

PRESCRIBING INFORMATION

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

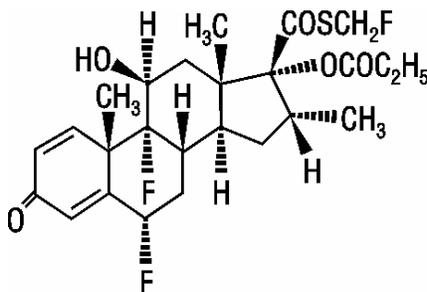
FLOVENT[®] HFA 110 mcg
(fluticasone propionate HFA 110 mcg)
Inhalation Aerosol

FLOVENT[®] HFA 220 mcg
(fluticasone propionate HFA 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 to off-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 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.

After priming, each actuation of the inhaler delivers 50, 125, or 250 mcg of fluticasone propionate in 60 mg of suspension (for the 44-mcg product) or in 75 mg of suspension (for the

34 110- and 220-mcg products) from the valve and 44, 110, or 220 mcg, respectively, of fluticasone
35 propionate from the actuator. The actual amount of drug delivered to the lung may depend on
36 patient factors, such as the coordination between the actuation of the device and inspiration
37 through the delivery system.

38 Each 10.6-g canister (44 mcg) and each 12-g canister (110 and 220 mcg) provides
39 120 inhalations.

40 FLOVENT HFA should be primed before using for the first time by releasing 4 test sprays
41 into the air away from the face, shaking well before each spray. In cases where the inhaler has
42 not been used for more than 7 days or when it has been dropped, prime the inhaler again by
43 shaking well and releasing 1 test spray into the air away 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 corticosteroid 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:** Propellant HFA-134a is devoid of pharmacological activity except at very high
68 doses in animals (i.e., 380 to 1,300 times the maximum human exposure based on comparisons of
69 area under the plasma concentration versus time curve [AUC] values), primarily producing
70 ataxia, tremors, dyspnea, or salivation. These events are similar to effects produced by the
71 structurally related CFCs, which have been used extensively in metered-dose inhalers.

72 In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly
73 eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to 7 minutes in
74 humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both
75 extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of
76 accumulation.

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) pg/mL , respectively. Systemic exposure from
88 fluticasone propionate HFA 220 mcg was 30% lower than that from the CFC-propelled
89 fluticasone propionate inhaler. Systemic exposure was measured in subjects with asthma who
90 received 2 inhalations of fluticasone propionate HFA 44 mcg (n = 20), 110 mcg (n = 15), or
91 220 mcg (n = 17) twice daily for at least 4 weeks. The geometric means (95% CI) of $AUC_{0-12\text{ hr}}$
92 for the 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) pg/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 91%.
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 17β -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 **Gender:** Systemic exposure for 19 male and 33 female subjects with asthma from
117 2 inhalations of CFC-propelled fluticasone propionate 44, 110, and 220 mcg twice daily was
118 similar.

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

121 **Drug Interactions:** Fluticasone propionate is a substrate of cytochrome P450 3A4.
122 Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor
123 ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18
124 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was
125 coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate
126 concentrations following fluticasone propionate aqueous nasal spray alone were undetectable
127 (<10 pg/mL) in most subjects, and when concentrations were detectable, peak levels (C_{max})
128 averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and $AUC_{(0-\tau)}$ averaged 8.43 pg•hr/mL (range,
129 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range,
130 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively,
131 after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This
132 significant increase in plasma fluticasone propionate exposure resulted in a significant decrease
133 (86%) in plasma cortisol AUC.

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

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

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

144 **Pharmacodynamics:** Serum cortisol concentrations, urinary excretion of cortisol, and urine
145 6- β -hydroxycortisol excretion collected over 24 hours in 24 healthy subjects following
146 8 inhalations of fluticasone propionate HFA 44, 110, and 220 mcg decreased with increasing
147 dose. However, in subjects with asthma treated with 2 inhalations of fluticasone propionate HFA
148 44, 110, and 220 mcg twice daily for at least 4 weeks, differences in serum cortisol $AUC_{(0-12\text{ hr})}$
149 concentrations (N = 65) and 24-hour urinary excretion of cortisol (N = 47) compared with
150 placebo were not related to dose and generally not significant. In the study with healthy
151 volunteers, the effect of propellant was also evaluated by comparing results following the

152 220-mcg strength inhaler containing HFA 134a propellant with the same strength of inhaler
153 containing CFC 11/12 propellant. A lesser effect on the hypothalamic-pituitary-adrenal (HPA)
154 axis with the HFA formulation was observed for serum cortisol, but not urine cortisol and
155 6-betahydroxy cortisol excretion.

156 The potential systemic effects of fluticasone propionate HFA on the HPA axis were also
157 studied in patients with asthma. Fluticasone propionate given by inhalation aerosol at dosages of
158 440 or 880 mcg twice daily was compared with placebo in oral corticosteroid-dependent subjects
159 with asthma (range of mean dose of prednisone at baseline, 13 to 14 mg/day) in a 16-week study.
160 Consistent with maintenance treatment with oral corticosteroids, abnormal plasma cortisol
161 responses to short cosyntropin stimulation (peak plasma cortisol <18 mcg/dL) were present at
162 baseline in the majority of subjects participating in this study (69% of patients later randomized
163 to placebo and 72% to 78% of patients later randomized to fluticasone propionate HFA). At
164 week 16, 8 subjects (73%) on placebo compared to 14 (54%) and 13 (68%) subjects receiving
165 fluticasone propionate HFA (440 and 880 mcg b.i.d., respectively) had post-stimulation cortisol
166 levels of <18 mcg/dL.

167 To confirm that systemic absorption does not play a role in the clinical response to inhaled
168 fluticasone propionate, a double-blind clinical study comparing inhaled fluticasone propionate
169 powder and oral fluticasone propionate was conducted. Fluticasone propionate inhalation powder
170 in dosages of 100 and 500 mcg twice daily was compared to oral fluticasone propionate
171 20,000 mcg once daily and placebo for 6 weeks. Plasma levels of fluticasone propionate were
172 detectable in all 3 active groups, but the mean values were highest in the oral group. Both
173 dosages of inhaled fluticasone propionate were effective in maintaining asthma stability and
174 improving lung function, while oral fluticasone propionate and placebo were ineffective. This
175 demonstrates that the clinical effectiveness of inhaled fluticasone propionate is due to its direct
176 local effect and not to an indirect effect through systemic absorption.

177 **CLINICAL TRIALS**

178 Three randomized, double-blind, parallel-group, placebo-controlled clinical trials were
179 conducted in the US in 980 adolescent and adult patients (≥ 12 years of age) with asthma to
180 assess the efficacy and safety of FLOVENT HFA in the treatment of asthma. Fixed dosages of
181 88, 220, and 440 mcg twice daily (each dose administered as 2 inhalations of the 44-, 110-, and
182 220-mcg strengths, respectively) and 880 mcg twice daily (administered as 4 inhalations of the
183 220-mcg strength) were compared with placebo to provide information about appropriate dosing
184 to cover a range of asthma severity. Patients in these studies included those inadequately
185 controlled with bronchodilators alone (Study 1), those already receiving inhaled corticosteroids
186 (Study 2), and those requiring oral corticosteroid therapy (Study 3). In all 3 studies, patients
187 (including placebo-treated patients) were allowed to use VENTOLIN[®] (albuterol, USP)
188 Inhalation Aerosol as needed for relief of acute asthma symptoms. In Studies 1 and 2, other
189 maintenance asthma therapies were discontinued.

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

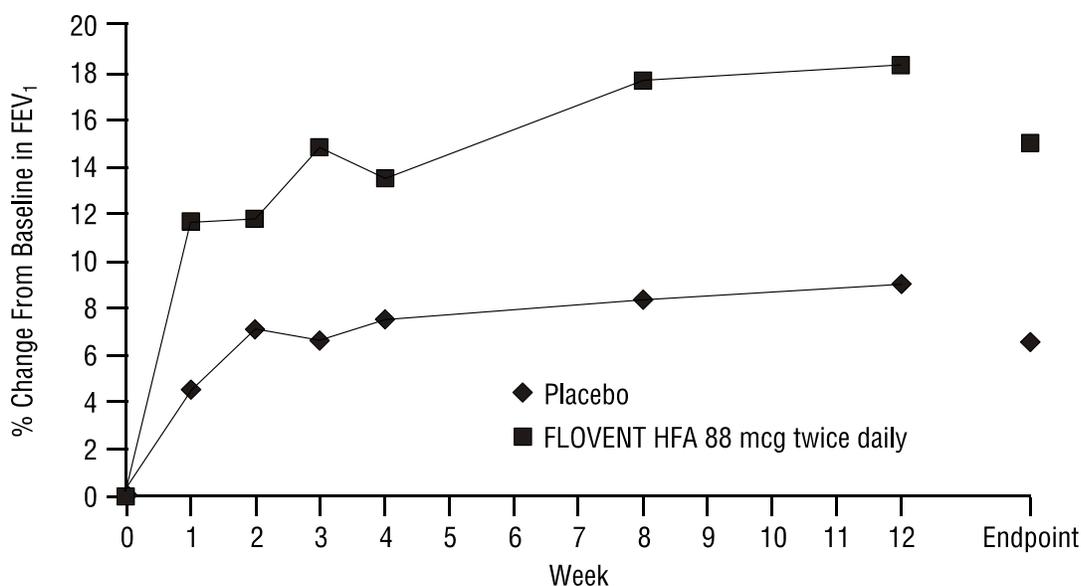
197 At Endpoint (last observation), mean change from baseline in AM pre-dose percent predicted
198 FEV₁ was greater in all 3 groups treated with FLOVENT HFA (9.0% to 11.2%) compared with
199 the placebo group (3.4%). The mean differences between the groups treated with
200 FLOVENT HFA 88, 220, and 440 mcg and the placebo group were significant, and the
201 corresponding 95% confidence intervals were (2.2%, 9.2%), (2.8%, 9.9%), and (4.3%, 11.3%),
202 respectively.

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

209

210 **Figure 1. A 12-Week Clinical Trial in Patients Inadequately Controlled on**
211 **Bronchodilators Alone: Mean Percent Change From Baseline in FEV₁ Prior**
212 **to AM Dose (Study 1)**

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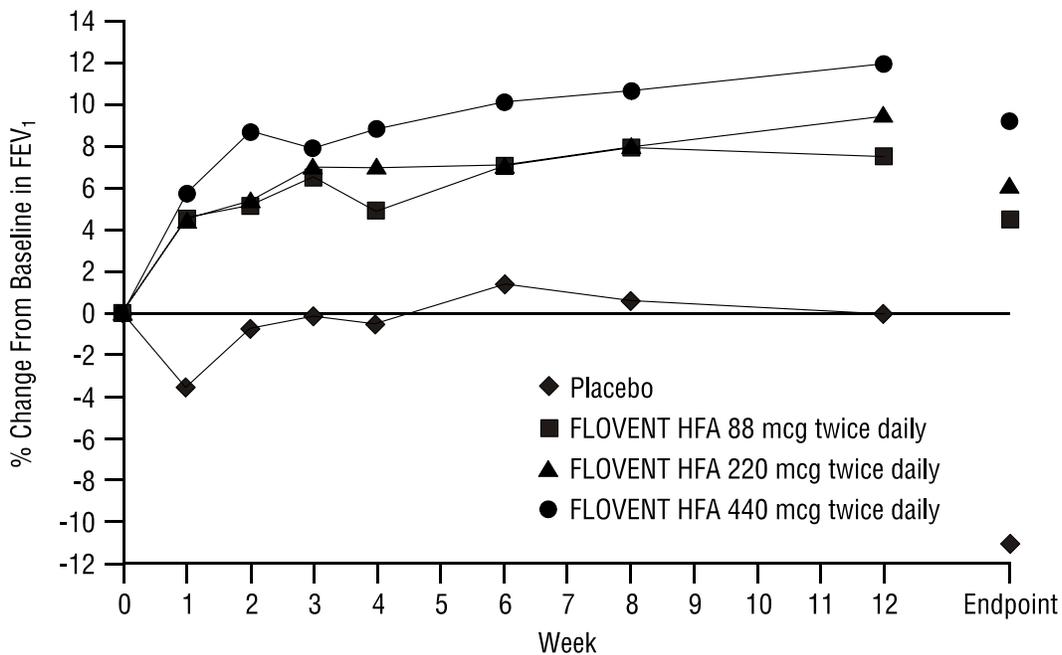
216 In Study 2, FLOVENT HFA at dosages of 88, 220, and 440 mcg twice daily was evaluated
217 over 12 weeks of treatment in 415 patients with asthma who were already receiving an inhaled

218 corticosteroid at a daily dose within its recommended dose range in addition to as-needed
 219 albuterol. Baseline FEV₁ values were similar across groups (mean 65% to 66% of predicted
 220 normal). All 3 dosages of FLOVENT HFA significantly improved asthma control (as measured
 221 by improvement in FEV₁), compared with placebo. Discontinuations from the study for lack of
 222 efficacy (defined by a pre-specified decrease in FEV₁ or peak expiratory flow [PEF], or an
 223 increase in use of VENTOLIN or nighttime awakenings requiring treatment with VENTOLIN)
 224 were lower in the groups treated with FLOVENT HFA (6% to 11%) compared to placebo (50%).
 225 Pulmonary function (AM pre-dose FEV₁) improved significantly with FLOVENT HFA
 226 compared with placebo after the first week of treatment, and the improvement was maintained
 227 over the 12-week treatment period.

228 At Endpoint (last observation), mean change from baseline in AM pre-dose percent predicted
 229 FEV₁ was greater in all 3 groups treated with FLOVENT HFA (2.2% to 4.6%) compared with
 230 the placebo group (-8.3%). The mean differences between the groups treated with
 231 FLOVENT HFA 88, 220, and 440 mcg and the placebo group were significant, and the
 232 corresponding 95% confidence intervals were (7.1%, 13.8%), (8.2%, 14.9%), and (9.6%,
 233 16.4%), respectively.

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

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 239 **Figure 2. A 12-Week Clinical Trial in Patients Already Receiving Daily**
 240 **Inhaled Corticosteroids: Mean Percent Change From Baseline in FEV₁ Prior**
 241 **to AM Dose (Study 2)**
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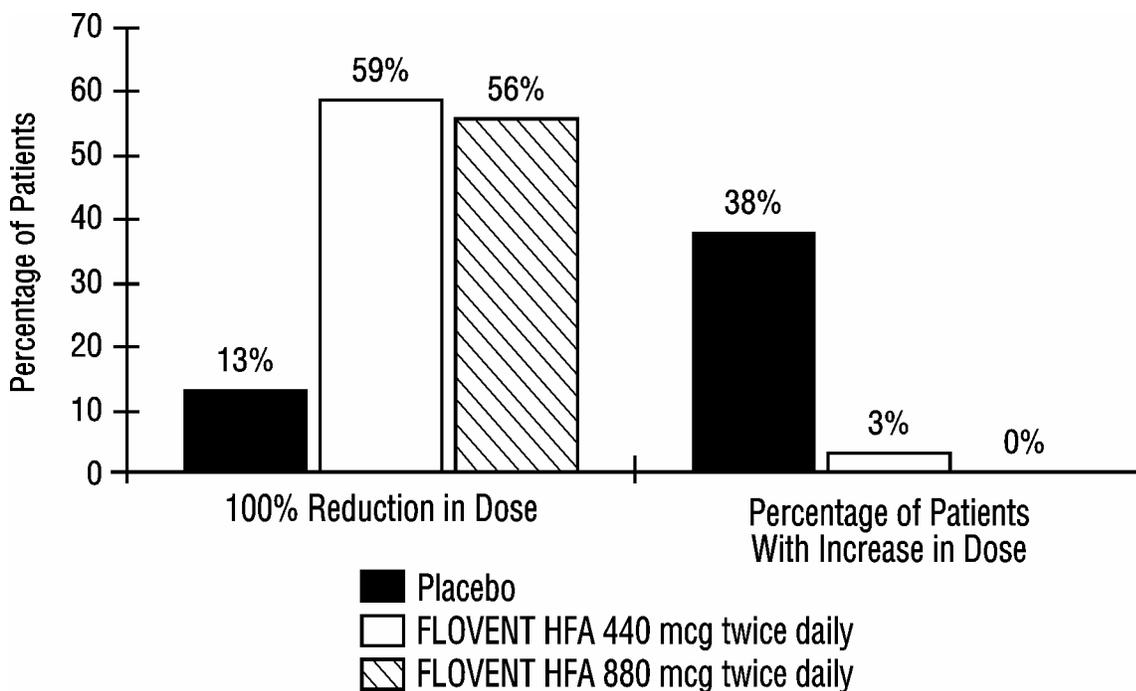
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In both studies, use of VENTOLIN, AM and PM PEF, and asthma symptom scores showed numerical improvement with FLOVENT HFA compared to placebo.

Study 3 enrolled 168 patients with asthma requiring oral prednisone therapy (average baseline daily prednisone dose ranged from 13 to 14 mg). FLOVENT HFA at dosages of 440 and 880 mcg twice daily was evaluated over a 16-week treatment period. Baseline FEV₁ values were similar across groups (mean 59% to 62% of predicted normal). Over the course of the study, patients treated with either dosage of FLOVENT HFA required a significantly lower mean daily oral prednisone dose (6 mg) compared with placebo-treated patients (15 mg). Both dosages of FLOVENT HFA enabled a larger percentage of patients (59% and 56% in the groups treated with FLOVENT HFA 440 and 880 mcg, respectively, twice daily) to eliminate oral prednisone as compared with placebo (13%) (see Figure 3). There was no efficacy advantage of FLOVENT HFA 880 mcg twice daily compared to 440 mcg twice daily. Accompanying the reduction in oral corticosteroid use, patients treated with either dosage of FLOVENT HFA had significantly improved lung function, fewer asthma symptoms, and less use of VENTOLIN Inhalation Aerosol compared with the placebo-treated patients.

Figure 3. A 16-Week Clinical Trial in Patients Requiring Chronic Oral Prednisone Therapy: Change in Maintenance Prednisone Dose



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Two long-term safety studies (Study 4 and Study 5) of ≥ 6 months' duration were conducted in 507 adolescent and adult patients with asthma. Study 4 was designed to monitor the safety of 2 doses of FLOVENT HFA, while Study 5 compared fluticasone propionate HFA and

269 CFC-propelled fluticasone propionate. Study 4 enrolled 182 patients who were treated daily with
270 low to high doses of inhaled corticosteroids, beta-agonists (short-acting [as needed or regularly
271 scheduled] or long-acting), theophylline, inhaled cromolyn or nedocromil sodium, leukotriene
272 receptor antagonists, or 5-lipoxygenase inhibitors at baseline. FLOVENT HFA at dosages of 220
273 and 440 mcg twice daily was evaluated over a 26-week treatment period in 89 and 93 patients,
274 respectively. Study 5 enrolled 325 patients who were treated daily with moderate to high doses
275 of inhaled corticosteroids, with or without concurrent use of salmeterol or albuterol, at baseline.
276 Fluticasone propionate HFA at a dosage of 440 mcg twice daily and CFC-propelled fluticasone
277 propionate at a dosage of 440 mcg twice daily were evaluated over a 52-week treatment period in
278 163 and 162 patients, respectively. Baseline FEV₁ values were similar across groups (mean 81%
279 to 84% of predicted normal). Throughout the 52-week treatment period, asthma control was
280 maintained with both formulations of fluticasone propionate compared to baseline. In both
281 studies, none of the patients were withdrawn due to lack of efficacy.

282 **INDICATIONS AND USAGE**

283 FLOVENT HFA Inhalation Aerosol is indicated for the maintenance treatment of asthma as
284 prophylactic therapy in adolescent and adult patients 12 years of age and older. It is also
285 indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients
286 may be able to reduce or eliminate their requirement for oral corticosteroids over time.

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

288 **CONTRAINDICATIONS**

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

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

293 **WARNINGS**

294 Particular care is needed for patients who are transferred from systemically active
295 corticosteroids to FLOVENT HFA because deaths due to adrenal insufficiency have occurred in
296 patients with asthma during and after transfer from systemic corticosteroids to less systemically
297 available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of
298 months are required for recovery of HPA function.

299 Patients who have been previously maintained on 20 mg or more per day of prednisone (or its
300 equivalent) may be most susceptible, particularly when their systemic corticosteroids have been
301 almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs
302 and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection
303 (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although
304 FLOVENT HFA may provide control of asthma symptoms during these episodes, in
305 recommended doses it supplies less than normal physiological amounts of corticosteroid

306 systemically and does NOT provide the mineralocorticoid activity that is necessary for coping
307 with these emergencies.

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

313 A drug interaction study in healthy subjects has shown that ritonavir (a highly potent
314 cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate
315 exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL
316 PHARMACOLOGY: Pharmacokinetics: *Drug Interactions* and PRECAUTIONS: Drug
317 Interactions: *Inhibitors of Cytochrome P450*). During postmarketing use, there have been reports
318 of clinically significant drug interactions in patients receiving fluticasone propionate and
319 ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal
320 suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not
321 recommended unless the potential benefit to the patient outweighs the risk of systemic
322 corticosteroid side effects.

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

333 Transfer of patients from systemic corticosteroid therapy to FLOVENT HFA may unmask
334 conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis,
335 conjunctivitis, eczema, arthritis, and eosinophilic conditions.

336 Persons who are using drugs that suppress the immune system are more susceptible to
337 infections than healthy individuals. Chickenpox and measles, for example, can have a more
338 serious or even fatal course in susceptible children or adults using corticosteroids. In such
339 children or adults who have not had these diseases or been properly immunized, particular care
340 should be taken to avoid exposure. How the dose, route, and duration of corticosteroid
341 administration affect the risk of developing a disseminated infection is not known. The
342 contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not
343 known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG)
344 may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin

345 (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing
346 information.) If chickenpox develops, treatment with antiviral agents may be considered.

347 FLOVENT HFA is not to be regarded as a bronchodilator and is not indicated for rapid relief
348 of bronchospasm.

349 As with other inhaled medications, bronchospasm may occur with an immediate increase in
350 wheezing after dosing. If bronchospasm occurs following dosing with FLOVENT HFA, it should
351 be treated immediately with a fast-acting inhaled bronchodilator. Treatment with
352 FLOVENT HFA should be discontinued and alternative therapy instituted.

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

356 **PRECAUTIONS**

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

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

362 Fluticasone propionate will often permit control of asthma symptoms with less suppression of
363 HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone
364 propionate is absorbed into the circulation and can be systemically active at higher doses, the
365 beneficial effects of FLOVENT HFA in minimizing HPA dysfunction may be expected only
366 when recommended dosages are not exceeded and individual patients are titrated to the lowest
367 effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory
368 effects on stimulated cortisol production has been shown after 4 weeks of treatment with
369 fluticasone propionate. Since individual sensitivity to effects on cortisol production exists,
370 physicians should consider this information when prescribing FLOVENT HFA.

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

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

381 The long-term effects of fluticasone propionate in human subjects are not fully known. In
382 particular, the effects resulting from chronic use of fluticasone propionate on developmental or
383 immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients

384 have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or
385 longer. In clinical studies with patients treated for 2 years with inhaled fluticasone propionate, no
386 apparent differences in the type or severity of adverse reactions were observed after long- versus
387 short-term treatment.

388 Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported
389 in patients following the long-term administration of inhaled corticosteroids, including
390 fluticasone propionate.

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

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

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

410 **Information for Patients:** Patients being treated with FLOVENT HFA should receive the
411 following information and instructions. This information is intended to aid them in the safe and
412 effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

413 It is important that patients understand how to use FLOVENT HFA in relation to other asthma
414 medications they are taking. Patients should be given the following information:

- 415 1. Patients should use FLOVENT HFA at regular intervals as directed. Individual patients will
416 experience a variable time to onset and degree of symptom relief and the full benefit may not
417 be achieved until treatment has been administered for 1 to 2 weeks or longer. The patient
418 should not increase the prescribed dosage but should contact the physician if symptoms do not
419 improve or if the condition worsens.
- 420 2. Patients who are pregnant or nursing should contact their physicians about the use of
421 FLOVENT HFA.
- 422 3. Patients should be warned to avoid exposure to chickenpox or measles and if they are
423 exposed, to consult their physicians without delay.

- 424 4. Prime the inhaler before using for the first time by releasing 4 test sprays into the air away
425 from the face, shaking well before each spray. In cases where the inhaler has not been used for
426 more than 7 days or when it has been dropped, prime the inhaler again by shaking well and
427 releasing 1 test spray into the air away from the face.
- 428 5. After inhalation, rinse the mouth with water and spit out. Do not swallow.
- 429 6. Clean the inhaler at least once a week after the evening dose. Keeping the canister and plastic
430 actuator clean is important to prevent medicine build-up. (See Patient's Instructions for Use
431 leaflet accompanying the product.)
- 432 7. Use FLOVENT HFA only with the actuator supplied with the product. Discard the inhaler
433 after the labeled number of inhalations have been used.
- 434 8. For the proper use of FLOVENT HFA and to attain maximum improvement, the patient
435 should read and carefully follow the Patient's Instructions for Use leaflet accompanying the
436 product.

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

447 In a placebo-controlled crossover study in 8 healthy volunteers, coadministration of a single
448 dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole
449 (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a
450 reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should
451 be exercised when FLOVENT HFA is coadministered with ketoconazole and other known
452 potent cytochrome P450 3A4 inhibitors.

453 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Fluticasone propionate
454 demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately
455 2 times the maximum recommended daily inhalation dose on a mcg/m² basis) for 78 weeks or in
456 rats at inhalation doses up to 57 mcg/kg (less than the maximum recommended daily inhalation
457 dose on a mcg/m² basis) for 104 weeks.

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

461 No evidence of impairment of fertility was observed in reproductive studies conducted in
462 male and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum

463 recommended daily inhalation dose ~~in adults~~ on a mcg/m² basis). Prostate weight was
464 significantly reduced in rats at a subcutaneous dose of 50 mcg/kg.

465 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Subcutaneous studies in the
466 mouse and rat at 45 and 100 mcg/kg, respectively (less than the maximum recommended daily
467 inhalation dose ~~in adults~~ on a mcg/m² basis), revealed fetal toxicity characteristic of potent
468 corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate,
469 and retarded cranial ossification. No teratogenicity was seen in the rat at inhalation doses up to
470 68.7 mcg/kg (less than the maximum recommended daily inhalation dose ~~in adults~~ on a mcg/m²
471 basis).

472 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of
473 4 mcg/kg (less than the maximum recommended daily inhalation dose ~~in adults~~ on a mcg/m²
474 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg
475 (approximately 3 times the maximum recommended daily inhalation dose ~~in adults~~ on a mcg/m²
476 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this
477 study, consistent with the established low bioavailability following oral administration (see
478 CLINICAL PHARMACOLOGY: Pharmacokinetics: *Absorption*).

479 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose
480 of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose ~~in adults~~ on a
481 mcg/m² basis), a subcutaneous or an oral dose of 100 mcg/kg to rats (less than the maximum
482 recommended daily inhalation dose ~~in adults~~ on a mcg/m² basis), and an oral dose of 300 mcg/kg
483 to rabbits (approximately 3 times the maximum recommended daily inhalation dose ~~in adults~~ on
484 a mcg/m² basis).

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

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

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

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

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

502 **Pediatric Use:** Orally inhaled corticosteroids may cause a reduction in growth velocity when
503 administered to pediatric patients. A reduction of growth velocity in children or teenagers may
504 occur as a result of poorly controlled asthma or from use of corticosteroids including inhaled
505 corticosteroids. The effects of long-term treatment of children and adolescents with inhaled
506 corticosteroids, including fluticasone propionate, on final adult height are not known.

507 Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in
508 growth in pediatric patients. In these studies, the mean reduction in growth velocity was
509 approximately 1 cm/year (range, 0.3 to 1.8 cm/year) and appears to depend upon dose and
510 duration of exposure. This effect was observed in the absence of laboratory evidence of HPA
511 axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic
512 corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis
513 function. The long-term effects of this reduction in growth velocity associated with orally
514 inhaled corticosteroids, including the impact on final adult height, are unknown. The potential
515 for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids
516 has not been adequately studied. The effects on growth velocity of treatment with orally inhaled
517 corticosteroids for over 1 year, including the impact on final adult height, are unknown. The
518 growth of children and adolescents receiving orally inhaled corticosteroids, including
519 FLOVENT HFA, should be monitored routinely (e.g., via stadiometry). The potential growth
520 effects of prolonged treatment should be weighed against the clinical benefits obtained and the
521 risks associated with alternative therapies. To minimize the systemic effects of orally inhaled
522 corticosteroids, including FLOVENT HFA, each patient should be titrated to the lowest dose that
523 effectively controls his/her symptoms.

524 Since a cross study comparison in adolescent and adult patients (≥ 12 years of age) indicated
525 that systemic exposure of inhaled fluticasone propionate from FLOVENT HFA would be higher
526 than exposure from FLOVENT[®] ROTADISK[®] (fluticasone propionate inhalation powder),
527 results from a study to assess the potential growth effects of FLOVENT ROTADISK in pediatric
528 patients (4-11 years of age) are provided.

529 A 52-week, placebo-controlled study to assess the potential growth effects of fluticasone
530 propionate inhalation powder (FLOVENT ROTADISK) at 50 and 100 mcg twice daily was
531 conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to
532 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were
533 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and
534 5.66 cm/year in the 100-mcg group (n = 89). An imbalance in the proportion of children entering
535 puberty between groups and a higher dropout rate in the placebo group due to poorly controlled
536 asthma may be confounding factors in interpreting these data. A separate subset analysis of
537 children who remained prepubertal during the study revealed growth rates at 52 weeks of
538 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and
539 5.67 cm/year in the 100-mcg group (n = 79). In children 8.5 years of age, the mean age of
540 children in this study, the range for expected growth velocity is: boys – 3rd

541 percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls –
542 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year.

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

548 The safety and effectiveness of FLOVENT HFA in children below 12 years of age have not
549 been established.

550 A total of 73 patients between the ages of 12 to 17 years of age were studied in the US pivotal
551 clinical trials. Improved asthma control (as measured by an improvement in FEV₁) was greater
552 for patients treated with FLOVENT HFA compared to those treated with placebo.

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

562 **ADVERSE REACTIONS**

563 The incidence of common adverse events in Table 1 is based upon 2 placebo-controlled US
564 clinical trials in which 812 adolescent and adult patients (457 females and 355 males) previously
565 treated with as-needed bronchodilators and/or inhaled corticosteroids were treated with
566 FLOVENT HFA (dosages of 88, 220, or 440 mcg twice daily for up to 12 weeks) or placebo.

567

568 **Table 1. Overall Adverse Events With >3% Incidence in US Controlled Clinical Trials**
569 **With FLOVENT HFA in Patients With Asthma Previously Receiving Bronchodilators**
570 **and/or Inhaled Corticosteroids**

Adverse Event	FLOVENT HFA 44 mcg Twice Daily (n = 203) %	FLOVENT HFA 110 mcg Twice Daily (n = 204) %	FLOVENT HFA 220 mcg Twice Daily (n = 202) %	Placebo Twice Daily (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

571
572 Table 1 includes all events (whether considered drug-related or nondrug-related by the
573 investigator) that occurred at a rate of over 3% in any of the groups treated with FLOVENT HFA
574 and were more common than in the placebo group. In considering these data, differences in
575 average duration of exposure should be taken into account.

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

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

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

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

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

585 **Neurological:** Dizziness, migraines.

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

587 **Skin:** Viral skin infections.

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

589 **Urogenital:** Urinary infections.

590 Fluticasone propionate inhalation aerosol (440 or 880 mcg twice daily) was administered for
591 16 weeks to patients with asthma requiring oral corticosteroids (Study 3). Adverse events not
592 included in Table 1, but reported by >3 patients in either group treated with FLOVENT HFA and
593 more commonly than in the placebo group included rhinitis, nausea and vomiting, arthralgia and
594 articular rheumatism, musculoskeletal pain, muscle pain, malaise and fatigue, and sleep
595 disorders.

596 In 2 long-term studies (26 and 52 weeks), treatment with FLOVENT HFA at dosages up to
597 440 mcg twice daily was well tolerated. The pattern of adverse events was similar to that
598 observed in the 12-week studies. There were no new and/or unexpected adverse events with
599 long-term treatment.

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

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

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

610 **Eye:** Cataracts.

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

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

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

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

618 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate may
619 present with systemic eosinophilic conditions, with some patients presenting with clinical
620 features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated
621 with systemic corticosteroid therapy. These events usually, but not always, have been associated
622 with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of
623 fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with
624 other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia,
625 vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy

626 presenting in their patients. A causal relationship between fluticasone propionate and these
627 underlying conditions has not been established (see PRECAUTIONS: Eosinophilic Conditions).

628 **OVERDOSAGE**

629 Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS:
630 General). Inhalation by healthy volunteers of a single dose of 1,760 or 3,520 mcg of
631 CFC-propelled fluticasone propionate inhalation aerosol was well tolerated. Doses of 1,320 mcg
632 administered to healthy human volunteers twice daily for 7 to 15 days were also well tolerated.
633 Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to
634 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or
635 moderate severity, and incidences were similar in active and placebo treatment groups. The oral
636 and subcutaneous median lethal doses in mice and rats were >1,000 mg/kg (>~~2,300~~~~2,000~~ and
637 >~~4,600~~~~4,100~~ times, ~~respectively~~; the maximum ~~recommended daily inhalation dose in adults and~~
638 >~~9,600~~ and >~~20,000~~ times, ~~respectively~~, the maximum recommended daily inhalation dose in
639 ~~children~~ on a mg/m² basis, ~~respectively~~).

640 **DOSAGE AND ADMINISTRATION**

641 FLOVENT HFA should be administered by the orally inhaled route only in patients 12 years
642 of age and older. Individual patients will experience a variable time to onset and degree of
643 symptom relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting
644 treatment.

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

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

652

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

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

Previous Therapy	Recommended Starting Dosage	Highest Recommended Dosage
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

* Starting dosages above 88 mcg twice daily may be considered for patients with poorer asthma control or those who have previously required doses of inhaled corticosteroids that are in the higher range for that specific agent.

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

656
 657 FLOVENT HFA should be primed before using for the first time by releasing 4 test sprays
 658 into the air away from the face, shaking well before each spray. In cases where the inhaler has
 659 not been used for more than 7 days or when it has been dropped, prime the inhaler again by
 660 shaking well and releasing 1 test spray into the air away from the face.

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

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

667 **HOW SUPPLIED**

668 FLOVENT HFA 44 mcg Inhalation Aerosol is supplied in 10.6-g pressurized aluminum
 669 canisters containing 120 metered inhalations in boxes of 1 (NDC 0173-0718-00). Each canister is
 670 supplied with a dark orange oral actuator with a peach strapcap packaged within a plastic-coated,
 671 moisture-protective foil pouch and patient's instructions. The moisture-protective foil pouch also
 672 contains a desiccant that should be discarded when the pouch is opened.

673 FLOVENT HFA 110 mcg Inhalation Aerosol is supplied in 12-g pressurized aluminum
 674 canisters containing 120 metered inhalations in boxes of 1 (NDC 0173-0719-00). Each canister is
 675 supplied with a dark orange oral actuator with a peach strapcap packaged within a plastic-coated,
 676 moisture-protective foil pouch and patient's instructions. The moisture-protective foil pouch also
 677 contains a desiccant that should be discarded when the pouch is opened.

678 FLOVENT HFA 220 mcg Inhalation Aerosol is supplied in 12-g pressurized aluminum
679 canisters containing 120 metered inhalations in boxes of 1 (NDC 0173-0720-00). Each canister is
680 supplied with a dark orange oral actuator with a peach strapcap packaged within a plastic-coated,
681 moisture-protective foil pouch and patient’s instructions. The moisture-protective foil pouch also
682 contains a desiccant that should be discarded when the pouch is opened.

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

686 **The correct amount of medication in each inhalation cannot be assured after**
687 **120 inhalations, even though the canister is not completely empty and will continue to**
688 **operate. The inhaler should be discarded when 120 actuations have been used. Never**
689 **immerse the canister into water to determine the amount remaining in the canister (“float**
690 **test”).**

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

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

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

698 FLOVENT HFA does not contain chlorofluorocarbons (CFCs) as the propellant.
699
700



701 GlaxoSmithKline
702 GlaxoSmithKline
703 Research Triangle Park, NC 27709
704

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706

707 ~~December~~ June 2005

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1 **Patient's Instructions for Use**

2
3 **(illustration of 3 products)**

4
5 **FLOVENT[®] HFA 44 mcg**
6 **(fluticasone propionate HFA, 44 mcg)**
7 **Inhalation Aerosol**

8
9 **FLOVENT[®] HFA 110 mcg**
10 **(fluticasone propionate HFA, 110 mcg)**
11 **Inhalation Aerosol**

12
13 **FLOVENT[®] HFA 220 mcg**
14 **(fluticasone propionate HFA, 220 mcg)**
15 **Inhalation Aerosol**

16
17 **FOR ORAL INHALATION ONLY**

18
19 **Read this leaflet carefully before using your FLOVENT HFA Inhalation Aerosol.**

20 **What Is FLOVENT HFA Inhalation Aerosol?**

21 Your doctor has prescribed FLOVENT HFA 44 mcg, FLOVENT HFA 110 mcg, or
22 FLOVENT HFA 220 mcg Inhalation Aerosol. The medicine is available in 3 different
23 strengths, and your doctor has chosen the one most suitable for you.

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

28 When inhaled regularly, corticosteroids also help to prevent symptoms of asthma.

29 Children should use FLOVENT HFA under adult supervision, as instructed by the
30 patient's doctor.

31 **Important Points to Remember About Using FLOVENT HFA Inhalation Aerosol**

- 32 1. FLOVENT HFA Inhalation Aerosol is not a bronchodilator and should not be used to
33 provide rapid relief of your breathing difficulties during an asthma attack. A
34 short-acting bronchodilator, such as albuterol inhaler, should be used during an acute
35 asthma attack. FLOVENT HFA must be taken at regular intervals as recommended
36 by your doctor, and not as an emergency measure.
- 37 2. **TELL YOUR DOCTOR BEFORE YOU START TAKING THIS MEDICINE if**
38 **you are:**

- 39 • pregnant or planning to become pregnant;
- 40 • breastfeeding a baby;
- 41 • allergic to FLOVENT HFA, either of its ingredients, or any other orally inhaled
- 42 corticosteroids~~any other medicines, or food products~~;
- 43 • taking a medicine containing ritonavir (commonly used to treat HIV infection or
- 44 AIDS); or
- 45 • taking other medicines, especially any other orally inhaled corticosteroid, over-the-
- 46 counter medicines, and herbal products.

47 In some circumstances, this medicine may not be suitable for you and your doctor
48 may wish to give you a different medicine. Make sure that your doctor knows what
49 other medicines you are taking.

- 50 3. It is important that you inhale each dose as your doctor has advised. The prescription
51 label provided by your pharmacist will usually tell you what dose to take and how often.
52 If it doesn't, or if you are not sure, ask your doctor or pharmacist. **DO NOT** inhale
53 more doses or use your FLOVENT HFA more often than your doctor advises.
- 54 4. It may take 1 to 2 weeks or longer for this medicine to work, and it is **VERY**
55 **IMPORTANT THAT YOU USE IT REGULARLY. DO NOT STOP**
56 **TREATMENT EVEN IF YOU ARE FEELING BETTER** unless told to do so by
57 your doctor.
- 58 5. If you miss a dose, just take your next scheduled dose when it is due. **DO NOT**
59 **DOUBLE** the dose.
- 60 6. Your doctor may prescribe additional medicine (such as bronchodilators) for
61 emergency relief if an acute asthma attack occurs. Contact your doctor if:
62 • an asthma attack does not respond to the additional medicine or
63 • you require more of the additional medicine than usual.
- 64 7. If you also use another medicine by inhalation, you should consult your doctor for
65 instructions on when to use it in relation to using FLOVENT HFA.

66 **How to Use Your FLOVENT HFA Inhalation Aerosol**

67 Before starting to use your FLOVENT HFA inhaler, remove it from the overwrap and
68 safely discard the overwrap and drying packet, which is also inside the overwrap. The
69 inhaler should be at room temperature before use.

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

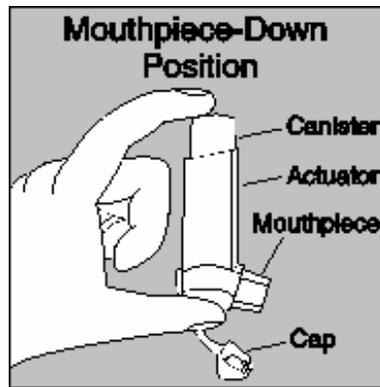
71 **The dark orange actuator supplied with FLOVENT HFA should not be used with**
72 **any other product canisters, and actuators from other products should not be used**
73 **with a FLOVENT HFA canister.**

74 **SHAKE THE INHALER WELL** for 5 seconds immediately before each use.

75 **PRIME THE INHALER BEFORE USING IT FOR THE FIRST TIME** by releasing
76 4 test sprays into the air away from your face, shaking well for 5 seconds before each
77 spray. In cases where the inhaler has not been used for more than 7 days or when it has
78 been dropped, prime the inhaler again by shaking well for 5 seconds and releasing 1 test
79 spray into the air away from your face.

80

81 **1. REMOVE THE CAP FROM THE MOUTHPIECE** (see Figure 1); the strap on the
82 cap will stay attached to the actuator. Inspect the inhaler mouthpiece for the presence of
83 foreign objects before each use, especially if the strap is no longer attached to the actuator
84 or if the cap is not being used to cover the mouthpiece. Make sure the canister is fully and
85 firmly inserted into the actuator. **SHAKE THE INHALER WELL** for 5 seconds
86 immediately before each use.



87

88

Figure 1

89

90 **2. BREATHE OUT FULLY THROUGH YOUR MOUTH**, expelling as much air
91 from your lungs as possible. Place the mouthpiece fully into your mouth, holding the
92 inhaler with the mouthpiece down (see Figure 1) and closing your lips around it.

93 **3. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH YOUR**
94 **MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER** with your
95 index finger (see Figure 2). Immediately after the spray is delivered, release your finger
96 from the canister. When you have breathed in fully, remove the inhaler from your mouth,
97 and close your mouth.

98

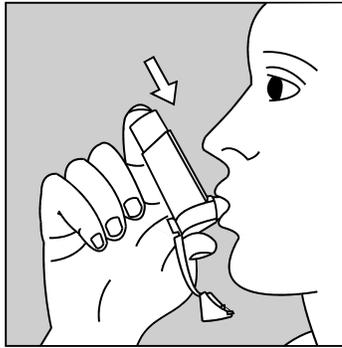


Figure 2

99

100

101

102 **4. HOLD YOUR BREATH AS LONG AS POSSIBLE**, or up to 10 seconds, then
103 breathe normally.

104 **5. WAIT ABOUT 30 SECONDS AND SHAKE** the inhaler again. Repeat steps 2
105 through 4.

106 **6. REPLACE THE MOUTHPIECE CAP AFTER EACH USE.**

107 **7.** After you finish taking your dose, rinse your mouth with water and spit it out. Do not
108 swallow.

109 **8.** Because of the difference in propellants, you may notice a slightly different taste or
110 feel of the spray in your mouth with FLOVENT HFA than you are used to with
111 FLOVENT[®] (fluticasone propionate) Inhalation Aerosol.

112 **9.** Never immerse the canister in water to determine the amount remaining in the canister
113 (“float test”).

114 **10. DISCARD THE INHALER AFTER YOU HAVE USED THE LABELED**
115 **NUMBER OF INHALATIONS.** The correct amount of medicine in each inhalation
116 cannot be assured after 60 inhalations from FLOVENT HFA 110 mcg 60-actuation
117 sample inhaler and after 120 inhalations from FLOVENT HFA 44 mcg, FLOVENT HFA
118 110 mcg, and FLOVENT HFA 220 mcg 120-actuation inhalers, even though the canister
119 is not completely empty and will continue to operate. The inhaler should be discarded
120 when the labeled number of inhalations have been used; therefore, it is recommended to
121 keep track of the number of actuations used from your inhaler. Before you reach the
122 labeled number of inhalations, however, you should consult your doctor to see if you
123 need to refill your prescription.

124 **DO NOT** use after the expiration date, shown as “EXP”, on the product label and box.

125

Cleaning Your FLOVENT HFA Inhalation Aerosol

126 Clean the inhaler at least once a week after the evening dose. Keeping the canister and
127 plastic actuator clean is important to prevent medicine build-up.

128 Step 1. Remove the mouthpiece cap but do not remove the canister from the plastic
129 actuator. The strap on the cap will stay attached to the actuator.

130 Step 2. Use a cotton swab dampened with water to clean the small circular opening where
131 the medicine is sprayed from the canister. Gently twist the swab in a circular motion to
132 remove any medicine (see Figure 3), then repeat with a clean, water-dampened swab to
133 remove any medicine still at the opening. Wipe the inside of the plastic actuator
134 mouthpiece with a clean tissue dampened with water and let the actuator air-dry
135 overnight.

136

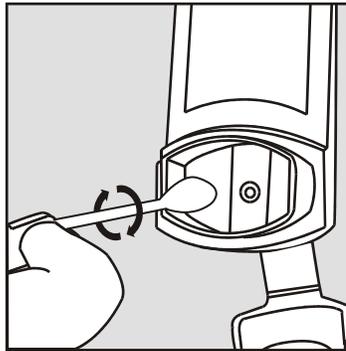


Figure 3

137

138

139

140 Step 3. Replace the mouthpiece cover after the actuator has dried.

141

Storing Your FLOVENT HFA Inhalation Aerosol

142 **Store at room temperature with the mouthpiece down.** Keep out of reach of children.

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

146

Further Information

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

149 Please note that the  symbol on each product box means that FLOVENT HFA
150 Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.
151 Instead, the inhaler contains a hydrofluoroalkane (HFA-134a) as the propellant.

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

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

157



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GlaxoSmithKline

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Research Triangle Park, NC 27709

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