

PRODUCT INFORMATION

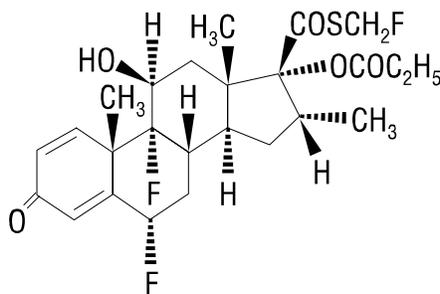
**FLOVENT<sup>®</sup> 44 mcg**  
**(fluticasone propionate, 44 mcg)**  
**Inhalation Aerosol**

**FLOVENT<sup>®</sup> 110 mcg**  
**(fluticasone propionate, 110 mcg)**  
**Inhalation Aerosol**

**FLOVENT<sup>®</sup> 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 $\alpha$ ,9-difluoro-11 $\beta$ ,17-dihydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -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 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.

34  
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 $\beta$ -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.

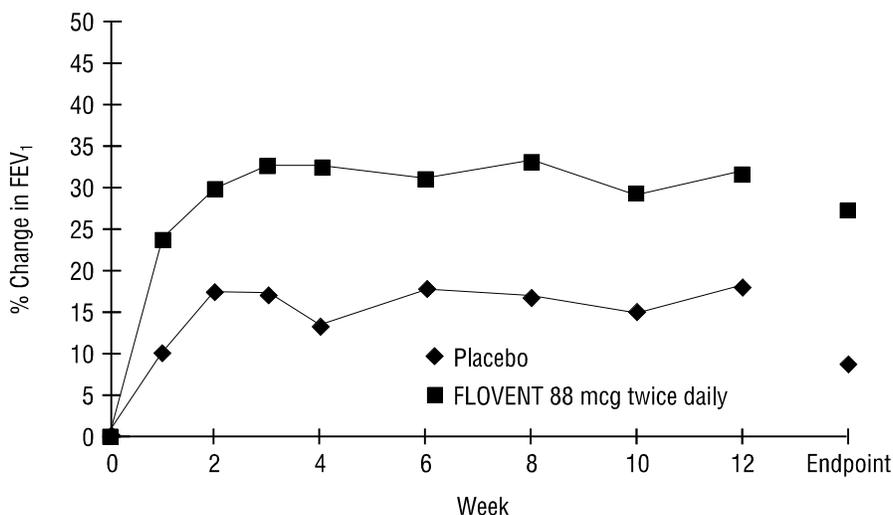
93 The potential systemic effects of inhaled fluticasone propionate on the  
94 hypothalamic-pituitary-adrenal (HPA) axis were also studied in asthma patients. Fluticasone  
95 propionate given by inhalation aerosol at doses of 220, 440, 660, or 880 mcg twice daily was  
96 compared with placebo or oral 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 [FEV<sub>1</sub>] and morning peak expiratory  
111 flow rate [AM PEFr]) 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 FEV<sub>1</sub> 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.

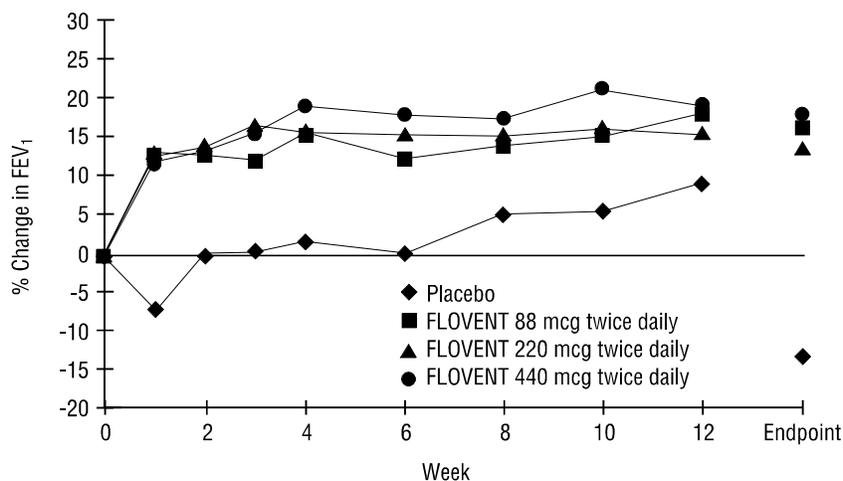
125  
126 **A 12-Week Clinical Trial In Patients Inadequately Controlled on**  
127 **Bronchodilators Alone: Mean Percent Change From Baseline in**  
128 **FEV<sub>1</sub> Prior to AM Dose**  
129



130  
131  
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<sub>R</sub>, albuterol use, and  
140 nighttime awakenings due to asthma).

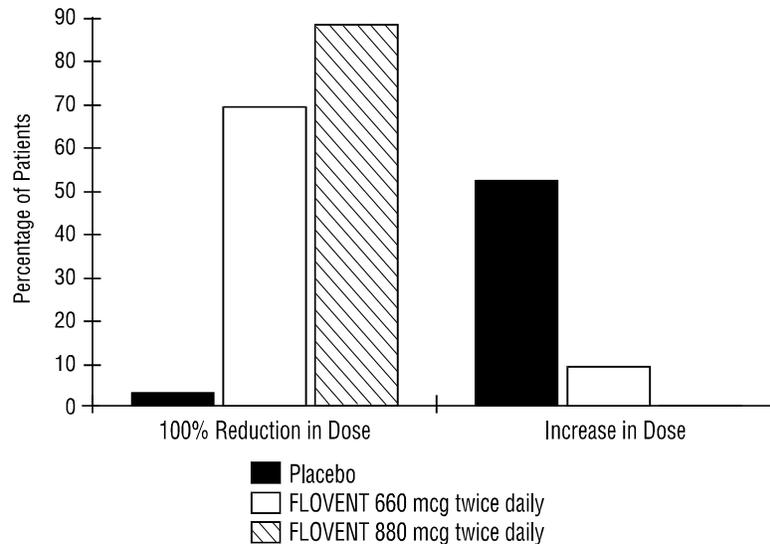
141 Displayed in the figure below are results of pulmonary function from a 12-week clinical trial  
 142 in patients with asthma already receiving daily inhaled corticosteroid therapy (beclomethasone  
 143 dipropionate 336 to 672 mcg/day). The mean percent change from baseline in lung function  
 144 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 Inhaled**  
 156 **Corticosteroids: Mean Percent Change From Baseline in FEV<sub>1</sub> Prior to**  
 157 **AM Dose**  
 158



159  
 160  
 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.

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



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

179 FLOVENT Inhalation Aerosol is NOT indicated for the relief of acute bronchospasm.  
 180

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

185 Hypersensitivity to any of the ingredients of these preparations contraindicates their use.  
 186

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

192 Patients who have been previously maintained on 20 mg or more per day of prednisone (or its  
 193 equivalent) may be most susceptible, particularly when their systemic corticosteroids have been  
 194 almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs  
 195 and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection  
 196 (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although  
 197 fluticasone propionate inhalation aerosol may provide control of asthma symptoms during these

198 episodes, in recommended doses it supplies less than normal physiological amounts of  
199 glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is  
200 necessary for coping with these emergencies.

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

206 Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid  
207 use after transferring to fluticasone propionate inhalation aerosol. In a trial of 96 patients,  
208 prednisone reduction was successfully accomplished by reducing the daily prednisone dose by  
209 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive reduction  
210 of prednisone dose was allowed only when lung function, symptoms, and as-needed beta-agonist  
211 use were better than or comparable to that seen before initiation of prednisone dose reduction.  
212 Lung function (FEV<sub>1</sub> or AM PEF<sub>R</sub>), beta-agonist use, and asthma symptoms should be carefully  
213 monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and  
214 symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as  
215 fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

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

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

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

232 As with other inhaled asthma medications, bronchospasm may occur with an immediate  
233 increase in wheezing after dosing. If bronchospasm occurs following dosing with FLOVENT  
234 Inhalation Aerosol, it should be treated immediately with a fast-acting inhaled bronchodilator.  
235 Treatment with FLOVENT Inhalation Aerosol should be discontinued and alternative therapy  
236 instituted.

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

241  
242 **PRECAUTIONS:**

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

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

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

260 It is possible that systemic corticosteroid effects such as hypercorticism and adrenal  
261 suppression may appear in a small number of patients, particularly at higher doses. If such  
262 changes occur, fluticasone propionate inhalation aerosol should be reduced slowly, consistent  
263 with accepted procedures for reducing systemic corticosteroids and for management of asthma  
264 symptoms.

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

270 The long-term effects of fluticasone propionate in human subjects are not fully known. In  
271 particular, the effects resulting from chronic use of fluticasone propionate on developmental or  
272 immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients  
273 have received fluticasone propionate inhalation aerosol on a continuous basis for periods of  
274 3 years or longer. In clinical studies with patients treated for nearly 2 years with inhaled  
275 fluticasone propionate, no apparent differences in the type or severity of adverse reactions were  
276 observed after long- versus short-term treatment.

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

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

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

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

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

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

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

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

310 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Fluticasone propionate  
311 demonstrated no tumorigenic potential in studies of oral doses up to 1000 mcg/kg (approximately  
312 2 times the maximum human daily inhalation dose based on mcg/m<sup>2</sup>) for 78 weeks in the mouse  
313 or inhalation of up to 57 mcg/kg (approximately 1/4 the maximum human daily inhalation dose  
314 based on mcg/m<sup>2</sup>) for 104 weeks in the rat.

315 Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in  
316 vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in

317 vitro or in the mouse micronucleus test when administered at high doses by the oral or  
318 subcutaneous routes. Furthermore, the compound did not delay erythroblast division in bone  
319 marrow.

320 No evidence of impairment of fertility was observed in reproductive studies conducted in rats  
321 dosed subcutaneously with doses up to 50 mcg/kg (approximately 1/4 the maximum human daily  
322 inhalation dose based on mcg/m<sup>2</sup>) in males and females. However, prostate weight was  
323 significantly reduced in rats.

324 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Subcutaneous studies in the mouse  
325 and rat at 45 and 100 mcg/kg, respectively (approximately 1/10 and 1/2 the maximum human  
326 daily inhalation dose based on mcg/m<sup>2</sup>, respectively), revealed fetal toxicity characteristic of  
327 potent glucocorticoid compounds, including embryonic growth retardation, omphalocele, cleft  
328 palate, and retarded cranial ossification.

329 In the rabbit, fetal weight reduction and cleft palate were observed following subcutaneous  
330 doses of 4 mcg/kg (approximately 1/25 the maximum human daily inhalation dose based on  
331 mcg/m<sup>2</sup>). However, following oral administration of up to 300 mcg/kg (approximately 3 times  
332 the maximum human daily inhalation dose based on mcg/m<sup>2</sup>) of fluticasone propionate to the  
333 rabbit, there were no maternal effects nor increased incidence of external, visceral, or skeletal  
334 fetal defects. No fluticasone propionate was detected in the plasma in this study, consistent with  
335 the established low bioavailability following oral administration (see CLINICAL  
336 PHARMACOLOGY).

337 Less than 0.008% of the administered dose crossed the placenta following oral administration  
338 of 100 mcg/kg to rats or 300 mcg/kg to rabbits (approximately 1/2 and 3 times the maximum  
339 human daily inhalation dose based on mcg/m<sup>2</sup>, respectively).

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

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

348 **Nursing Mothers:** It is not known whether fluticasone propionate is excreted in human breast  
349 milk. Subcutaneous administration of 10 mcg/kg tritiated drug to lactating rats (approximately  
350 1/20 the maximum human daily inhalation dose based on mcg/m<sup>2</sup>) resulted in measurable  
351 radioactivity in both plasma and milk. Because glucocorticoids are excreted in human milk,  
352 caution should be exercised when fluticasone propionate inhalation aerosol is administered to a  
353 nursing woman.

354 **Pediatric Use:** One hundred thirty-seven (137) patients between the ages of 12 and 16 years  
355 were treated with fluticasone propionate inhalation aerosol in the US pivotal clinical trials. The  
356 safety and effectiveness of FLOVENT Inhalation Aerosol in children below 12 years of age have

357 not been established. Oral corticosteroids have been shown to cause a reduction in growth  
 358 velocity in children and teenagers with extended use. If a child or teenager on any corticosteroid  
 359 appears to have growth suppression, the possibility that they are particularly sensitive to this  
 360 effect of corticosteroids should be considered (see PRECAUTIONS).

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

364  
 365 **ADVERSE REACTIONS:** The following incidence of common adverse experiences is based  
 366 upon 7 placebo-controlled US clinical trials in which 1243 patients (509 female and 734 male  
 367 adolescents and adults previously treated with as-needed bronchodilators and/or inhaled  
 368 corticosteroids) were treated with fluticasone propionate inhalation aerosol (doses of 88 to  
 369 440 mcg twice daily for up to 12 weeks) or placebo.

370  
 371 **Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in US**  
 372 **Controlled Clinical Trials With MDI in Patients Previously Receiving Bronchodilators**  
 373 **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

374  
 375 The table above includes all events (whether considered drug-related or nondrug-related by the  
 376 investigator) that occurred at a rate of over 3% in the combined fluticasone propionate inhalation

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

379 These adverse reactions were mostly mild to moderate in severity, with  $\leq 2\%$  of patients  
380 discontinuing the studies because of adverse events. Rare cases of immediate and delayed  
381 hypersensitivity reactions, including urticaria and rash and other rare events of angioedema and  
382 bronchospasm, have been reported.

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

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

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

391 **Eye:** Irritation of the eye(s).

392 **Gastrointestinal:** Nausea and vomiting, diarrhea, dyspepsia and stomach disorder.

393 **Miscellaneous:** Fever.

394 **Mouth and Teeth:** Dental problem.

395 **Musculoskeletal:** Pain in joint, sprain/strain, aches and pains, pain in limb.

396 **Neurological:** Dizziness/giddiness.

397 **Respiratory:** Bronchitis, chest congestion.

398 **Skin:** Dermatitis, rash/skin eruption.

399 **Urogenital:** Dysmenorrhea.

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

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

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

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

414 **Observed During Clinical Practice:** In addition to adverse experiences reported from  
415 clinical trials, the following experiences have been identified during postapproval use of  
416 fluticasone propionate. Because they are reported voluntarily from a population of unknown size,

417 estimates of frequency cannot be made. These experiences have been chosen for inclusion due to  
418 either their seriousness, frequency of reporting, causal connection to fluticasone propionate or a  
419 combination of these factors.

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

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

424 **Eye:** Cataracts.

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

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

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

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

439  
440 **OVERDOSAGE:** Chronic overdose may result in signs/symptoms of hypercorticism (see  
441 PRECAUTIONS). Inhalation by healthy volunteers of a single dose of 1760 or 3520 mcg of  
442 fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by  
443 inhalation aerosol at doses of 1320 mcg twice daily for 7 to 15 days to healthy human volunteers  
444 was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and  
445 repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions  
446 were of mild or moderate severity, and incidences were similar in active and placebo treatment  
447 groups. The oral and subcutaneous median lethal doses in rats and mice were >1000 mg/kg  
448 (>2000 times the maximum human daily inhalation dose based on mg/m<sup>2</sup>).

449  
450 **DOSAGE AND ADMINISTRATION:** FLOVENT Inhalation Aerosol should be administered  
451 by the orally inhaled route in patients 12 years of age and older. Individual patients will  
452 experience a variable time to onset and degree of symptom relief. Generally, fluticasone  
453 propionate inhalation aerosol has a relatively rapid onset of action for an inhaled glucocorticoid.  
454 Improvement in asthma control following inhaled administration of fluticasone propionate can  
455 occur within 24 hours of beginning treatment, although maximum benefit may not be achieved  
456 for 1 to 2 weeks or longer after starting treatment.

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

462 Rinsing the mouth after inhalation is advised.

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

465

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 <sup>†</sup>	880 mcg twice daily	880 mcg twice daily

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

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

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

477

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

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

484

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

491 FLOVENT 110 mcg Inhalation Aerosol is supplied in 7.9-g canisters containing 60 metered  
492 inhalations in boxes of one (NDC 0173-0498-00) and in 13-g canisters containing 120 metered

493 inhalations in boxes of one (NDC 0173-0494-00). Each canister is supplied with a dark  
494 orange-colored oral actuator with a peach-colored strapcap and patient's instructions. Each  
495 actuation of the inhaler delivers 110 mcg of fluticasone propionate from the actuator.

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

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

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

507 Store between 2° and 30°C (36° and 86°F). Store canister with nozzle end down. Protect from  
508 freezing temperatures and direct sunlight.

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

512

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

515

516 **WARNING:** Contains trichlorofluoromethane and dichlorodifluoromethane, substances  
517 which harm public health and environment by destroying ozone in the upper atmosphere.

518

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

521

522



523

524 GlaxoSmithKline

525 Research Triangle Park, NC 27709

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530 February 2002

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