 is
 685 based upon 2 placebo-controlled US clinical trials in which 812 adolescent and adult patients
 686 (457 females and 355 males) previously treated with as-needed bronchodilators and/or inhaled
 687 corticosteroids were treated twice daily for up to 12 weeks with 2 inhalations of FLOVENT HFA
 688 44 mcg Inhalation Aerosol, FLOVENT HFA 110 mcg Inhalation Aerosol, FLOVENT HFA
 689 220 mcg Inhalation Aerosol (dosages of 88, 220, or 440 mcg twice daily) or placebo.

690

691 **Table 2. Overall Adverse Events With >3% Incidence in US Controlled Clinical Trials**
 692 **With FLOVENT HFA in Patients ≥12 Years of Age With Asthma Previously Receiving**
 693 **Bronchodilators and/or Inhaled Corticosteroids**

Adverse Event	FLOVENT HFA 88 mcg Twice Daily (n = 203) %	FLOVENT HFA 220 mcg Twice Daily (n = 204) %	FLOVENT HFA 440 mcg Twice Daily (n = 202) %	Placebo (n = 203) %
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 & 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

694

695 Table 2 includes all events (whether considered drug-related or nondrug-related by the
 696 investigator) that occurred at a rate of over 3% in any of the groups treated with FLOVENT HFA

697 and were more common than in the placebo group. In considering these data, differences in
698 average duration of exposure should be taken into account.

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

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

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

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

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

708 **Neurological:** Dizziness, migraines.

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

710 **Skin:** Viral skin infections.

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

712 **Urogenital:** Urinary infections.

713 Fluticasone propionate inhalation aerosol (440 or 880 mcg twice daily) was administered for
714 16 weeks to patients with asthma requiring oral corticosteroids (Study 3). Adverse events not
715 included in Table 2, but reported by >3 patients in either group treated with FLOVENT HFA and
716 more commonly than in the placebo group included rhinitis, nausea and vomiting, arthralgia and
717 articular rheumatism, musculoskeletal pain, muscle pain, malaise and fatigue, and sleep
718 disorders.

719 In 2 long-term studies (26 and 52 weeks), treatment with FLOVENT HFA at dosages up to
720 440 mcg twice daily was well tolerated. The pattern of adverse events was similar to that
721 observed in the 12-week studies. There were no new and/or unexpected adverse events with
722 long-term treatment.

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

726 **Observed During Clinical Practice:** In addition to adverse events reported from clinical
727 trials, the following events have been identified during postmarketing use of fluticasone
728 propionate. Because they are reported voluntarily from a population of unknown size, estimates
729 of frequency cannot be made. These events have been chosen for inclusion due to a combination
730 of their seriousness, frequency of reporting, or potential causal connection to fluticasone
731 propionate.

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

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

736 **Eye:** Cataracts.

737 **Non-Site Specific:** Very rare anaphylactic reaction.
738 **Psychiatry:** Agitation, aggression, anxiety, depression, and restlessness. Behavioral
739 changes, including hyperactivity and irritability, have been reported very rarely and primarily in
740 children.
741 **Respiratory:** Asthma exacerbation, chest tightness, cough, dyspnea, immediate and delayed
742 bronchospasm, paradoxical bronchospasm, pneumonia, and wheeze.
743 **Skin:** Contusions, cutaneous hypersensitivity reactions, ecchymoses, and pruritus.
744 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate may
745 present with systemic eosinophilic conditions, with some patients presenting with clinical
746 features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated
747 with systemic corticosteroid therapy. These events usually, but not always, have been associated
748 with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of
749 fluticasone propionate (see PRECAUTIONS: Eosinophilic Conditions).

750 **OVERDOSAGE**

751 Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS:
752 General). Inhalation by healthy volunteers of a single dose of 1,760 or 3,520 mcg of fluticasone
753 propionate CFC inhalation aerosol was well tolerated. Doses of 1,320 mcg administered to
754 healthy human volunteers twice daily for 7 to 15 days were also well tolerated. Repeat oral doses
755 up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for
756 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and
757 incidences were similar in active and placebo treatment groups. The oral median lethal dose in
758 mice was >1,000 mg/kg (approximately $\geq 2,300$ and >11,000 times the maximum human daily
759 inhalation dose in adults and children on a mg/m² basis, respectively), and the subcutaneous
760 median lethal dose in rats was >1,000 mg/kg (approximately >4,600 and >22,000 times the
761 maximum human daily inhalation dose in adults and children on a mg/m² basis, respectively).

762 **DOSAGE AND ADMINISTRATION**

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

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

771 The recommended starting dosage and the highest recommended dosage of FLOVENT HFA,
772 based on prior asthma therapy, are listed in Table 3.

773

774 **Table 3. Recommended Dosages of FLOVENT HFA**

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

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

777 * **For Patients Currently Receiving Inhaled Corticosteroid Therapy:** Starting dosages above
 778 88 mcg twice daily may be considered for patients with poorer asthma control or those who
 779 have previously required doses of inhaled corticosteroids that are in the higher range for that
 780 specific agent.

781 † **For Patients Currently Receiving Chronic Oral Corticosteroid Therapy:** Prednisone
 782 should be reduced no faster than 2.5 to 5 mg/day on a weekly basis, beginning after at least
 783 1 week of therapy with FLOVENT HFA. Patients should be carefully monitored for signs of
 784 asthma instability, including serial objective measures of airflow, and for signs of adrenal
 785 insufficiency (see WARNINGS). Once prednisone reduction is complete, the dosage of
 786 fluticasone propionate HFA should be reduced to the lowest effective dosage.

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

788
 789 FLOVENT HFA should be primed before using for the first time by releasing 4 test sprays
 790 into the air away from the face, shaking well for 5 seconds before each spray. In cases where the
 791 inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler
 792 again by shaking well for 5 seconds and releasing 1 test spray into the air away from the face.

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

797 **Directions for Use:** An Information for the Patient leaflet containing illustrated instructions for
 798 use accompany each package of FLOVENT HFA.

799 **HOW SUPPLIED**

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

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

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

806 Each canister is fitted with a dose counter, supplied with a dark orange oral actuator with a
807 peach strapcap, and sealed in a plastic-coated, moisture-protective foil pouch with a desiccant
808 that should be discarded when the pouch is opened. Each canister is packaged with an
809 Information for the Patient leaflet.

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

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

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

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

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

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

824

825 DISKUS, FLOVENT, ROTADISK, and VENTOLIN are registered trademarks of
826 GlaxoSmithKline.

827 AeroChamber Plus is a registered trademark and AeroChamber Z-STAT Plus is a trademark of
828 Monaghan Medical Corp. or an affiliate of Monaghan Medical Corp.

829

830



831

832 GlaxoSmithKline

833 Research Triangle Park, NC 27709

834

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836

837 June 2008

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838

839

PHARMACIST—DETACH HERE AND GIVE LEAFLET TO PATIENT

840

841

842 **Information for the Patient**

843
844 **FLOVENT[®] [flō'vent] HFA 44 mcg**
845 **(fluticasone propionate 44 mcg)**
846 **Inhalation Aerosol**

847
848 **FLOVENT[®] HFA 110 mcg**
849 **(fluticasone propionate 110 mcg)**
850 **Inhalation Aerosol**

851
852 **FLOVENT[®] HFA 220 mcg**
853 **(fluticasone propionate 220 mcg)**
854 **Inhalation Aerosol**

855
856 **FOR ORAL INHALATION ONLY**

857
858 Read this leaflet carefully before you start to use FLOVENT HFA Inhalation Aerosol.

859 Keep this leaflet because it has important summary information about FLOVENT HFA. This
860 leaflet does not contain all the information about your medicine. If you have any questions or are
861 not sure about something, you should ask your doctor or pharmacist.

862 Read the new leaflet that comes with each refill of your prescription because there may be
863 new information.

864
865 **What is FLOVENT HFA?**

866 FLOVENT HFA contains a medicine called fluticasone propionate, which is a synthetic
867 corticosteroid. Corticosteroids are natural substances found in the body that help fight
868 inflammation. Corticosteroids are used to treat asthma because they reduce airway inflammation.

869 FLOVENT HFA is used to treat asthma in patients 4 years of age and older. When inhaled
870 regularly, FLOVENT HFA also helps to prevent symptoms of asthma.

871 FLOVENT HFA comes in 3 strengths. Your doctor has prescribed the one that is best for your
872 condition.

873
874 **Who should not use FLOVENT HFA?**

875 Do not use FLOVENT HFA if you:

- 876 • are allergic to any of the ingredients in FLOVENT HFA or other inhaled corticosteroids. See
877 “What are the ingredients in FLOVENT HFA?” below.
- 878 • have an acute asthma attack or status asthmaticus. **FLOVENT HFA is not a bronchodilator**
879 **and should not be used to give you fast relief from your breathing problems during an**
880 **asthma attack.** Always use a short-acting bronchodilator (rescue medicine), such as

881 albuterol inhaler, during a sudden asthma attack. You must take FLOVENT HFA at regular
882 times as recommended by your doctor, and not as an emergency medicine.

883

884 **What should I tell my doctor before taking FLOVENT HFA?**

885 **Tell your doctor if you are:**

- 886 • pregnant or planning to become pregnant. It is not known if FLOVENT HFA will harm your
887 unborn baby.
- 888 • breastfeeding a baby. It is not known if FLOVENT HFA passes into your breast milk.
- 889 • exposed to chickenpox or measles.

890 Tell your doctor about all the medicines you take including prescription and non-prescription
891 medicines, vitamins, and herbal supplements. FLOVENT HFA may affect the way other
892 medicines work, and other medicines may affect how FLOVENT HFA works. Especially, tell
893 your doctor if you take:

- 894 • a medicine containing ritonavir (commonly used to treat HIV infection or AIDS). The
895 anti-HIV medicines NORVIR[®] (ritonavir capsules) Soft Gelatin, NORVIR (ritonavir oral
896 solution), and KALETRA[®] (lopinavir/ritonavir) Tablets contain ritonavir.
- 897 • any other corticosteroids.

898

899 **How should I use FLOVENT HFA?**

- 900 1. It is important that you inhale each dose as your doctor has prescribed. The prescription label
901 provided by your pharmacist will usually tell you what dose to take and how often. If it
902 doesn't, or if you are not sure, ask your doctor or pharmacist. **DO NOT** inhale more doses or
903 use your FLOVENT HFA more often than your doctor has prescribed.
- 904 2. It may take 1 to 2 weeks or longer for this medicine to work, and it is very important that you
905 use it regularly. **Do not stop taking FLOVENT HFA, even if you are feeling better,**
906 **unless your doctor tells you to.**
- 907 3. If you miss a dose, just take your next scheduled dose when it is due. **Do not double the**
908 **dose.**
- 909 4. Your doctor may prescribe additional medicine (such as fast-acting bronchodilators) for
910 emergency relief if a sudden asthma attack occurs. Contact your doctor if:
 - 911 • an asthma attack does not respond to the additional medicine or
 - 912 • you need more of the additional medicine than usual.
- 913 5. If you also use another medicine by inhalation, you should ask your doctor for instructions on
914 when to use it while you are also using FLOVENT HFA.

915

916 **What are the possible side effects of FLOVENT HFA?**

917 Common side effects in adults and children using FLOVENT HFA include:

- 918 • a cold or upper respiratory tract infection
- 919 • throat irritation

- 920 • headache
- 921 • thrush (fungal infection) in the mouth and throat
- 922 Other common side effects in children include:
- 923 • fever
- 924 • diarrhea
- 925 • ear infection
- 926 • vomiting
- 927 • bronchitis
- 928 • inflammation of the nose and throat
- 929 • viral infection

930 Tell your doctor if you have any side effect that bothers you or that does not go away. These
 931 are not all the possible side effects of FLOVENT HFA. For more information ask your doctor or
 932 pharmacist.

933 Call your doctor for medical advice about side effects. You may report side effects to FDA at
 934 1-800-FDA-1088.

935

936 **What are the ingredients in FLOVENT HFA?**

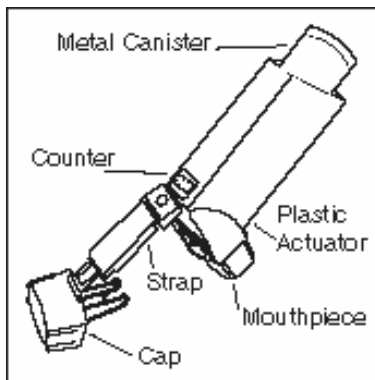
937 Active ingredient: fluticasone propionate (micronized)

938 Inactive ingredient: propellant HFA-134a

939

940 **Instructions for Using FLOVENT HFA**

941 **The parts of your FLOVENT HFA**



942 **Figure 1**

944 There are 2 main parts to your FLOVENT HFA
 945 inhaler—the metal canister that holds the medicine and the
 946 dark orange plastic actuator that sprays the medicine from
 947 the canister (see Figure 1).

948 The canister has a counter to show how many sprays of
 949 medicine you have left. The number shows through a
 950 window in the back of the actuator. The counter starts at
 951 124. The number will count down by 1 each time you spray
 952 the inhaler. The counter will stop counting at 000.

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

955 The mouthpiece of the actuator is covered by a cap. A strap on this cap keeps it attached to the
 956 actuator.

957 **Do not use the actuator with a canister of medicine from any other inhaler. And do not**
958 **use a FLOVENT HFA canister with an actuator from any other inhaler.**

959

960 **Using your FLOVENT HFA**

- 961 • The inhaler should be at room temperature before you use it.
- 962 • Take your FLOVENT HFA inhaler out of the moisture-protective foil pouch just before you
963 use it for the first time. Safely throw away the foil pouch and the drying packet that comes
964 inside the pouch.

- 965 • **Priming the inhaler:**

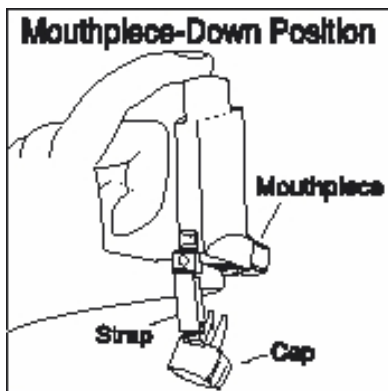
966 **Before you use FLOVENT HFA for the first time, you must prime the inhaler so that**
967 **you will get the right amount of medicine when you use it.** To prime the inhaler, take the
968 cap off the mouthpiece and shake the inhaler well for 5 seconds. Then spray the inhaler into
969 the air away from your face. **Avoid spraying in eyes.** Shake and spray the inhaler like this 3
970 more times to finish priming it. The counter should now read 120.

971 You must prime the inhaler again if you have not used it in more than 7 days or if you
972 drop it. Take the cap off the mouthpiece and shake the inhaler well for 5 seconds. Then spray
973 it 1 time into the air away from your face.

- 974 • An adult should watch a child use the inhaler to be sure it is used correctly. If a child needs
975 help using the inhaler, an adult should help the child use the inhaler with or without a holding
976 chamber attached to a facemask. The adult should follow the instructions that came with the
977 holding chamber.

978

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



981
982

Figure 2

- 983 1. **Take the cap off the mouthpiece of the actuator** (see
984 Figure 2).
985 Look inside the mouthpiece for foreign objects, and
986 take out any you see.
987 Make sure the canister fits firmly in the actuator.
988 **Shake the inhaler well** for 5 seconds.
- 989 2. Hold the inhaler with the mouthpiece down (see Figure
990 2). **Breathe out through your mouth** and push as
991 much air from your lungs as you can. Put the
992 mouthpiece in your mouth and close your lips around it.

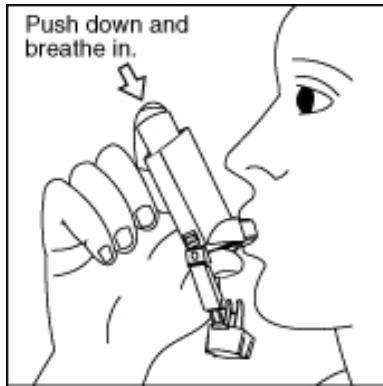


Figure 3

- 995 3. Push the top of the canister all the way down while you
996 breathe in deeply and slowly through your mouth (see
997 Figure 3)
998 Right after the spray comes out, take your finger off
999 the canister. After you have breathed in all the way,
1000 take the inhaler out of your mouth and close your
1001 mouth.
- 1002 4. **Hold your breath as long as you can**, up to 10
1003 seconds. Then breathe normally.
- 1004 5. **Wait about 30 seconds and shake the inhaler well** for
1005 5 seconds. Repeat steps 2 through 4.
- 1006 6. After you finish taking this medicine, rinse your mouth
1007 with water. Spit out the water. Do not swallow it.
- 1008 7. Put the cap back on the mouthpiece after each time you
1009 use the inhaler. Make sure it snaps firmly into place.

1010 **Cleaning your FLOVENT HFA**

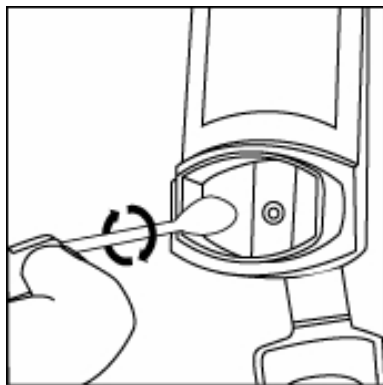


Figure 4

- 1013 Clean the inhaler at least once a week after your
1014 evening dose. It is important to keep the canister and
1015 plastic actuator clean so the medicine will not build-up
1016 and block the spray.
- 1017 1. Take the cap off the mouthpiece. The strap on the cap
1018 will stay attached to the actuator. Do not take the
1019 canister out of the plastic actuator.
- 1020 2. Use a clean cotton swab dampened with water to clean
1021 the small circular opening where the medicine sprays
1022 out of the canister. Gently twist the swab in a circular
1023 motion to take off any medicine (see Figure 4). Repeat
1024 with a new swab dampened with water to take off any
1025 medicine still at the opening.
- 1026 3. Wipe the inside of the mouthpiece with a clean tissue
1027 dampened with water. Let the actuator air-dry
1028 overnight.
- 1029 4. Put the cap back on the mouthpiece after the actuator
1030 has dried.

1031 **Storing your FLOVENT HFA**

- 1032 **Store at room temperature with the mouthpiece down.**
1033 Keep out of reach of children.

1034 **Contents Under Pressure:** Do not puncture. Do not use or store near heat or open flame.
1035 Exposure to temperatures above 120°F may cause bursting. Never throw into fire or incinerator.
1036

1037 **Replacing your FLOVENT HFA**

- 1038 • **When the counter reads 020**, you should refill your prescription or ask your doctor if you
1039 need a refill of your prescription.
- 1040 • **When the counter reads 000**, throw the inhaler away. You should not keep using the inhaler
1041 because you will not receive the right amount of medicine.
- 1042 • **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.
1043

1044 For more information go to www.floventdiskus.com or call 1-888-825-5249.

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1047
1048



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1055 June 2008

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