

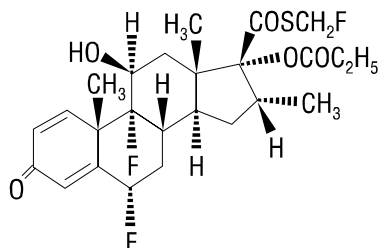
**FLOVENT<sup>®</sup> ROTADISK<sup>®</sup> 50 mcg**  
**(fluticasone propionate inhalation powder, 50 mcg)**

**FLOVENT<sup>®</sup> ROTADISK<sup>®</sup> 100 mcg**  
**(fluticasone propionate inhalation powder, 100 mcg)**

**FLOVENT<sup>®</sup> ROTADISK<sup>®</sup> 250 mcg**  
**(fluticasone propionate inhalation powder, 250 mcg)**

**For Oral Inhalation Only**  
**For Use With the DISKHALER<sup>®</sup> Inhalation Device**

**DESCRIPTION:** The active component of FLOVENT ROTADISK 50 mcg, FLOVENT ROTADISK 100 mcg, and FLOVENT ROTADISK 250 mcg is fluticasone propionate, a corticosteroid 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, and the empirical formula is C<sub>25</sub>H<sub>31</sub>F<sub>3</sub>O<sub>5</sub>S. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FLOVENT ROTADISK 50 mcg, FLOVENT ROTADISK 100 mcg, and FLOVENT ROTADISK 250 mcg contain a dry powder presentation of fluticasone propionate intended for oral inhalation only. Each double-foil ROTADISK contains 4 blisters. Each blister contains a mixture of 50, 100, or 250 mcg of microfine fluticasone propionate blended with lactose (which contains milk proteins) to a total weight of 25 mg. The contents of each blister are inhaled using a specially designed plastic device for inhaling powder called the DISKHALER. After a fluticasone propionate ROTADISK is loaded into the DISKHALER, a blister containing medication is pierced and the fluticasone propionate is dispersed into the air stream created when the patient inhales through the mouthpiece.

34 The amount of drug delivered to the lung will depend on patient factors such as inspiratory  
35 flow. Under standardized in vitro testing, FLOVENT ROTADISK delivers 44, 88, or 220 mcg of  
36 fluticasone propionate from FLOVENT ROTADISK 50 mcg, FLOVENT ROTADISK 100 mcg,  
37 or FLOVENT ROTADISK 250 mcg, respectively, when tested at a flow rate of 60 L/min for  
38 3 seconds. In adult and adolescent patients with asthma, mean peak inspiratory flow (PIF)  
39 through the DISKHALER was 123 L/min (range, 88 to 159 L/min), and in pediatric patients 4 to  
40 11 years of age with asthma, mean PIF was 110 L/min (range, 43 to 175 L/min).

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

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

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

60 **Pharmacokinetics: Absorption:** The activity of FLOVENT ROTADISK Inhalation Powder  
61 is due to the parent drug, fluticasone propionate. Studies using oral dosing of labeled and  
62 unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate  
63 is negligible (<1%), primarily due to incomplete absorption and pre-systemic metabolism in the  
64 gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is  
65 systemically absorbed. The systemic bioavailability of fluticasone propionate inhalation powder  
66 in healthy volunteers averaged about 13.5% of the nominal dose.

67 Peak plasma concentrations after a 1000-mcg dose of fluticasone propionate inhalation  
68 powder ranged from 0.1 to 1.0 ng/mL.

69 **Distribution:** Following intravenous administration, the initial disposition phase for  
70 fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding.  
71 The volume of distribution averaged 4.2 L/kg. The percentage of fluticasone propionate bound to  
72 human plasma proteins averaged 91%.

73 Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate  
74 is not significantly bound to human transcortin.

75 **Metabolism:** The total clearance of fluticasone propionate is high (average, 1093 mL/min),  
76 with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite  
77 detected in man is the 17 $\beta$ -carboxylic acid derivative of fluticasone propionate, which is formed  
78 through the cytochrome P450 3A4 pathway. This metabolite had approximately 2,000 times less  
79 affinity than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and  
80 negligible pharmacological activity in animal studies. Other metabolites detected in vitro using  
81 cultured human hepatoma cells have not been detected in man.

82 In a multiple-dose drug interaction study, coadministration of fluticasone propionate  
83 (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone  
84 propionate pharmacokinetics.

85 In a drug interaction study, coadministration of fluticasone propionate (1000 mcg) and  
86 ketoconazole (200 mg once daily) resulted in increased fluticasone propionate concentrations, a  
87 reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

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

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

98 Plasma concentrations of fluticasone propionate were measured 20 and 40 minutes after  
99 dosing from 29 children aged 4 to 11 years who were taking either 50 or 100 mcg twice daily of  
100 fluticasone propionate inhalation powder. Plasma concentration values ranged from below the  
101 limit of quantitation (25 pg/mL) to 117 pg/mL (50-mcg dose) or 154 pg/mL (100-mcg dose). In a  
102 study with adults taking the 100-mcg twice-daily dose, the plasma concentrations observed  
103 ranged from below the limit of quantitation to 73.1 pg/mL. The median fluticasone propionate  
104 plasma concentrations for the 100-mcg dose in children was 58.7 pg/mL; in adults the median  
105 plasma concentration was 39.5 pg/mL.

106 **Pharmacodynamics:** To confirm that systemic absorption does not play a role in the clinical  
107 response to inhaled fluticasone propionate, a double-blind clinical study comparing inhaled and  
108 oral fluticasone propionate was conducted. Doses of 100 and 500 mcg twice daily of fluticasone  
109 propionate inhalation powder were compared to oral fluticasone propionate, 20,000 mcg given  
110 once daily, and placebo for 6 weeks. Plasma levels of fluticasone propionate were detectable in  
111 all 3 active groups, but the mean values were highest in the oral group. Both doses of inhaled  
112 fluticasone propionate were effective in maintaining asthma stability and improving lung

113 function while oral fluticasone propionate and placebo were ineffective. This demonstrates that  
114 the clinical effectiveness of inhaled fluticasone propionate is due to its direct local effect and not  
115 to an indirect effect through systemic absorption.

116 The potential systemic effects of inhaled fluticasone propionate on the  
117 hypothalamic-pituitary-adrenal (HPA) axis were also studied in asthma patients. Fluticasone  
118 propionate given by inhalation aerosol at doses of 220, 440, 660, or 880 mcg twice daily was  
119 compared with placebo or oral prednisone 10 mg given once daily for 4 weeks. For most  
120 patients, the ability to increase cortisol production in response to stress, as assessed by 6-hour  
121 cosyntropin stimulation, remained intact with inhaled fluticasone propionate treatment. No  
122 patient had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing with placebo or  
123 fluticasone propionate 220 mcg twice daily. For patients treated with 440, 660, and 880 mcg  
124 twice daily, 10%, 16%, and 12%, respectively, had an abnormal response as compared to 29% of  
125 patients treated with prednisone.

126 In clinical trials with fluticasone propionate inhalation powder, using doses up to and  
127 including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol  
128 <18 mcg/dL) were noted in patients receiving fluticasone propionate or placebo. The incidence  
129 of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out  
130 in 64 patients randomized to fluticasone propionate 500 mcg twice daily or placebo, 1 patient  
131 receiving fluticasone propionate (4%) had an abnormal response to 6-hour cosyntropin infusion  
132 at 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving  
133 fluticasone propionate (5%) had an abnormal response at 2 years. No patient on placebo had an  
134 abnormal response at 1 or 2 years.

135 **Clinical Trials:** Double-blind, parallel, placebo-controlled, US clinical trials were conducted  
136 in 1197 adolescent and adult asthma patients to assess the efficacy and safety of FLOVENT  
137 ROTADISK in the treatment of asthma. Fixed doses of 50, 100, 250, and 500 mcg twice daily  
138 were compared to placebo to provide information about appropriate dosing to cover a range of  
139 asthma severity. Asthmatic patients included in these studies were those not adequately  
140 controlled with beta-agonists alone, and those already maintained on daily inhaled  
141 corticosteroids. In these efficacy trials, at all doses, measures of pulmonary function (forced  
142 expiratory volume in 1 second [FEV<sub>1</sub>] and morning peak expiratory flow rate [AM PEF<sub>R</sub>]) were  
143 statistically significantly improved as compared with placebo. All doses were delivered by  
144 inhalation of the contents of 1 or 2 blisters from the DISKHALER twice daily.

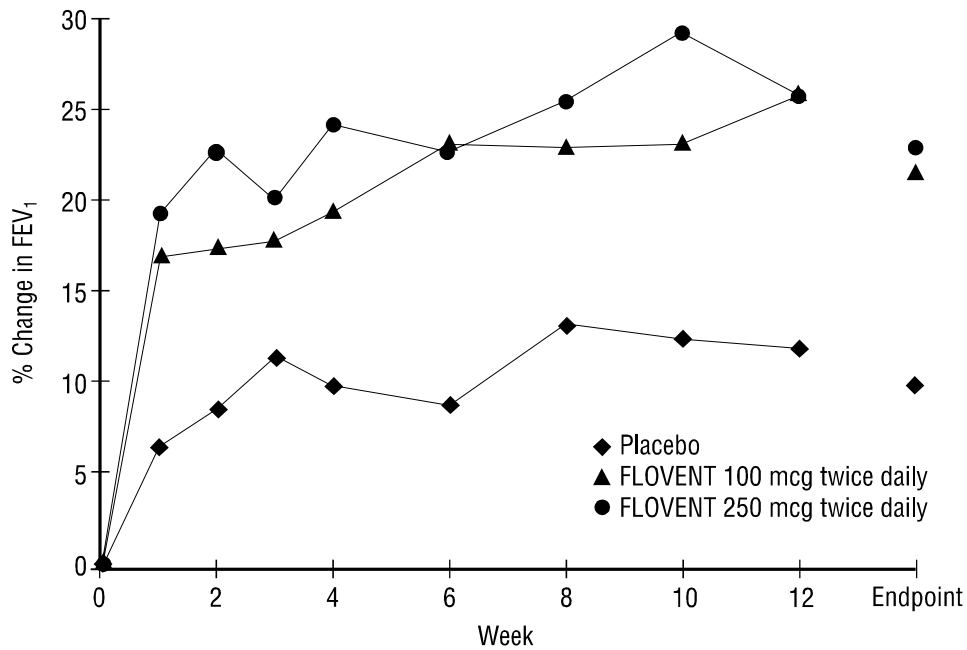
145 Displayed in the figure below are results of pulmonary function tests for 2 recommended  
146 dosages of fluticasone propionate inhalation powder (100 and 250 mcg twice daily) and placebo  
147 from a 12-week trial in 331 adolescent and adult asthma patients (baseline FEV<sub>1</sub> = 2.63 L/sec)  
148 inadequately controlled on bronchodilators alone. Because this trial used predetermined criteria  
149 for lack of efficacy, which caused more patients in the placebo group to be withdrawn,  
150 pulmonary function results at Endpoint, which is the last evaluable FEV<sub>1</sub> result and includes  
151 most patients' lung function data, are also provided. Pulmonary function at both fluticasone

152 propionate dosages improved significantly compared with placebo by the first week of treatment,  
153 and this improvement was maintained over the duration of the trial.

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155 **A 12-Week Clinical Trial in Patients Inadequately Controlled**  
156 **on Bronchodilators Alone: Mean Percent Change From Baseline**  
157 **in FEV<sub>1</sub> Prior to AM Dose**

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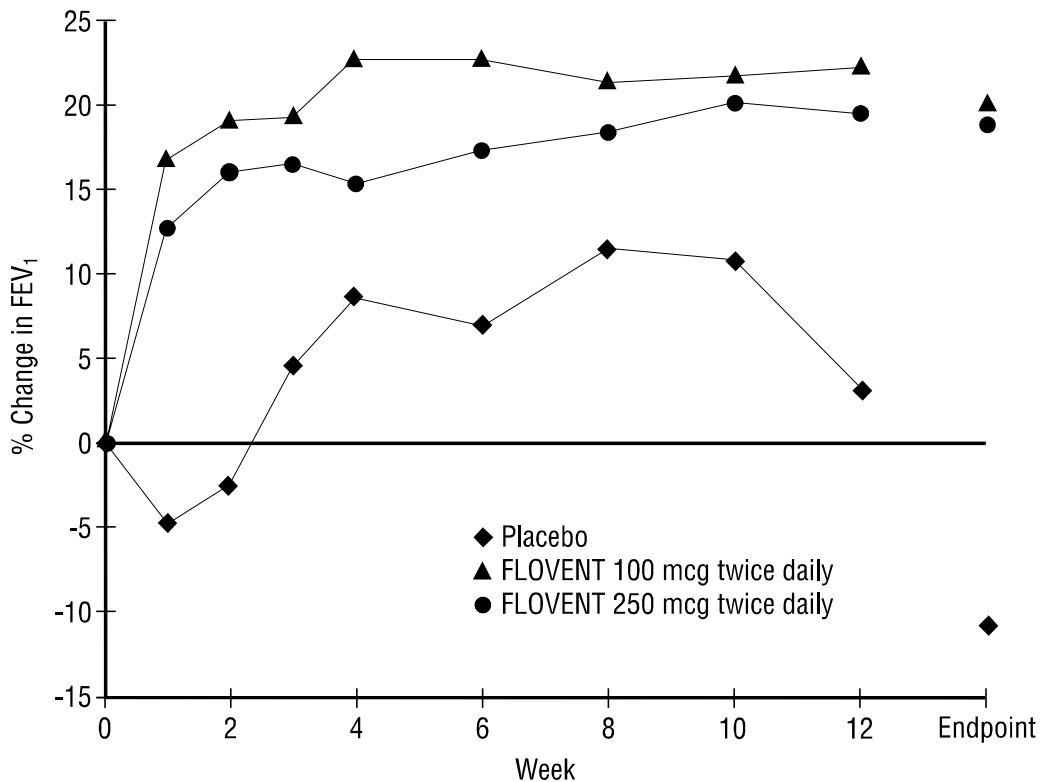
161 In a second clinical study of 75 patients, 500 mcg twice daily was evaluated in a similar  
162 population. In this trial fluticasone propionate significantly improved pulmonary function as  
163 compared with placebo.

164 Displayed in the figure below are results of pulmonary function tests for 2 recommended  
165 dosages of fluticasone propionate inhalation powder (100 and 250 mcg twice daily) and placebo  
166 from a 12-week trial in 342 adolescent and adult asthma patients (baseline FEV<sub>1</sub> = 2.49 L/sec)  
167 already receiving daily inhaled corticosteroid therapy (≥336 mcg/day of beclomethasone  
168 dipropionate or ≥800 mcg/day of triamcinolone acetonide) in addition to as-needed albuterol and  
169 theophylline (38% of all patients). Because this trial also used predetermined criteria for lack of  
170 efficacy, which caused more patients in the placebo group to be withdrawn, pulmonary function  
171 results at Endpoint are included. Pulmonary function at both fluticasone propionate dosages  
172 improved significantly compared with placebo by the first week of treatment and the  
173 improvement was maintained over the duration of the trial.

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**A 12-Week Clinical Trial in Patients Already Receiving Inhaled  
Corticosteroids: Mean Percent Change From Baseline in FEV<sub>1</sub>  
Prior to AM Dose**



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181 In a second clinical study of 139 patients, treatment with 500 mcg twice daily was evaluated  
182 in a similar patient population. In this trial fluticasone propionate significantly improved  
183 pulmonary function as compared with placebo.

184 In the 4 trials described above, all dosages of fluticasone propionate were efficacious;  
185 however, at higher dosages, patients were less likely to discontinue study participation due to  
186 asthma deterioration (as defined by predetermined criteria for lack of efficacy including lung  
187 function and patient-recorded variables such as AM PEFR, albuterol use, and nighttime  
188 awakenings due to asthma).

189 In a clinical trial of 96 severe asthmatic patients requiring chronic oral prednisone therapy  
190 (average baseline daily prednisone dose was 10 mg), fluticasone propionate given by inhalation  
191 aerosol at doses of 660 and 880 mcg twice daily was evaluated. Both doses enabled a statistically  
192 significantly larger percentage of patients to wean successfully from oral prednisone as  
193 compared with placebo (69% of the patients on 660 mcg twice daily and 88% of the patients on  
194 880 mcg twice daily as compared with 3% of patients on placebo). Accompanying the reduction  
195 in oral corticosteroid use, patients treated with fluticasone propionate had significantly improved  
196 lung function and fewer asthma symptoms as compared with the placebo group. These data were  
197 obtained from a clinical study using fluticasone propionate inhalation aerosol; no direct

198 assessment of the clinical comparability of equal nominal doses for the FLOVENT ROTADISK  
199 and FLOVENT Inhalation Aerosol formulations in this population has been conducted.

200 **Pediatric Experience:** In a 12-week, placebo-controlled clinical trial of 263 patients aged  
201 4 to 11 years inadequately controlled on bronchodilators alone (baseline morning peak expiratory  
202 flow = 200 L/min), fluticasone propionate inhalation powder doses of 50 and 100 mcg twice  
203 daily significantly improved morning peak expiratory flow (28% and 34% change from baseline  
204 at Endpoint, respectively) compared to placebo (11% change). In a second placebo-controlled,  
205 52-week trial of 325 patients aged 4 to 11 years, approximately half of whom were receiving  
206 inhaled corticosteroids at baseline, doses of fluticasone propionate inhalation powder of 50 and  
207 100 mcg twice daily improved lung function by the first week of treatment, and the improvement  
208 continued over 1 year compared to placebo. In both studies, patients on active treatment were  
209 significantly less likely to discontinue treatment due to lack of efficacy.

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211 **INDICATIONS AND USAGE:** FLOVENT ROTADISK is indicated for the maintenance  
212 treatment of asthma as prophylactic therapy in patients 4 years of age and older. It is also  
213 indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients  
214 may be able to reduce or eliminate their requirement for oral corticosteroids over time.

215 FLOVENT ROTADISK is NOT indicated for the relief of acute bronchospasm.

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217 **CONTRAINDICATIONS:** FLOVENT ROTADISK is contraindicated in the primary treatment  
218 of status asthmaticus or other acute episodes of asthma where intensive measures are required.

219 Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see  
220 DESCRIPTION and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site*  
221 *Specific*).

222

#### 223 **WARNINGS:**

224 Particular care is needed for patients who are transferred from systemically active  
225 corticosteroids to FLOVENT ROTADISK because deaths due to adrenal insufficiency have  
226 occurred in asthmatic patients during and after transfer from systemic corticosteroids to less  
227 systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a  
228 number of months are required for recovery of HPA function.

229 Patients who have been previously maintained on 20 mg or more per day of prednisone (or its  
230 equivalent) may be most susceptible, particularly when their systemic corticosteroids have been  
231 almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs  
232 and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection  
233 (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although  
234 fluticasone propionate inhalation powder may provide control of asthma symptoms during these  
235 episodes, in recommended doses it supplies less than normal physiological amounts of  
236 corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary  
237 for coping with these emergencies.

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

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

253 Transfer of patients from systemic corticosteroid therapy to fluticasone propionate inhalation  
254 powder may unmask conditions previously suppressed by the systemic corticosteroid therapy,  
255 e.g., rhinitis, conjunctivitis, eczema, and arthritis.

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

267 Fluticasone propionate inhalation powder is not to be regarded as a bronchodilator and is not  
268 indicated for rapid relief of bronchospasm.

269 As with other inhaled asthma medications, bronchospasm may occur with an immediate  
270 increase in wheezing after dosing. If bronchospasm occurs following dosing with FLOVENT  
271 ROTADISK, it should be treated immediately with a fast-acting inhaled bronchodilator.  
272 Treatment with inhaled fluticasone propionate should be discontinued and alternative therapy  
273 instituted.

274 Patients should be instructed to contact their physicians immediately when episodes of asthma  
275 that are not responsive to bronchodilators occur during the course of treatment with fluticasone  
276 propionate inhalation powder. During such episodes, patients may require therapy with oral  
277 corticosteroids.



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**PRECAUTIONS:**

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

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

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

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

A reduction of growth velocity in children or adolescents may occur as a result of poorly controlled asthma or from the therapeutic use of corticosteroids, including inhaled corticosteroids. A 52-week placebo-controlled study to assess the potential growth effects of fluticasone propionate inhalation powder at 50 and 100 mcg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) 4 to 11 years of age. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and 5.66 cm/year in the 100-mcg group (n = 89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the 100-mcg group (n = 79). The clinical significance of these growth data is not certain. In children 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: boys – 3<sup>rd</sup> percentile = 3.8 cm/year, 50<sup>th</sup> percentile = 5.4 cm/year, and 97<sup>th</sup>

318 percentile = 7.0 cm/year; girls – 3<sup>rd</sup> percentile = 4.2 cm/year, 50<sup>th</sup> percentile = 5.7 cm/year, and  
319 97<sup>th</sup> percentile = 7.3 cm/year. The effects of long-term treatment of children with inhaled  
320 corticosteroids, including fluticasone propionate, on final adult height are not known. Physicians  
321 should closely follow the growth of children and adolescents taking corticosteroids by any route,  
322 and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if  
323 growth appears slowed. Patients should be maintained on the lowest dose of inhaled  
324 corticosteroid that effectively controls their asthma.

325 The long-term effects of fluticasone propionate in human subjects are not fully known. In  
326 particular, the effects resulting from chronic use of fluticasone propionate on developmental or  
327 immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients  
328 have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or  
329 longer. In clinical studies with patients treated for 2 years with inhaled fluticasone propionate, no  
330 apparent differences in the type or severity of adverse reactions were observed after long- versus  
331 short-term treatment.

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

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

339 Inhaled corticosteroids should be used with caution, if at all, in patients with active or  
340 quiescent tuberculous infections of the respiratory tract; untreated systemic fungal, bacterial,  
341 viral, or parasitic infections; or ocular herpes simplex.

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

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

356 Patients should use FLOVENT ROTADISK at regular intervals as directed. Results of clinical  
357 trials indicated significant improvement may occur within the first day or two of treatment;

358 however, the full benefit may not be achieved until treatment has been administered for 1 to  
359 2 weeks or longer. The patient should not increase the prescribed dosage but should contact the  
360 physician if symptoms do not improve or if the condition worsens.

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

363 For the proper use of FLOVENT ROTADISK Inhalation Powder and to attain maximum  
364 improvement, the patient should read and follow carefully the accompanying Patient's  
365 Instructions for Use.

366 **Drug Interactions:** In a placebo-controlled, crossover study in 8 healthy volunteers,  
367 coadministration of a single dose of fluticasone propionate (1000 mcg) with multiple doses of  
368 ketoconazole (200 mg) to steady state resulted in increased mean fluticasone propionate  
369 concentrations, a reduction in plasma cortisol AUC, and no effect on urinary excretion of  
370 cortisol. This interaction may be due to an inhibition of the cytochrome P450 3A4 isoenzyme  
371 system by ketoconazole, which is also the route of metabolism of fluticasone propionate. Care  
372 should be exercised when FLOVENT is coadministered with long-term ketoconazole and other  
373 known cytochrome P450 3A4 inhibitors.

374 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Fluticasone propionate  
375 demonstrated no tumorigenic potential in mice at oral doses up to 1000 mcg/kg (approximately 2  
376 times the maximum recommended daily inhalation dose in adults and approximately 10 times  
377 the maximum recommended daily inhalation dose in children on a mcg/m<sup>2</sup> basis) for 78 weeks  
378 or in rats at inhalation doses up to 57 mcg/kg (approximately 1/4 the maximum recommended  
379 daily inhalation dose in adults and comparable to the maximum recommended daily inhalation  
380 dose in children on a mcg/m<sup>2</sup> basis) for 104 weeks.

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

386 No evidence of impairment of fertility was observed in reproductive studies conducted in  
387 male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 1/5 the maximum  
388 recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis). Prostate weight was  
389 significantly reduced at a subcutaneous dose of 50 mcg/kg.

390 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Subcutaneous studies in the  
391 mouse and rat at 45 and 100 mcg/kg, respectively, (approximately 1/10 and 1/3, respectively, the  
392 maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) revealed fetal  
393 toxicity characteristic of potent corticosteroid compounds, including embryonic growth  
394 retardation, omphalocele, cleft palate, and retarded cranial ossification.

395 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of  
396 4 mcg/kg (approximately 1/30 the maximum recommended daily inhalation dose in adults on a  
397 mcg/m<sup>2</sup> basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg

398 (approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
399 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this  
400 study, consistent with the established low bioavailability following oral administration (see  
401 CLINICAL PHARMACOLOGY).

402 Fluticasone propionate crossed the placenta following oral administration of 100 mcg/kg to  
403 rats or 300 mcg/kg to rabbits (approximately 1/3 and 2 times, respectively, the maximum  
404 recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis).

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

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

413 **Nursing Mothers:** It is not known whether fluticasone propionate is excreted in human breast  
414 milk. Subcutaneous administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate  
415 (approximately 1/25 the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup>  
416 basis) resulted in measurable radioactivity in milk. Because other corticosteroids are excreted in  
417 human milk, caution should be exercised when fluticasone propionate inhalation powder is  
418 administered to a nursing woman.

419 **Pediatric Use:** Two hundred fourteen (214) patients 4 to 11 years of age and 142 patients 12 to  
420 16 years of age were treated with fluticasone propionate inhalation powder in US clinical trials.  
421 The safety and effectiveness of FLOVENT ROTADISK Inhalation Powder in children below  
422 4 years of age have not been established.

423 Inhaled corticosteroids, including fluticasone propionate, may cause a reduction in growth in  
424 children and adolescents (see PRECAUTIONS). If a child or adolescent on any corticosteroid  
425 appears to have growth suppression, the possibility that they are particularly sensitive to this  
426 effect of corticosteroids should be considered. Patients should be maintained on the lowest dose  
427 of inhaled corticosteroid that effectively controls their asthma.

428 **Geriatric Use:** Safety data have been collected on 280 patients (FLOVENT<sup>®</sup> DISKUS<sup>®</sup> n = 83,  
429 FLOVENT ROTADISK n = 197) 65 years of age or older and 33 patients (FLOVENT DISKUS  
430 n = 14, FLOVENT ROTADISK n = 19) 75 years of age or older who have been treated with  
431 fluticasone propionate inhalation powder in US and non-US clinical trials. There were no  
432 differences in adverse reactions compared to those reported by younger patients. In addition,  
433 there were no apparent differences in efficacy between patients 65 years of age or older and  
434 younger patients. Fifteen patients 65 years of age or older and 1 patient 75 years of age or older  
435 were included in the efficacy evaluation of US clinical studies.

436

437 **ADVERSE REACTIONS:** The following incidence of common adverse experiences is based  
 438 upon 6 placebo-controlled clinical trials in which 1384 patients ≥4 years of age (520 females and  
 439 864 males) previously treated with as-needed bronchodilators and/or inhaled corticosteroids  
 440 were treated with fluticasone propionate inhalation powder (doses of 50 to 500 mcg twice daily  
 441 for up to 12 weeks) or placebo.

442

443 **Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate**  
 444 **in Controlled Clinical Trials With FLOVENT ROTADISK in Patients ≥4 Years**  
 445 **Previously Receiving Bronchodilators and/or Inhaled Corticosteroids**

| Adverse Event                          | Placebo<br>(n = 438)<br>% | FLOVENT<br>50 mcg<br>Twice Daily<br>(n = 255)<br>% | FLOVENT<br>100 mcg<br>Twice Daily<br>(n = 331)<br>% | FLOVENT<br>250 mcg<br>Twice Daily<br>(n = 176)<br>% | FLOVENT<br>500 mcg<br>Twice Daily<br>(n = 184)<br>% |
|--|---------------------------|--|---|---|---|
| Ear, nose, and throat                  |                           |  |   |   |   |
| Pharyngitis                            | 7                         | 6  | 8   | 8   | 13  |
| Nasal congestion                       | 5                         | 4  | 4   | 7   | 7   |
| Sinusitis                              | 4                         | 5  | 4   | 6   | 4   |
| Rhinitis                               | 4                         | 4  | 9   | 2   | 3   |
| Dysphonia                              | 0                         | <1   | 4   | 6   | 4   |
| Oral candidiasis                       | 1                         | 3  | 3   | 4   | 11  |
| Respiratory                            |                           |  |   |   |   |
| Upper respiratory infection            | 13                        | 16   | 17  | 22  | 16  |
| Influenza                              | 2                         | 3  | 3   | 3   | 4   |
| Bronchitis                             | 2                         | 4  | 2   | 1   | 2   |
| Other                                  |                           |  |   |   |   |
| Headache                               | 11                        | 11   | 9   | 14  | 15  |
| Diarrhea                               | 1                         | 2  | 2   | 0   | 4   |
| Back problems                          | <1                        | <1   | 1   | 1   | 4   |
| Fever                                  | 3                         | 4  | 4   | 2   | 2   |
| Average duration of exposure<br>(days) | 53                        | 77   | 68  | 78  | 60  |

446

447 The table above includes all events (whether considered drug-related or nondrug-related by  
 448 the investigator) that occurred at a rate of over 3% in any of the fluticasone propionate inhalation  
 449 powder groups and were more common than in the placebo group. In considering these data,  
 450 differences in average duration of exposure should be taken into account.

451 These adverse reactions were mostly mild to moderate in severity, with <2% of patients  
 452 discontinuing the studies because of adverse events. Rare cases of immediate and delayed

453 hypersensitivity reactions, including rash and other rare events of angioedema and  
454 bronchospasm, have been reported.

455 Other adverse events that occurred in these clinical trials using fluticasone propionate  
456 inhalation powder with an incidence of 1% to 3% and which occurred at a greater incidence than  
457 with placebo were:

458 **Ear, Nose, and Throat:** Otitis media, tonsillitis, nasal discharge, earache, laryngitis,  
459 epistaxis, sneezing.

460 **Eye:** Conjunctivitis.

461 **Gastrointestinal:** Abdominal pain, viral gastroenteritis, gastroenteritis/colitis, abdominal  
462 discomfort.

463 **Miscellaneous:** Injury.

464 **Mouth and Teeth:** Mouth irritation.

465 **Musculoskeletal:** Sprain/strain, pain in joint, disorder/symptoms of neck, muscular  
466 soreness, aches and pains.

467 **Neurological:** Migraine, nervousness.

468 **Respiratory:** Chest congestion, acute nasopharyngitis, dyspnea, irritation due to inhalant.

469 **Skin:** Dermatitis, urticaria.

470 **Urogenital:** Dysmenorrhea, candidiasis of vagina, pelvic inflammatory disease,  
471 vaginitis/vulvovaginitis, irregular menstrual cycle.

472 There were no clinically relevant differences in the pattern or severity of adverse events in  
473 children compared with those reported in adults.

474 Fluticasone propionate inhalation aerosol (660 or 880 mcg twice daily) was administered for  
475 16 weeks to asthmatics requiring oral corticosteroids. Adverse events reported more frequently  
476 in these patients compared to patients not on oral corticosteroids included sinusitis, nasal  
477 discharge, oropharyngeal candidiasis, headache, joint pain, nausea and vomiting, muscular  
478 soreness, malaise/fatigue, and insomnia.

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

485 **Ear, Nose, and Throat:** Aphonia, facial and oropharyngeal edema, hoarseness, and throat  
486 soreness and irritation.

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

489 **Eye:** Cataracts.

490 **Non-Site Specific:** Very rare anaphylactic reaction, very rare anaphylactic reaction in  
491 patients with severe milk protein allergy.

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

493 **Respiratory:** Asthma exacerbation, bronchospasm, chest tightness, cough, immediate  
494 bronchospasm, paradoxical bronchospasm, pneumonia, and wheeze.

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

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

506  
507 **OVERDOSAGE:** Chronic overdose may result in signs/symptoms of hypercorticism (see  
508 PRECAUTIONS). Inhalation by healthy volunteers of a single dose of 4000 mcg of fluticasone  
509 propionate inhalation powder or single doses of 1760 or 3520 mcg of fluticasone propionate  
510 inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses  
511 of 1320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated.  
512 Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to  
513 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or  
514 moderate severity, and incidences were similar in active and placebo treatment groups. The oral  
515 and subcutaneous median lethal doses in mice and rats were >1000 mg/kg (>2000 and >4100  
516 times, respectively, the maximum recommended daily inhalation dose in adults and >9600 and  
517 >19,000 times, respectively, the maximum recommended daily inhalation dose in children on a  
518 mg/m<sup>2</sup> basis).

519  
520 **DOSAGE AND ADMINISTRATION:** FLOVENT ROTADISK should be administered by the  
521 orally inhaled route in patients 4 years of age and older. Individual patients will experience a  
522 variable time to onset and degree of symptom relief. Generally, fluticasone propionate inhalation  
523 powder has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in  
524 asthma control following inhaled administration of fluticasone propionate can occur within  
525 24 hours of beginning treatment, although maximum benefit may not be achieved for 1 to  
526 2 weeks or longer after starting treatment.

527 After asthma stability has been achieved, it is always desirable to titrate to the lowest effective  
528 dose to reduce the possibility of side effects. Doses as low as 50 mcg twice daily have been  
529 shown to be effective in some patients. For patients who do not respond adequately to the  
530 starting dose after 2 weeks of therapy, higher doses may provide additional asthma control. The  
531 safety and efficacy of FLOVENT ROTADISK when administered in excess of recommended  
532 doses have not been established.

533 Rinsing the mouth after inhalation is advised.

534 The recommended starting dose and the highest recommended dose of fluticasone propionate  
535 inhalation powder, based on prior anti-asthma therapy, are listed in the following table.

536

| Previous Therapy                  | Recommended Starting Dose         | Highest Recommended Dose          |
|-----------------------------------|-----------------------------------|-----------------------------------|
| <b>Adults and Adolescents</b>     |                                   |                                   |
| Bronchodilators alone             | 100 mcg twice daily               | 500 mcg twice daily               |
| Inhaled corticosteroids           | 100-250 mcg twice daily*          | 500 mcg twice daily               |
| Oral corticosteroids <sup>†</sup> | 1000 mcg twice daily <sup>‡</sup> | 1000 mcg twice daily <sup>‡</sup> |
| <b>Children 4 to 11 Years</b>     |                                   |                                   |
| Bronchodilators alone             | 50 mcg twice daily                | 100 mcg twice daily               |
| Inhaled corticosteroids           | 50 mcg twice daily                | 100 mcg twice daily               |

537 \* Starting doses above 100 mcg twice daily for adults and adolescents and 50 mcg twice daily  
538 for children 4 to 11 years of age may be considered for patients with poorer asthma control  
539 or those who have previously required doses of inhaled corticosteroids that are in the higher  
540 range for that specific agent.

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

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

549 <sup>‡</sup> This dosing recommendation is based on clinical data from a study conducted using  
550 FLOVENT Inhalation Aerosol. No clinical trials have been conducted in patients on oral  
551 corticosteroids using the ROTADISK formulation; no direct assessment of the clinical  
552 comparability of equal nominal doses for the FLOVENT ROTADISK and FLOVENT  
553 Inhalation Aerosol formulations in this population has been conducted.

554

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

559 **Directions for Use:** Illustrated Patient's Instructions for Use accompany each package of  
560 FLOVENT ROTADISK.

561

562 **HOW SUPPLIED:** FLOVENT ROTADISK 50 mcg is a circular double-foil pack containing 4  
563 blisters of the drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and  
564 the tube is packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the



565 foil pouch of 15 ROTADISKS and 1 dark orange- and peach-colored DISKHALER inhalation  
566 device (NDC 0173-0511-00).

567 FLOVENT ROTADISK 100 mcg is a circular double-foil pack containing 4 blisters of the  
568 drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and the tube is  
569 packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the foil pouch of  
570 15 ROTADISKS and 1 dark orange- and peach-colored DISKHALER inhalation device (NDC  
571 0173-0509-00).

572 FLOVENT ROTADISK 250 mcg is a circular double-foil pack containing 4 blisters of the  
573 drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and the tube is  
574 packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the foil pouch of  
575 15 ROTADISKS and 1 dark orange- and peach-colored DISKHALER inhalation device (NDC  
576 0173-0504-00).

577 **Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place.**  
578 **Keep out of reach of children. Do not puncture any fluticasone propionate ROTADISK**  
579 **blister until taking a dose using the DISKHALER.**

580 **Use the ROTADISK blisters within 2 months after opening of the moisture-protective**  
581 **foil overwrap or before the expiration date, whichever comes first. Place the sticker**  
582 **provided with the product on the tube and enter the date the foil overwrap is opened and**  
583 **the 2-month use date.**

584  
585



586  
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