

PRODUCT INFORMATION

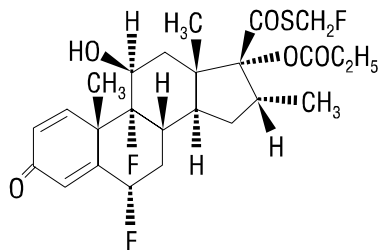
FLOVENT[®] 44 mcg
(fluticasone propionate, 44 mcg)
Inhalation Aerosol

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

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

For Oral Inhalation Only

DESCRIPTION: The active component of FLOVENT 44 mcg Inhalation Aerosol, FLOVENT 110 mcg Inhalation Aerosol, and FLOVENT 220 mcg Inhalation Aerosol is fluticasone propionate, a glucocorticoid 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. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FLOVENT 44 mcg Inhalation Aerosol, FLOVENT 110 mcg Inhalation Aerosol, and FLOVENT 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 a mixture of two chlorofluorocarbon propellants (trichlorofluoromethane and dichlorodifluoromethane) with soya lecithin. Each actuation of the inhaler delivers 50, 125, or 250 mcg of fluticasone propionate from the valve and 44, 110, or 220 mcg, respectively, of fluticasone propionate from the actuator.

35 **CLINICAL PHARMACOLOGY:** Fluticasone propionate is a synthetic, trifluorinated
36 glucocorticoid with potent anti-inflammatory activity. In vitro assays using human lung cytosol
37 preparations have established fluticasone propionate as a human glucocorticoid receptor agonist
38 with an affinity 18 times greater than dexamethasone, almost twice that of
39 beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone
40 dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay
41 in man are consistent with these results.

42 The precise mechanisms of glucocorticoid action in asthma are unknown. Inflammation is
43 recognized as an important component in the pathogenesis of asthma. Glucocorticoids have been
44 shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes,
45 macrophages, and neutrophils) and mediator production or secretion (e.g., histamine,
46 eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These
47 anti-inflammatory actions of glucocorticoids may contribute to their efficacy in asthma.

48 Though highly effective for the treatment of asthma, glucocorticoids do not affect asthma
49 symptoms immediately. However, improvement following inhaled administration of fluticasone
50 propionate can occur within 24 hours of beginning treatment, although maximum benefit may
51 not be achieved for 1 to 2 weeks or longer after starting treatment. When glucocorticoids are
52 discontinued, asthma stability may persist for several days or longer.

53 **Pharmacokinetics: Absorption:** The activity of FLOVENT Inhalation Aerosol is due to the
54 parent drug, fluticasone propionate. Studies using oral dosing of labeled and unlabeled drug have
55 demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%),
56 primarily due to incomplete absorption and pre-systemic metabolism in the gut and liver. In
57 contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed.
58 The systemic bioavailability of fluticasone propionate inhalation aerosol in healthy volunteers
59 averaged about 30% of the dose delivered from the actuator.

60 Peak plasma concentrations after an 880-mcg inhaled dose ranged from 0.1 to 1.0 ng/mL.

61 **Distribution:** Following intravenous administration, the initial disposition phase for
62 fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding.
63 The volume of distribution averaged 4.2 L/kg. The percentage of fluticasone propionate bound to
64 human plasma proteins averaged 91%. Fluticasone propionate is weakly and reversibly bound to
65 erythrocytes. Fluticasone propionate is not significantly bound to human transcortin.

66 **Metabolism:** The total clearance of fluticasone propionate is high (average, 1093 mL/min),
67 with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite
68 detected in man is the 17 β -carboxylic acid derivative of fluticasone propionate, which is formed
69 through the cytochrome P450 3A4 pathway. This metabolite had approximately 2000 times less
70 affinity than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and
71 negligible pharmacological activity in animal studies. Other metabolites detected in vitro using
72 cultured human hepatoma cells have not been detected in man.

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

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

77 **Special Populations:** Formal pharmacokinetic studies using fluticasone propionate were not
78 carried out in any special populations. In a clinical study using fluticasone propionate inhalation
79 powder, trough fluticasone propionate plasma concentrations were collected in 76 males and 74
80 females after inhaled administration of 100 and 500 mcg twice daily. Full pharmacokinetic
81 profiles were obtained from 7 female patients and 13 male patients at these doses, and no overall
82 differences in pharmacokinetic behavior were found.

83 **Pharmacodynamics:** To confirm that systemic absorption does not play a role in the clinical
84 response to inhaled fluticasone propionate, a double-blind clinical study comparing inhaled and
85 oral fluticasone propionate was conducted. Doses of 100 and 500 mcg twice daily of fluticasone
86 propionate inhalation powder were compared to oral fluticasone propionate, 20,000 mcg given
87 once daily, and placebo for 6 weeks. Plasma levels of fluticasone propionate were detectable in
88 all three active groups, but the mean values were highest in the oral group. Both doses of inhaled
89 fluticasone propionate were effective in maintaining asthma stability and improving lung
90 function while oral fluticasone propionate and placebo were ineffective. This demonstrates that
91 the clinical effectiveness of inhaled fluticasone propionate is due to its direct local effect and not
92 to an indirect effect through systemic absorption.

93 The potential systemic effects of inhaled fluticasone propionate on the
94 hypothalamic-pituitary-adrenal (HPA) axis were also studied in asthma patients. Fluticasone
95 propionate given by inhalation aerosol at doses of 220, 440, 660, or 880 mcg twice daily was
96 compared with placebo or oral prednisone 10 mg given once daily for 4 weeks. For most patients,
97 the ability to increase cortisol production in response to stress, as assessed by 6-hour cosyntropin
98 stimulation, remained intact with inhaled fluticasone propionate treatment. No patient had an
99 abnormal response (peak less than 18 mcg/dL) after dosing with placebo or 220 mcg twice daily.
100 Ten percent (10%) to 16% of patients treated with fluticasone propionate at doses of 440 mcg or
101 more twice daily had an abnormal response as compared to 29% of patients treated with
102 prednisone.

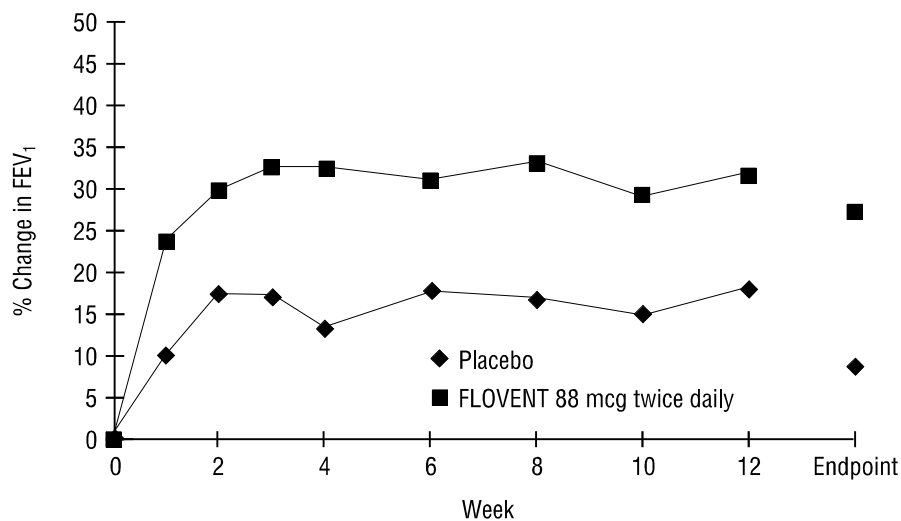
103 **Clinical Trials:** Double-blind, parallel, placebo-controlled, US clinical trials were conducted in
104 1818 adolescent and adult patients with asthma to assess the efficacy and/or safety of FLOVENT
105 Inhalation Aerosol in the treatment of asthma. Fixed doses ranging from 22 to 880 mcg twice
106 daily were compared to placebo to provide information about appropriate dosing to cover a range
107 of asthma severity. Patients with asthma included in these studies were those not adequately
108 controlled with beta-agonists alone, those already maintained on daily inhaled corticosteroids,
109 and those requiring oral corticosteroid therapy. In all efficacy trials, at all doses, measures of
110 pulmonary function (forced expiratory volume in 1 second [FEV₁] and morning peak expiratory
111 flow rate [AM PEF_R]) were statistically significantly improved as compared with placebo.

112 In 2 clinical trials of 660 patients with asthma inadequately controlled on bronchodilators
113 alone, fluticasone propionate administered by inhalation aerosol was evaluated at doses of 44 and

114 88 mcg twice daily. Both doses of fluticasone propionate improved asthma control significantly
115 as compared with placebo.

116 Displayed in the figure below are results of pulmonary function tests for the recommended
117 starting dosage of fluticasone propionate inhalation aerosol (88 mcg twice daily) and placebo
118 from a 12-week trial in patients with asthma inadequately controlled on bronchodilators alone.
119 Because this trial used predetermined criteria for lack of efficacy, which caused more patients in
120 the placebo group to be withdrawn, pulmonary function results at endpoint, which is the last
121 evaluable FEV₁ result and includes most patients' lung function data, are also provided.
122 Pulmonary function improved significantly with fluticasone propionate compared with placebo
123 by the second week of treatment, and this improvement was maintained over the duration of the
124 trial.

126 **A 12-Week Clinical Trial In Patients Inadequately Controlled**
127 **on Bronchodilators Alone: Mean Percent Change From Baseline**
128 **in FEV₁ Prior to AM Dose**
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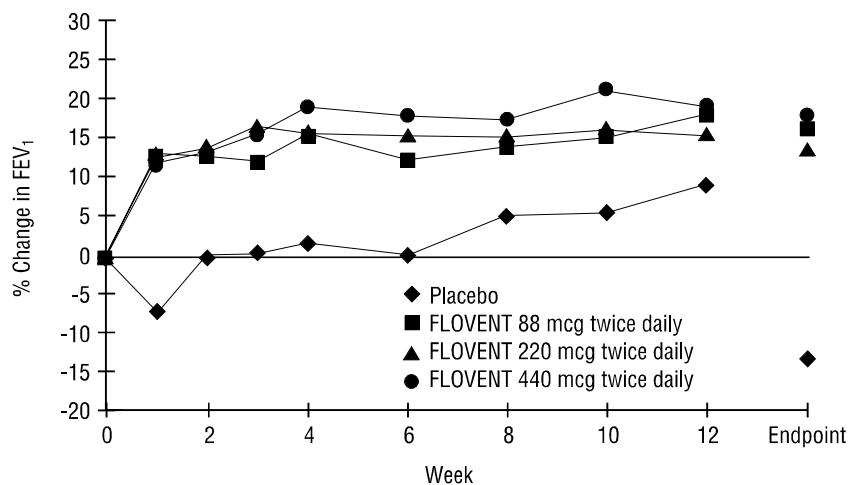
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132 In clinical trials of 924 patients with asthma already receiving daily inhaled corticosteroid
133 therapy (doses of at least 336 mcg/day of beclomethasone dipropionate) in addition to as-needed
134 albuterol and theophylline (46% of all patients), fluticasone propionate inhalation aerosol doses
135 of 22 to 440 mcg twice daily were also evaluated. All doses of fluticasone propionate were
136 efficacious when compared to placebo on major endpoints including lung function and symptom
137 scores. Patients treated with fluticasone propionate were also less likely to discontinue study
138 participation due to asthma deterioration (as defined by predetermined criteria for lack of efficacy
139 including lung function and patient-recorded variables such as AM PEF_R, albuterol use, and
140 nighttime awakenings due to asthma).

141 Displayed in the figure below are results of pulmonary function from a 12-week clinical trial
142 in patients with asthma already receiving daily inhaled corticosteroid therapy (beclomethasone

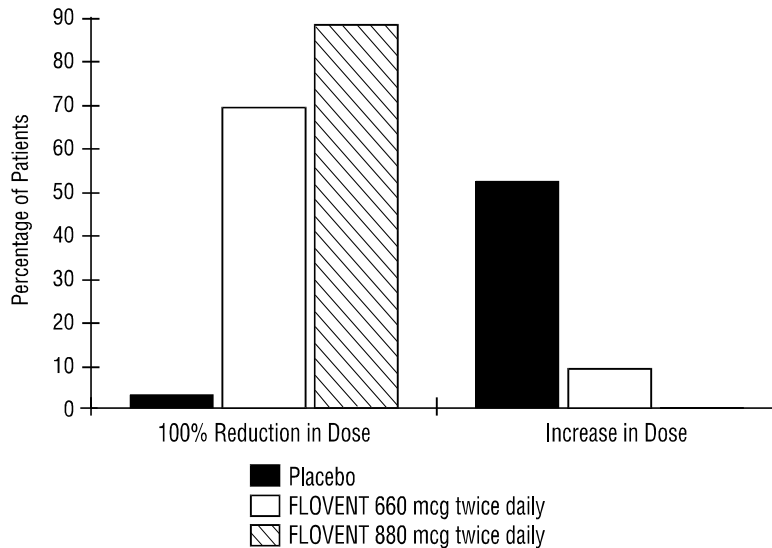
143 dipropionate 336 to 672 mcg/day). The mean percent change from baseline in lung function
 144 results for fluticasone propionate inhalation aerosol dosages of 88, 220, and 440 mcg twice daily
 145 and placebo are shown over the 12-week trial. Because this trial also used predetermined criteria
 146 for lack of efficacy, which caused more patients in the placebo group to be withdrawn,
 147 pulmonary function results at endpoint are included. Pulmonary function improved significantly
 148 with fluticasone propionate compared with placebo by the first week of treatment, and the
 149 improvement was maintained over the duration of the trial. Analysis of the endpoint results that
 150 adjusted for differential withdrawal rates indicated that pulmonary function significantly
 151 improved with fluticasone propionate compared with placebo treatment. Similar improvements
 152 in lung function were seen in the other two trials in patients treated with inhaled corticosteroids
 153 at baseline.

154
 155 **A 12-Week Clinical Trial With Patients Already Receiving**
 156 **Inhaled Corticosteroids: Mean Percent Change**
 157 **From Baseline in FEV₁ Prior to AM Dose**
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 161 In a clinical trial of 96 patients with severe asthma requiring chronic oral prednisone therapy
 162 (average baseline daily prednisone dose was 10 mg), twice-daily doses of 660 and 880 mcg of
 163 FLOVENT Inhalation Aerosol were evaluated. Both doses enabled a statistically significantly
 164 larger percentage of patients to wean successfully from oral prednisone as compared with
 165 placebo (69% of the patients on 660 mcg twice daily and 88% of the patients on 880 mcg twice
 166 daily as compared with 3% of patients on placebo). Accompanying the reduction in oral
 167 corticosteroid use, patients treated with FLOVENT Inhalation Aerosol had significantly
 168 improved lung function and fewer asthma symptoms as compared with the placebo group.
 169

170 **A 16-Week Clinical Trial in Patients Requiring Chronic**
 171 **Oral Prednisone Therapy: Change in Maintenance**
 172 **Prednisone Dose**
 173



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 176
 177 **INDICATIONS AND USAGE:** FLOVENT Inhalation Aerosol is indicated for the maintenance
 178 treatment of asthma as prophylactic therapy. It is also indicated for patients requiring oral
 179 corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their
 180 requirement for oral corticosteroids over time.

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

182
 183 **CONTRAINDICATIONS:** FLOVENT Inhalation Aerosol is contraindicated in the primary
 184 treatment of status asthmaticus or other acute episodes of asthma where intensive measures are
 185 required.

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

188
 189 **WARNINGS:**

190 Particular care is needed for patients who are transferred from systemically active
 191 corticosteroids to FLOVENT Inhalation Aerosol because deaths due to adrenal insufficiency
 192 have occurred in patients with asthma during and after transfer from systemic corticosteroids to
 193 less systemically available inhaled corticosteroids. After withdrawal from systemic
 194 corticosteroids, a number of months are required for recovery of HPA function.

195 Patients who have been previously maintained on 20 mg or more per day of prednisone (or its
 196 equivalent) may be most susceptible, particularly when their systemic corticosteroids have been
 197 almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs

198 and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection
199 (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although
200 fluticasone propionate inhalation aerosol may provide control of asthma symptoms during these
201 episodes, in recommended doses it supplies less than normal physiological amounts of
202 glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is
203 necessary for coping with these emergencies.

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

209 Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid
210 use after transferring to fluticasone propionate inhalation aerosol. In a trial of 96 patients,
211 prednisone reduction was successfully accomplished by reducing the daily prednisone dose by
212 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive reduction
213 of prednisone dose was allowed only when lung function, symptoms, and as-needed beta-agonist
214 use were better than or comparable to that seen before initiation of prednisone dose reduction.
215 Lung function (FEV₁ or AM PEF_R), beta-agonist use, and asthma symptoms should be carefully
216 monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and
217 symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as
218 fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

219 Transfer of patients from systemic corticosteroid therapy to fluticasone propionate inhalation
220 aerosol may unmask conditions previously suppressed by the systemic corticosteroid therapy,
221 e.g., rhinitis, conjunctivitis, eczema, and arthritis.

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

233 Fluticasone propionate inhalation aerosol is not to be regarded as a bronchodilator and is not
234 indicated for rapid relief of bronchospasm.

235 As with other inhaled asthma medications, bronchospasm may occur with an immediate
236 increase in wheezing after dosing. If bronchospasm occurs following dosing with FLOVENT
237 Inhalation Aerosol, it should be treated immediately with a fast-acting inhaled bronchodilator.

238 Treatment with FLOVENT Inhalation Aerosol should be discontinued and alternative therapy
239 instituted.

240 Patients should be instructed to contact their physicians immediately when episodes of asthma
241 that are not responsive to bronchodilators occur during the course of treatment with fluticasone
242 propionate inhalation aerosol. During such episodes, patients may require therapy with oral
243 corticosteroids.

244

245 **PRECAUTIONS:**

246 **General:** During withdrawal from oral corticosteroids, some patients may experience symptoms
247 of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and
248 depression, despite maintenance or even improvement of respiratory function.

249 Fluticasone propionate will often permit control of asthma symptoms with less suppression of
250 HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone
251 propionate is absorbed into the circulation and can be systemically active at higher doses, the
252 beneficial effects of fluticasone propionate inhalation aerosol in minimizing HPA dysfunction
253 may be expected only when recommended dosages are not exceeded and individual patients are
254 titrated to the lowest effective dose. A relationship between plasma levels of fluticasone
255 propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks
256 of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects
257 on cortisol production exists, physicians should consider this information when prescribing
258 fluticasone propionate inhalation aerosol.

259 Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated
260 with these drugs should be observed carefully for any evidence of systemic corticosteroid effects.
261 Particular care should be taken in observing patients postoperatively or during periods of stress
262 for evidence of inadequate adrenal response.

263 It is possible that systemic corticosteroid effects such as hypercorticism and adrenal
264 suppression (including adrenal crisis) may appear in a small number of patients, particularly
265 when fluticasone propionate is administered at higher than recommended doses over prolonged
266 periods of time. If such effects occur, fluticasone propionate inhalation aerosol should be reduced
267 slowly, consistent with accepted procedures for reducing systemic corticosteroids and for
268 management of asthma symptoms.

269 A reduction of growth velocity in children or teenagers may occur as a result of inadequate
270 control of chronic diseases such as asthma or from use of corticosteroids for treatment.
271 Physicians should closely follow the growth of adolescents taking corticosteroids by any route
272 and weigh the benefits of corticosteroid therapy and asthma control against the possibility of
273 growth suppression if an adolescent's growth appears slowed.

274 The long-term effects of fluticasone propionate in human subjects are not fully known. In
275 particular, the effects resulting from chronic use of fluticasone propionate on developmental or
276 immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients
277 have received fluticasone propionate inhalation aerosol on a continuous basis for periods of

278 3 years or longer. In clinical studies with patients treated for nearly 2 years with inhaled
279 fluticasone propionate, no apparent differences in the type or severity of adverse reactions were
280 observed after long- versus short-term treatment.

281 Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported
282 following the inhaled administration of corticosteroids, including fluticasone propionate.

283 In clinical studies with inhaled fluticasone propionate, the development of localized infections
284 of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should
285 be treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on
286 treatment with fluticasone propionate inhalation aerosol, but at times therapy with fluticasone
287 propionate may need to be interrupted.

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

291 **Eosinophilic Conditions:** In rare cases, patients on inhaled fluticasone propionate may
292 present with systemic eosinophilic conditions, with some patients presenting with clinical
293 features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated
294 with systemic corticosteroid therapy. These events usually, but not always, have been associated
295 with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of
296 fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with
297 other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia,
298 vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy
299 presenting in their patients. A causal relationship between fluticasone propionate and these
300 underlying conditions has not been established (see ADVERSE REACTIONS).

301 **Information for Patients:** Patients being treated with FLOVENT Inhalation Aerosol should
302 receive the following information and instructions. This information is intended to aid them in
303 the safe and effective use of this medication. It is not a disclosure of all possible adverse or
304 intended effects.

305 Patients should use FLOVENT Inhalation Aerosol at regular intervals as directed. Results of
306 clinical trials indicated significant improvement may occur within the first day or two of
307 treatment; however, the full benefit may not be achieved until treatment has been administered
308 for 1 to 2 weeks or longer. The patient should not increase the prescribed dosage but should
309 contact the physician if symptoms do not improve or if the condition worsens.

310 After inhalation, rinse the mouth with water without swallowing.

311 Patients should be warned to avoid exposure to chickenpox or measles and, if they are
312 exposed, to consult their physicians without delay.

313 For the proper use of FLOVENT Inhalation Aerosol and to attain maximum improvement, the
314 patient should read and follow carefully the accompanying Patient's Instructions for Use.

315 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Fluticasone propionate
316 demonstrated no tumorigenic potential in studies of oral doses up to 1000 mcg/kg (approximately
317 2 times the maximum human daily inhalation dose based on mcg/m²) for 78 weeks in the mouse

318 or inhalation of up to 57 mcg/kg (approximately 1/4 the maximum human daily inhalation dose
319 based on mcg/m²) for 104 weeks in the rat.

320 Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in
321 vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in
322 vitro or in the mouse micronucleus test when administered at high doses by the oral or
323 subcutaneous routes. Furthermore, the compound did not delay erythroblast division in bone
324 marrow.

325 No evidence of impairment of fertility was observed in reproductive studies conducted in rats
326 dosed subcutaneously with doses up to 50 mcg/kg (approximately 1/4 the maximum human daily
327 inhalation dose based on mcg/m²) in males and females. However, prostate weight was
328 significantly reduced in rats.

329 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Subcutaneous studies in the mouse
330 and rat at 45 and 100 mcg/kg, respectively (approximately 1/10 and 1/2 the maximum human
331 daily inhalation dose based on mcg/m², respectively), revealed fetal toxicity characteristic of
332 potent glucocorticoid compounds, including embryonic growth retardation, omphalocele, cleft
333 palate, and retarded cranial ossification.

334 In the rabbit, fetal weight reduction and cleft palate were observed following subcutaneous
335 doses of 4 mcg/kg (approximately 1/25 the maximum human daily inhalation dose based on
336 mcg/m²). However, following oral administration of up to 300 mcg/kg (approximately 3 times
337 the maximum human daily inhalation dose based on mcg/m²) of fluticasone propionate to the
338 rabbit, there were no maternal effects nor increased incidence of external, visceral, or skeletal
339 fetal defects. No fluticasone propionate was detected in the plasma in this study, consistent with
340 the established low bioavailability following oral administration (see CLINICAL
341 PHARMACOLOGY).

342 Less than 0.008% of the administered dose crossed the placenta following oral administration
343 of 100 mcg/kg to rats or 300 mcg/kg to rabbits (approximately 1/2 and 3 times the maximum
344 human daily inhalation dose based on mcg/m², respectively).

345 There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate
346 should be used during pregnancy only if the potential benefit justifies the potential risk to the
347 fetus.

348 Experience with oral glucocorticoids since their introduction in pharmacologic, as opposed to
349 physiologic, doses suggests that rodents are more prone to teratogenic effects from
350 glucocorticoids than humans. In addition, because there is a natural increase in glucocorticoid
351 production during pregnancy, most women will require a lower exogenous glucocorticoid dose
352 and many will not need glucocorticoid treatment during pregnancy.

353 **Nursing Mothers:** It is not known whether fluticasone propionate is excreted in human breast
354 milk. Subcutaneous administration of 10 mcg/kg tritiated drug to lactating rats (approximately
355 1/20 the maximum human daily inhalation dose based on mcg/m²) resulted in measurable
356 radioactivity in both plasma and milk. Because glucocorticoids are excreted in human milk,

357 caution should be exercised when fluticasone propionate inhalation aerosol is administered to a
358 nursing woman.

359 **Pediatric Use:** One hundred thirty-seven (137) patients between the ages of 12 and 16 years
360 were treated with fluticasone propionate inhalation aerosol in the US pivotal clinical trials. The
361 safety and effectiveness of FLOVENT Inhalation Aerosol in children below 12 years of age have
362 not been established. Oral corticosteroids have been shown to cause a reduction in growth
363 velocity in children and teenagers with extended use. If a child or teenager on any corticosteroid
364 appears to have growth suppression, the possibility that they are particularly sensitive to this
365 effect of corticosteroids should be considered (see PRECAUTIONS).

366 **Geriatric Use:** Five hundred seventy-four (574) patients 65 years of age or older have been
367 treated with fluticasone propionate inhalation aerosol in US and non-US clinical trials. There
368 were no differences in adverse reactions compared to those reported by younger patients.

369
370 **ADVERSE REACTIONS:** The following incidence of common adverse experiences is based
371 upon 7 placebo-controlled US clinical trials in which 1243 patients (509 female and 734 male
372 adolescents and adults previously treated with as-needed bronchodilators and/or inhaled
373 corticosteroids) were treated with fluticasone propionate inhalation aerosol (doses of 88 to
374 440 mcg twice daily for up to 12 weeks) or placebo.

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Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in US Controlled Clinical Trials With MDI in Patients Previously Receiving Bronchodilators and/or Inhaled Corticosteroids

Adverse Event	Placebo (n = 475) %	FLOVENT 88 mcg twice daily (n = 488) %	FLOVENT 220 mcg twice daily (n = 95) %	FLOVENT 440 mcg twice daily (n = 185) %
Ear, nose, and throat				
Pharyngitis	7	10	14	14
Nasal congestion	8	8	16	10
Sinusitis	4	3	6	5
Nasal discharge	3	5	4	4
Dysphonia	1	4	3	8
Allergic rhinitis	4	5	3	3
Oral candidiasis	1	2	3	5
Respiratory				
Upper respiratory infection	12	15	22	16
Influenza	2	3	8	5
Neurological				
Headache	14	17	22	17
Average duration of exposure (days)	44	66	64	59

379

380 The table above includes all events (whether considered drug-related or non-drug-related by the
381 investigator) that occurred at a rate of over 3% in the combined fluticasone propionate inhalation
382 aerosol groups and were more common than in the placebo group. In considering these data,
383 differences in average duration of exposure should be taken into account.

384 These adverse reactions were mostly mild to moderate in severity, with ≤2% of patients
385 discontinuing the studies because of adverse events. Rare cases of immediate and delayed
386 hypersensitivity reactions, including urticaria and rash and other rare events of angioedema and
387 bronchospasm, have been reported.

388 Systemic glucocorticoid side effects were not reported during controlled clinical trials with
389 fluticasone propionate inhalation aerosol. If recommended doses are exceeded, however, or if
390 individuals are particularly sensitive, symptoms of hypercorticism, e.g., Cushing's syndrome,
391 could occur.

392 Other adverse events that occurred in these clinical trials using fluticasone propionate
393 inhalation aerosol with an incidence of 1% to 3% and which occurred at a greater incidence than
394 with placebo were:

395 **Ear, Nose, and Throat:** Pain in nasal sinus(es), rhinitis.

396 **Eye:** Irritation of the eye(s).
397 **Gastrointestinal:** Nausea and vomiting, diarrhea, dyspepsia and stomach disorder.
398 **Miscellaneous:** Fever.
399 **Mouth and Teeth:** Dental problem.
400 **Musculoskeletal:** Pain in joint, sprain/strain, aches and pains, pain in limb.
401 **Neurological:** Dizziness/giddiness.
402 **Respiratory:** Bronchitis, chest congestion.
403 **Skin:** Dermatitis, rash/skin eruption.
404 **Urogenital:** Dysmenorrhea.

405 In a 16-week study in patients with asthma requiring oral corticosteroids, the effects of
406 fluticasone propionate inhalation aerosol, 660 mcg twice daily (n = 32) and 880 mcg twice daily
407 (n = 32), were compared with placebo. Adverse events (whether considered drug-related or
408 nondrug-related by the investigator) reported by more than 3 patients in either fluticasone
409 propionate group and which were more common with fluticasone propionate than placebo are
410 shown below:

411 **Ear, Nose, and Throat:** Pharyngitis (9% and 25%), nasal congestion (19% and 22%),
412 sinusitis (19% and 22%), nasal discharge (16% and 16%), dysphonia (19% and 9%), pain in
413 nasal sinus(es) (13% and 0%), Candida-like oral lesions (16% and 9%), oropharyngeal
414 candidiasis (25% and 19%).

415 **Respiratory:** Upper respiratory infection (31% and 19%), influenza (0% and 13%).

416 **Other:** Headache (28% and 34%), pain in joint (19% and 13%), nausea and vomiting (22%
417 and 16%), muscular soreness (22% and 13%), malaise/fatigue (22% and 28%), insomnia (3%
418 and 13%).

419 **Observed During Clinical Practice:** In addition to adverse experiences reported from
420 clinical trials, the following experiences have been identified during postapproval use of
421 fluticasone propionate. Because they are reported voluntarily from a population of unknown size,
422 estimates of frequency cannot be made. These experiences have been chosen for inclusion due to
423 either their seriousness, frequency of reporting, causal connection to fluticasone propionate or a
424 combination of these factors.

425 **Ear, Nose, and Throat:** Aphonia, facial and oropharyngeal edema, hoarseness, laryngitis,
426 and throat soreness and irritation.

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

429 **Eye:** Cataracts.

430 **Non-site Specific:** Very rare anaphylactic reaction.

431 **Psychiatry:** Agitation, aggression, depression, and restlessness.

432 **Respiratory:** Asthma exacerbation, bronchospasm, chest tightness, cough, dyspnea,
433 immediate bronchospasm, paradoxical bronchospasm, pneumonia, and wheeze.

434 **Skin:** Contusions, ecchymoses, and pruritus.

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

445
446 **OVERDOSAGE:** Chronic overdosage may result in signs/symptoms of hypercorticism (see
447 PRECAUTIONS). Inhalation by healthy volunteers of a single dose of 1760 or 3520 mcg of
448 fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by
449 inhalation aerosol at doses of 1320 mcg twice daily for 7 to 15 days to healthy human volunteers
450 was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and
451 repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions
452 were of mild or moderate severity, and incidences were similar in active and placebo treatment
453 groups. The oral and subcutaneous median lethal doses in rats and mice were >1000 mg/kg
454 (>2000 times the maximum human daily inhalation dose based on mg/m²).

455
456 **DOSAGE AND ADMINISTRATION:** FLOVENT Inhalation Aerosol should be administered
457 by the orally inhaled route in patients 12 years of age and older. Individual patients will
458 experience a variable time to onset and degree of symptom relief. Generally, fluticasone
459 propionate inhalation aerosol has a relatively rapid onset of action for an inhaled glucocorticoid.
460 Improvement in asthma control following inhaled administration of fluticasone propionate can
461 occur within 24 hours of beginning treatment, although maximum benefit may not be achieved
462 for 1 to 2 weeks or longer after starting treatment.

463 After asthma stability has been achieved (see below), it is always desirable to titrate to the
464 lowest effective dose to reduce the possibility of side effects. For patients who do not respond
465 adequately to the starting dose after 2 weeks of therapy, higher doses may provide additional
466 asthma control. The safety and efficacy of FLOVENT Inhalation Aerosol when administered in
467 excess of recommended doses has not been established.

468 The recommended starting dose and the highest recommended dose of fluticasone propionate
469 inhalation aerosol, based on prior antiasthma therapy, are listed in the following table.

470

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone	88 mcg twice daily	440 mcg twice daily
Inhaled corticosteroids	88-220 mcg twice daily*	440 mcg twice daily
Oral corticosteroids [†]	880 mcg twice daily	880 mcg twice daily

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

474 **NOTE:** In all patients, it is desirable to titrate to the lowest effective dose once asthma
475 stability is achieved.

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

482
483 **Geriatric Use:** In studies where geriatric patients (65 years of age or older, see PRECAUTIONS)
484 have been treated with fluticasone propionate inhalation aerosol, efficacy and safety did not
485 differ from that in younger patients. Consequently, no dosage adjustment is recommended.

486 **Directions for Use:** Illustrated Patient's Instructions for Use accompany each package of
487 FLOVENT Inhalation Aerosol.

488
489 **HOW SUPPLIED:** FLOVENT 44 mcg Inhalation Aerosol is supplied in 7.9-g canisters
490 containing 60 metered inhalations in boxes of one (NDC 0173-0497-00) and in 13-g canisters
491 containing 120 metered inhalations in boxes of one (NDC 0173-0491-00). Each canister is
492 supplied with a dark orange-colored oral actuator with a peach-colored strapcap and patient's
493 instructions. Each actuation of the inhaler delivers 44 mcg of fluticasone propionate from the
494 actuator.

495 FLOVENT 110 mcg Inhalation Aerosol is supplied in 7.9-g canisters containing 60 metered
496 inhalations in boxes of one (NDC 0173-0498-00) and in 13-g canisters containing 120 metered
497 inhalations in boxes of one (NDC 0173-0494-00). Each canister is supplied with a dark
498 orange-colored oral actuator with a peach-colored strapcap and patient's instructions. Each
499 actuation of the inhaler delivers 110 mcg of fluticasone propionate from the actuator.

500 FLOVENT 220 mcg Inhalation Aerosol is supplied in 7.9-g canisters containing 60 metered
501 inhalations in boxes of one (NDC 0173-0499-00) and in 13-g canisters containing 120 metered
502 inhalations in boxes of one (NDC 0173-0495-00). Each canister is supplied with a dark
503 orange-colored oral actuator with a peach-colored strapcap and patient's instructions. Each
504 actuation of the inhaler delivers 220 mcg of fluticasone propionate from the actuator.

505 FLOVENT canisters are for use with FLOVENT Inhalation Aerosol actuators only. The
506 actuators should not be used with other aerosol medications.

507 The correct amount of medication in each inhalation cannot be assured after 60 inhalations
508 from the 7.9-g canister or 120 inhalations from the 13-g canister even though the canister is not
509 completely empty. The canister should be discarded when the labeled number of actuations has
510 been used.

511 Store between 2° and 30°C (36° and 86°F). Store canister with mouthpiece down. Protect
512 from freezing temperatures and direct sunlight.

513 Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store
514 at temperatures above 120°F. Keep out of reach of children. For best results, the canister should
515 be at room temperature before use. Shake well before using.

516

517 **Note:** The indented statement below is required by the Federal Government's Clean Air Act for
518 all products containing or manufactured with chlorofluorocarbons (CFCs).

519

520 **WARNING:** Contains trichlorofluoromethane and dichlorodifluoromethane, substances that
521 harm public health and environment by destroying ozone in the upper atmosphere.

522

523 A notice similar to the above WARNING has been placed in the patient information leaflet of
524 this product pursuant to EPA regulations.

525

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527

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529 Research Triangle Park, NC 27709

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533 March 2003

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