

1 **PRODUCT INFORMATION**

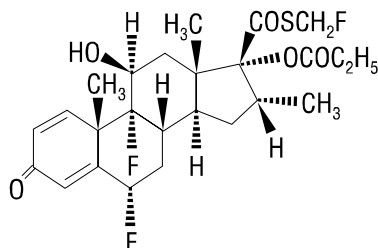
2 **FLOVENT[®] ROTADISK[®] 50 mcg**
3 **(fluticasone propionate inhalation powder, 50 mcg)**

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5 **FLOVENT[®] ROTADISK[®] 100 mcg**
6 **(fluticasone propionate inhalation powder, 100 mcg)**

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8 **FLOVENT[®] ROTADISK[®] 250 mcg**
9 **(fluticasone propionate inhalation powder, 250 mcg)**

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11 **For Oral Inhalation Only**
12 **For Use With the DISKHALER[®] Inhalation Device**

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14 **DESCRIPTION:** The active component of FLOVENT ROTADISK 50 mcg, FLOVENT
15 ROTADISK 100 mcg, and FLOVENT ROTADISK 250 mcg is fluticasone propionate, a
16 corticosteroid having the chemical name S-(fluoromethyl)6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -
17 methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, 17-propionate and the following chemical
18 structure:



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

25 FLOVENT ROTADISK 50 mcg, FLOVENT ROTADISK 100 mcg, and FLOVENT
26 ROTADISK 250 mcg contain a dry powder presentation of fluticasone propionate intended for
27 oral inhalation only. Each double-foil ROTADISK contains 4 blisters. Each blister contains a
28 mixture of 50, 100, or 250 mcg of microfine fluticasone propionate blended with lactose to a
29 total weight of 25 mg. The contents of each blister are inhaled using a specially designed plastic
30 device for inhaling powder called the DISKHALER. After a fluticasone propionate ROTADISK
31 is loaded into the DISKHALER, a blister containing medication is pierced and the fluticasone
32 propionate is dispersed into the air stream created when the patient inhales through the
33 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).

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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 β -carboxylic acid derivative of fluticasone propionate, which is formed
78 through the cytochrome P450 3A4 pathway. This metabolite had approximately 2000 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.

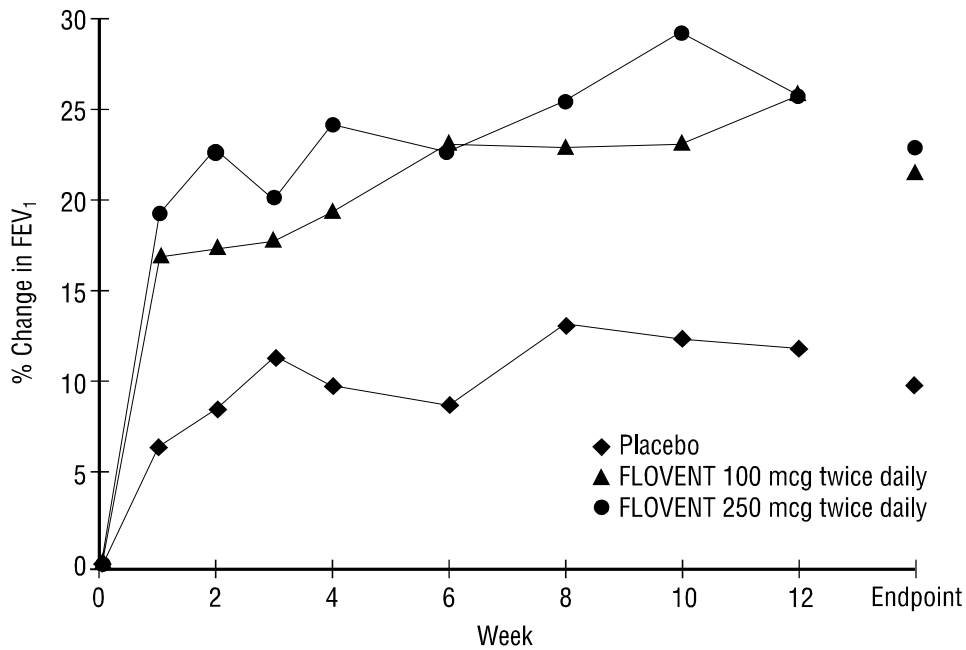
135 **Clinical Trials:** Double-blind, parallel, placebo-controlled, US clinical trials were conducted
136 in 1197 adolescent and adult asthma patients to assess the efficacy and safety of FLOVENT
137 ROTADISK in the treatment of asthma. Fixed doses of 50, 100, 250, and 500 mcg twice daily
138 were compared 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 [FEV₁] and morning peak expiratory flow rate [AM PEFR]) 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 FEV₁ = 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 FEV₁ 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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**A 12-Week Clinical Trial in Patients Inadequately Controlled
on Bronchodilators Alone:
Mean Percent Change From Baseline in FEV₁ Prior to AM Dose**



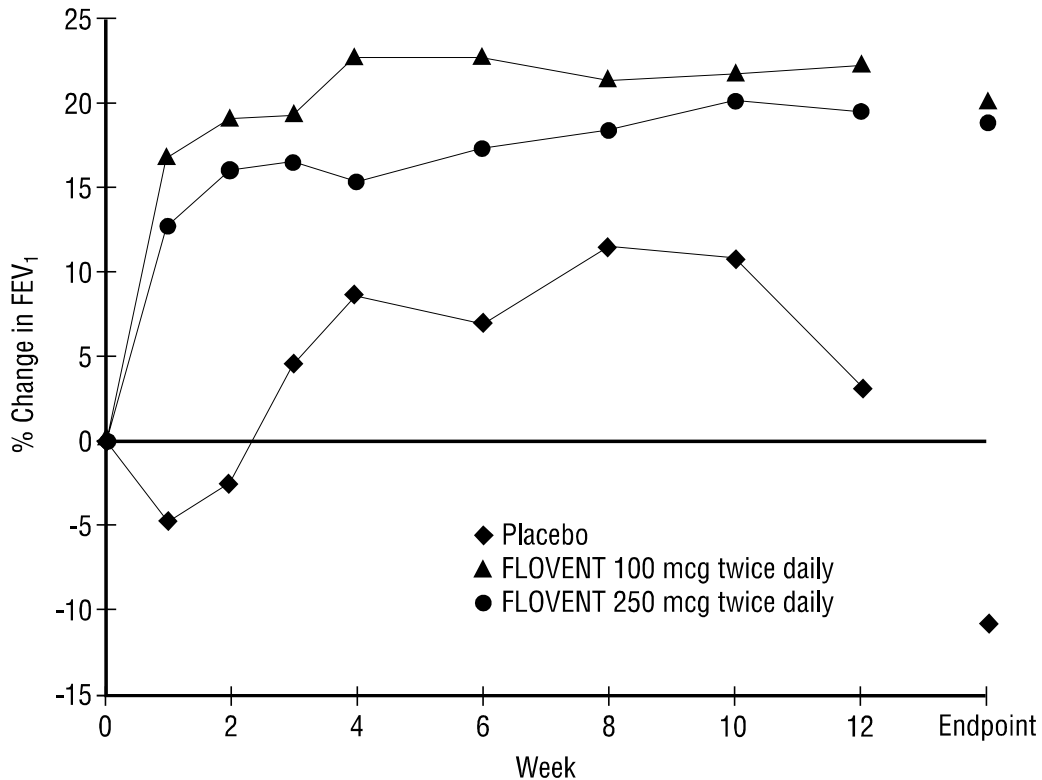
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In a second clinical study of 75 patients, 500 mcg twice daily was evaluated in a similar population. In this trial fluticasone propionate significantly improved pulmonary function as compared with placebo.

Displayed in the figure below are results of pulmonary function tests for 2 recommended dosages of fluticasone propionate inhalation powder (100 and 250 mcg twice daily) and placebo from a 12-week trial in 342 adolescent and adult asthma patients (baseline FEV₁ = 2.49 L/sec) already receiving daily inhaled corticosteroid therapy (≥336 mcg/day of beclomethasone dipropionate or ≥800 mcg/day of triamcinolone acetonide) in addition to as-needed albuterol and theophylline (38% of all patients). Because this trial also used predetermined criteria for lack of efficacy, which caused more patients in the placebo group to be withdrawn, pulmonary function results at Endpoint are included. Pulmonary function at both fluticasone propionate dosages improved significantly compared with placebo by the first week of treatment and the 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 FEV₁ 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.

220

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

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

235 During periods of stress or a severe asthma attack, patients who have been withdrawn from
236 systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses)
237 immediately and to contact their physicians for further instruction. These patients should also be

238 instructed to carry a warning card indicating that they may need supplementary systemic
239 corticosteroids during periods of stress or a severe asthma attack.

240 Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid
241 use after transferring to fluticasone propionate inhalation powder. In a clinical trial of 96
242 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone
243 dose by 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive
244 reduction of prednisone dose was allowed only when lung function, symptoms, and as-needed
245 beta-agonist use were better than or comparable to that seen before initiation of prednisone dose
246 reduction. Lung function (FEV₁ or AM PEF_R), beta-agonist use, and asthma symptoms should
247 be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring
248 asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal
249 insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

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

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

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

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

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

275
276 **PRECAUTIONS:**

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

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

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

294 It is possible that systemic corticosteroid effects such as hypercorticism and adrenal
295 suppression may appear in a small number of patients, particularly at higher doses. If such
296 changes occur, fluticasone propionate inhalation powder should be reduced slowly, consistent
297 with accepted procedures for reducing systemic corticosteroids and for management of asthma
298 symptoms.

299 A reduction of growth velocity in children or adolescents may occur as a result of poorly
300 controlled asthma or from the therapeutic use of corticosteroids, including inhaled
301 corticosteroids. A 52-week placebo-controlled study to assess the potential growth effects of
302 fluticasone propionate inhalation powder at 50 and 100 mcg twice daily was conducted in the US
303 in 325 prepubescent children (244 males and 81 females) 4 to 11 years of age. The mean growth
304 velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the
305 placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and 5.66 cm/year in the
306 100-mcg group (n = 89). An imbalance in the proportion of children entering puberty between
307 groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be
308 confounding factors in interpreting these data. A separate subset analysis of children who
309 remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the
310 placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the
311 100-mcg group (n = 79). The clinical significance of these growth data is not certain. In children
312 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is:
313 boys – 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th
314 percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and
315 97th percentile = 7.3 cm/year. The effects of long-term treatment of children with inhaled
316 corticosteroids, including fluticasone propionate, on final adult height are not known. Physicians

317 should closely follow the growth of children and adolescents taking corticosteroids by any route,
318 and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if
319 growth appears slowed. Patients should be maintained on the lowest dose of inhaled
320 corticosteroid that effectively controls their asthma.

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

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

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

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

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

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

352 Patients should use FLOVENT ROTADISK at regular intervals as directed. Results of clinical
353 trials indicated significant improvement may occur within the first day or two of treatment;
354 however, the full benefit may not be achieved until treatment has been administered for 1 to
355 2 weeks or longer. The patient should not increase the prescribed dosage but should contact the
356 physician if symptoms do not improve or if the condition worsens.

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

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

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

370 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Fluticasone propionate
371 demonstrated no tumorigenic potential in mice at oral doses up to 1000 mcg/kg (approximately 2
372 times the maximum recommended daily inhalation dose in adults and approximately 10 times
373 the maximum recommended daily inhalation dose in children on a mcg/m² basis) for 78 weeks
374 or in rats at inhalation doses up to 57 mcg/kg (approximately 1/4 the maximum recommended
375 daily inhalation dose in adults and comparable to the maximum recommended daily inhalation
376 dose in children on a mcg/m² basis) for 104 weeks.

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

382 No evidence of impairment of fertility was observed in reproductive studies conducted in
383 male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 1/5 the maximum
384 recommended daily inhalation dose in adults on a mcg/m² basis). Prostate weight was
385 significantly reduced at a subcutaneous dose of 50 mcg/kg.

386 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Subcutaneous studies in the
387 mouse and rat at 45 and 100 mcg/kg, respectively, (approximately 1/10 and 1/3, respectively, the
388 maximum recommended daily inhalation dose in adults on a mcg/m² basis) revealed fetal
389 toxicity characteristic of potent corticosteroid compounds, including embryonic growth
390 retardation, omphalocele, cleft palate, and retarded cranial ossification.

391 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of
392 4 mcg/kg (approximately 1/30 the maximum recommended daily inhalation dose in adults on a
393 mcg/m² basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg
394 (approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/m²
395 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this

396 study, consistent with the established low bioavailability following oral administration (see
397 CLINICAL PHARMACOLOGY).

398 Fluticasone propionate crossed the placenta following oral administration of 100 mcg/kg to
399 rats or 300 mcg/kg to rabbits (approximately 1/3 and 2 times, respectively, the maximum
400 recommended daily inhalation dose in adults on a mcg/m² basis).

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

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

409 **Nursing Mothers:** It is not known whether fluticasone propionate is excreted in human breast
410 milk. Subcutaneous administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate
411 (approximately 1/25 the maximum recommended daily inhalation dose in adults on a mcg/m²
412 basis) resulted in measurable radioactivity in milk. Because other corticosteroids are excreted in
413 human milk, caution should be exercised when fluticasone propionate inhalation powder is
414 administered to a nursing woman.

415 **Pediatric Use:** Two hundred fourteen (214) patients 4 to 11 years of age and 142 patients 12 to
416 16 years of age were treated with fluticasone propionate inhalation powder in US clinical trials.
417 The safety and effectiveness of FLOVENT ROTADISK Inhalation Powder in children below
418 4 years of age have not been established.

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

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

432
433 **ADVERSE REACTIONS:** The following incidence of common adverse experiences is based
434 upon 6 placebo-controlled clinical trials in which 1384 patients ≥4 years of age (520 females and
435 864 males) previously treated with as-needed bronchodilators and/or inhaled corticosteroids

436 were treated with fluticasone propionate inhalation powder (doses of 50 to 500 mcg twice daily
 437 for up to 12 weeks) or placebo.

438

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

Adverse Event	Placebo (n = 438) %	FLOVENT 50 mcg Twice Daily (n = 255) %	FLOVENT 100 mcg Twice Daily (n = 331) %	FLOVENT 250 mcg Twice Daily (n = 176) %	FLOVENT 500 mcg Twice Daily (n = 184) %
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 (days)	53	77	68	78	60

442

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

447 These adverse reactions were mostly mild to moderate in severity, with <2% of patients
 448 discontinuing the studies because of adverse events. Rare cases of immediate and delayed
 449 hypersensitivity reactions, including rash and other rare events of angioedema and
 450 bronchospasm, have been reported.

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

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

456 **Eye:** Conjunctivitis.

457 **Gastrointestinal:** Abdominal pain, viral gastroenteritis, gastroenteritis/colitis, abdominal
458 discomfort.

459 **Miscellaneous:** Injury.

460 **Mouth and Teeth:** Mouth irritation.

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

463 **Neurological:** Migraine, nervousness.

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

465 **Skin:** Dermatitis, urticaria.

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

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

470 Fluticasone propionate inhalation aerosol (660 or 880 mcg twice daily) was administered for
471 16 weeks to asthmatics requiring oral corticosteroids. Adverse events reported more frequently
472 in these patients compared to patients not on oral corticosteroids included sinusitis, nasal
473 discharge, oropharyngeal candidiasis, headache, joint pain, nausea and vomiting, muscular
474 soreness, malaise/fatigue, and insomnia.

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

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

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

485 **Eye:** Cataracts.

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

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

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

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

500
501 **OVERDOSAGE:** Chronic overdose may result in signs/symptoms of hypercorticism (see
502 PRECAUTIONS). Inhalation by healthy volunteers of a single dose of 4000 mcg of fluticasone
503 propionate inhalation powder or single doses of 1760 or 3520 mcg of fluticasone propionate
504 inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses
505 of 1320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated.
506 Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to
507 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or
508 moderate severity, and incidences were similar in active and placebo treatment groups. The oral
509 and subcutaneous median lethal doses in mice and rats were >1000 mg/kg (>2000 and >4100
510 times, respectively, the maximum recommended daily inhalation dose in adults and >9600 and
511 >19,000 times, respectively, the maximum recommended daily inhalation dose in children on a
512 mg/m² basis).

513
514 **DOSAGE AND ADMINISTRATION:** FLOVENT ROTADISK should be administered by the
515 orally inhaled route in patients 4 years of age and older. Individual patients will experience a
516 variable time to onset and degree of symptom relief. Generally, fluticasone propionate inhalation
517 powder has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in
518 asthma control following inhaled administration of fluticasone propionate can occur within
519 24 hours of beginning treatment, although maximum benefit may not be achieved for 1 to
520 2 weeks or longer after starting treatment.

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

527 Rinsing the mouth after inhalation is advised.

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

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults and Adolescents		
Bronchodilators alone	100 mcg twice daily	500 mcg twice daily
Inhaled corticosteroids	100-250 mcg twice daily [*]	500 mcg twice daily
Oral corticosteroids [†]	1000 mcg twice daily [‡]	1000 mcg twice daily [‡]
Children 4 to 11 Years		
Bronchodilators alone	50 mcg twice daily	100 mcg twice daily
Inhaled corticosteroids	50 mcg twice daily	100 mcg twice daily

531 ^{*} Starting doses above 100 mcg twice daily for adults and adolescents and 50 mcg twice daily
532 for children 4 to 11 years of age may be considered for patients with poorer asthma control
533 or those who have previously required doses of inhaled corticosteroids that are in the higher
534 range for that specific agent.

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

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

543 [‡] This dosing recommendation is based on clinical data from a study conducted using
544 FLOVENT Inhalation Aerosol. No clinical trials have been conducted in patients on oral
545 corticosteroids using the ROTADISK formulation; no direct assessment of the clinical
546 comparability of equal nominal doses for the FLOVENT ROTADISK and FLOVENT
547 Inhalation Aerosol formulations in this population has been conducted.

548

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

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

555

556 **HOW SUPPLIED:** FLOVENT ROTADISK 50 mcg is a circular double-foil pack containing 4
557 blisters of the drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and
558 the tube is packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the
559 foil pouch of 15 ROTADISKS and 1 dark orange- and peach-colored DISKHALER inhalation
560 device (NDC 0173-0511-00).

561 FLOVENT ROTADISK 100 mcg is a circular double-foil pack containing 4 blisters of the
562 drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and the tube is
563 packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the foil pouch of
564 15 ROTADISKS and 1 dark orange- and peach-colored DISKHALER inhalation device (NDC
565 0173-0509-00).

566 FLOVENT ROTADISK 250 mcg is a circular double-foil pack containing 4 blisters of the
567 drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and the tube is
568 packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the foil pouch of
569 15 ROTADISKS and 1 dark orange- and peach-colored DISKHALER inhalation device (NDC
570 0173-0504-00).

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

574 Use the ROTADISK blisters within 2 months after opening of the moisture-protective foil
575 overwrap or before the expiration date, whichever comes first. Place the sticker provided with
576 the product on the tube and enter the date the foil overwrap is opened and the 2-month use date.
577



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580 Research Triangle Park, NC 27709

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