

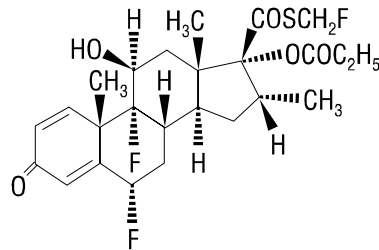
FLOVENT[®] DISKUS[®] 50 mcg
(fluticasone propionate inhalation powder, 50 mcg)

FLOVENT[®] DISKUS[®] 100 mcg
(fluticasone propionate inhalation powder, 100 mcg)

FLOVENT[®] DISKUS[®] 250 mcg
(fluticasone propionate inhalation powder, 250 mcg)

For Oral Inhalation Only

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



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

FLOVENT DISKUS 50 mcg, FLOVENT DISKUS 100 mcg, and FLOVENT DISKUS 250 mcg are specially designed plastic devices containing a double-foil blister strip of a powder formulation of fluticasone propionate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 50, 100, or 250 mcg of microfine fluticasone propionate in 12.5 mg of formulation containing lactose. After a blister containing medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, FLOVENT DISKUS delivers 46^{(b)(4)}, or 235 mcg of fluticasone propionate from FLOVENT DISKUS 50 mcg, FLOVENT DISKUS 100 mcg, or FLOVENT DISKUS 250 mcg, respectively, when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in 1 second [FEV₁] 20% to 30% of predicted), mean

35 peak inspiratory flow (PIF) through a DISKUS[®] device was 82.4 L/min (range, 46.1 to
36 115.3 L/min). In children with asthma 4 and 8 years old, mean PIF through FLOVENT DISKUS
37 was 70 and 104 L/min, respectively (range, 48 to 123 L/min).

38 The actual amount of drug delivered to the lung will depend on patient factors, such as
39 inspiratory flow profile.

40

41 **CLINICAL PHARMACOLOGY:**

42 **Mechanism of Action:** Fluticasone propionate is a synthetic, trifluorinated corticosteroid with
43 potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have
44 established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18
45 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate
46 (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of
47 budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these
48 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 Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory
61 activity and systemic corticosteroid effects over recommended doses of FLOVENT DISKUS.
62 This is explained by a combination of a relatively high local anti-inflammatory effect, negligible
63 oral systemic bioavailability (<1%), and the minimal pharmacological activity of the only
64 metabolite detected in man. Lung absorption does occur (see below).

65 **Pharmacokinetics: Absorption:** The activity of FLOVENT DISKUS is due to the parent
66 drug, fluticasone propionate. Studies using oral dosing of labeled and unlabeled drug have
67 demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%),
68 primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In
69 contrast, the majority of the fluticasone propionate delivered to the lung is systemically
70 absorbed. The systemic bioavailability of fluticasone propionate from the DISKUS[®] device in
71 healthy adult volunteers averages about 18%.

72 Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma
73 (n = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone

74 propionate inhalation powder using the DISKUS device. The mean fluticasone propionate
75 plasma concentration was 110 pg/mL.

76 **Distribution:** Following intravenous administration, the initial disposition phase for
77 fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding.
78 The volume of distribution averaged 4.2 L/kg.

79 The percentage of fluticasone propionate bound to human plasma proteins averages 91%.
80 Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate is
81 not significantly bound to human transcortin.

82 **Metabolism:** The total clearance of fluticasone propionate is high (average, 1093 mL/min),
83 with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite
84 detected in man is the 17 β -carboxylic acid derivative of fluticasone propionate, which is formed
85 through the cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately
86 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and
87 negligible pharmacological activity in animal studies. Other metabolites detected in vitro using
88 cultured human hepatoma cells have not been detected in man.

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

93 **Hepatic Impairment:** Since fluticasone propionate is predominantly cleared by hepatic
94 metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in
95 plasma. Therefore, patients with hepatic disease should be closely monitored.

96 **Gender:** Full pharmacokinetic profiles were obtained from 9 female and 16 male patients
97 given 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics
98 were observed.

99 **Pediatrics:** In a clinical study conducted in patients 4 to 11 years of age with mild to
100 moderate asthma, fluticasone propionate concentrations were obtained in 61 patients at 20 and
101 40 minutes after dosing with 50 and 100 mcg twice daily of fluticasone propionate inhalation
102 powder using the DISKUS. Plasma concentrations were low and ranged from undetectable
103 (about 80% of the plasma samples) to 88 pg/mL. Mean fluticasone propionate plasma
104 concentrations at the 2 dose levels were 5 and 8 pg/mL, respectively.

105 **Special Populations:** Formal pharmacokinetic studies using fluticasone propionate were not
106 carried out in other special populations.

107 **Drug-Drug Interactions:** In a multiple-dose drug interaction study, coadministration of
108 fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not
109 affect fluticasone propionate pharmacokinetics. In another drug interaction study,
110 coadministration of fluticasone propionate (1000 mcg) and ketoconazole (200 mg once daily)
111 resulted in increased fluticasone propionate concentrations and reduced plasma cortisol area
112 under the plasma concentration versus time curve (AUC), but had no effect on urinary excretion
113 of cortisol. Since fluticasone propionate is a substrate of cytochrome P450 3A4, caution should

114 be exercised when cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole) are
115 coadministered with fluticasone propionate as this could result in increased plasma
116 concentrations of fluticasone propionate.

117 **Pharmacodynamics:** To confirm that systemic absorption does not play a role in the clinical
118 response to inhaled fluticasone propionate, a double-blind clinical study comparing inhaled and
119 oral fluticasone propionate was conducted. Doses of 100 and 500 mcg twice daily of fluticasone
120 propionate inhalation powder were compared to oral fluticasone propionate, 20,000 mcg given
121 once daily, and placebo for 6 weeks. Plasma levels of fluticasone propionate were detectable in
122 all 3 active groups, but the mean values were highest in the oral group. Both doses of inhaled
123 fluticasone propionate were effective in maintaining asthma stability and improving lung
124 function while oral fluticasone propionate and placebo were ineffective. This demonstrates that
125 the clinical effectiveness of inhaled fluticasone propionate is due to its direct local effect and not
126 to an indirect effect through systemic absorption.

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

137 In clinical trials with fluticasone propionate inhalation powder using doses up to and
138 including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol
139 <18 mcg/dL) were noted both in patients receiving fluticasone propionate and in patients
140 receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than
141 placebo. In a 2-year study carried out with the DISKHALER[®] inhalation device in 64 patients
142 with mild, persistent asthma (mean FEV₁ 91% of predicted) randomized to fluticasone
143 propionate 500 mcg twice daily or placebo, no patient receiving fluticasone propionate had an
144 abnormal response to 6-hour cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a
145 peak cortisol threshold <35 mcg/dL, one patient receiving fluticasone propionate (4%) had an
146 abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another patient
147 receiving fluticasone propionate (5%) had an abnormal response at 2 years. No patient on
148 placebo had an abnormal response at 1 or 2 years.

149 In a placebo-controlled clinical study conducted in patients 4 to 11 years of age, a 30-minute
150 cosyntropin stimulation test was performed in 41 patients after 12 weeks of dosing with 50 or
151 100 mcg twice daily of fluticasone propionate via the DISKUS device. One patient receiving
152 fluticasone propionate via DISKUS had a prestimulation plasma cortisol concentration

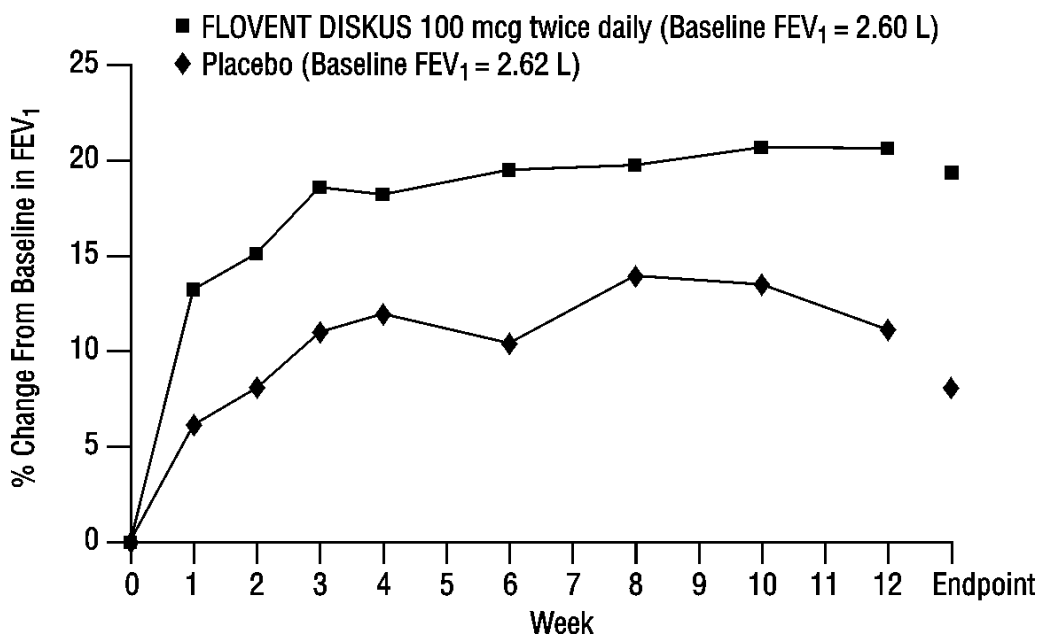
153 <5 mcg/dL, and 2 patients had a rise in cortisol of <7 mcg/dL. However, all poststimulation
154 values were >18 mcg/dL.

155 **Clinical Trials:** Four double-blind, parallel, placebo-controlled, US clinical trials were
156 conducted in 1036 adolescent and adult patients (≥ 12 years of age) with asthma to assess the
157 efficacy and safety of FLOVENT DISKUS. These studies included fixed doses of 100, 250, and
158 500 mcg twice daily compared to placebo to provide information about appropriate dosing to
159 cover a range of asthma severity. Patients with asthma included in these studies were those not
160 adequately controlled with bronchodilators alone, and those already maintained on daily inhaled
161 corticosteroids. All doses were delivered by inhalation of the contents of 1 or 2 blisters from the
162 DISKUS twice daily.

163 Displayed in the figures below are results of pulmonary function tests (mean percent change
164 from baseline in FEV₁ prior to AM dose) for 3 recommended dosages of fluticasone propionate
165 inhalation powder (100, 250, and 500 mcg twice daily) and placebo from the four 12-week trials
166 in adolescents and adults. Because these trials used predetermined criteria for lack of efficacy,
167 which caused more patients in the placebo group to be withdrawn, pulmonary function results at
168 Endpoint, which is the last evaluable FEV₁ result and includes most patients' lung function data,
169 are also provided. Pulmonary function at recommended dosages of fluticasone propionate
170 improved significantly compared with placebo by the first week of treatment, and improvement
171 was maintained for up to 1 year or more.

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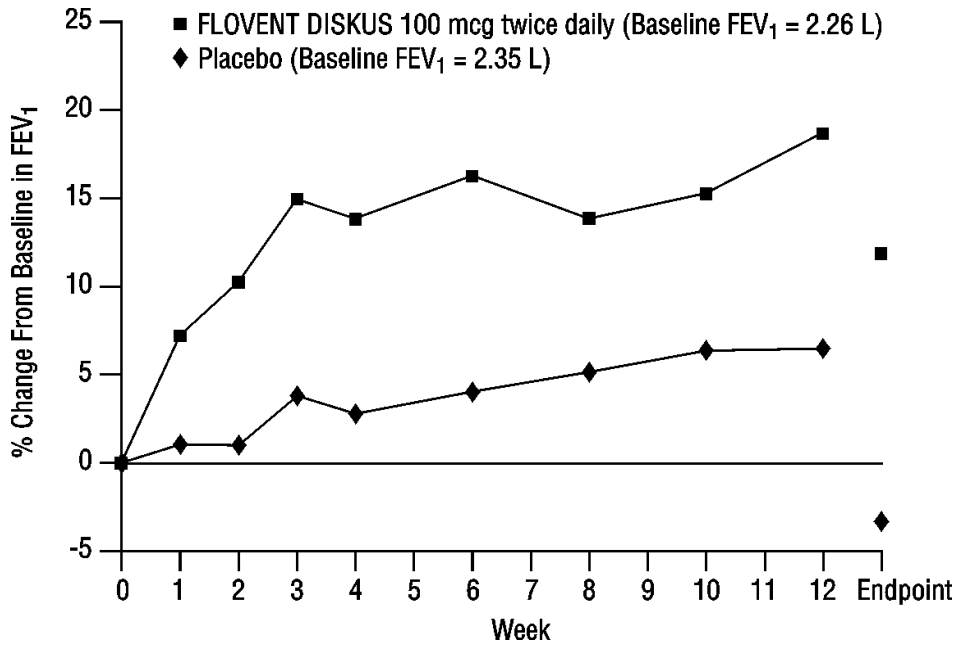
**Figure 1: A 12-Week Clinical Trial Evaluating
FLOVENT DISKUS 100 mcg Twice Daily in Adolescents and Adults
Receiving Bronchodilators Alone**



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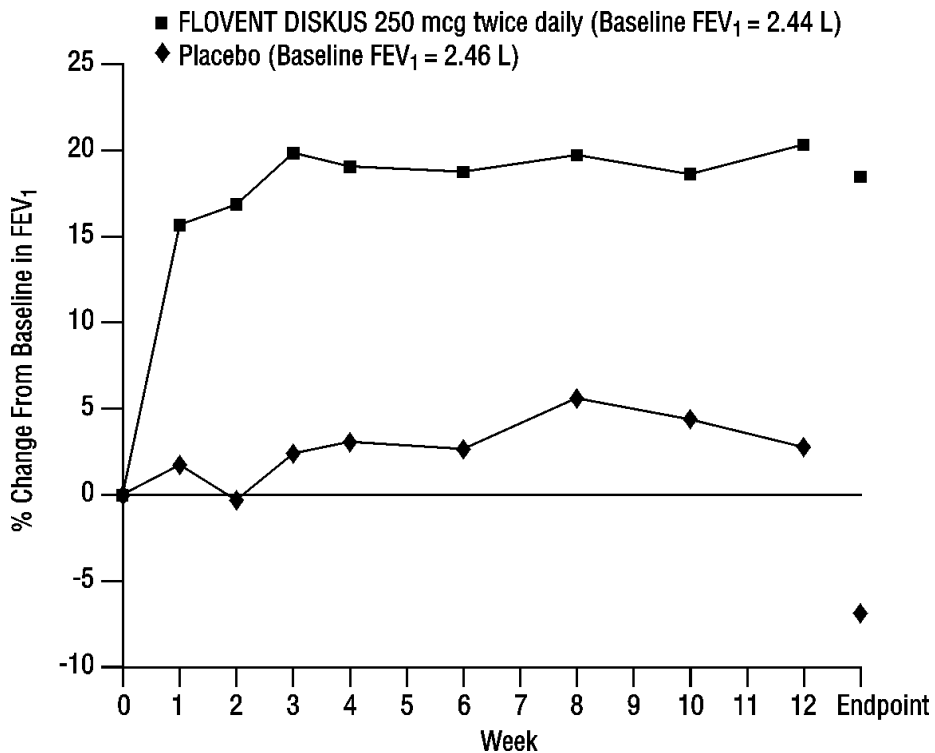
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Figure 2: A 12-Week Clinical Trial Evaluating FLOVENT DISKUS 100 mcg Twice Daily in Adolescents and Adults Receiving Inhaled Corticosteroids



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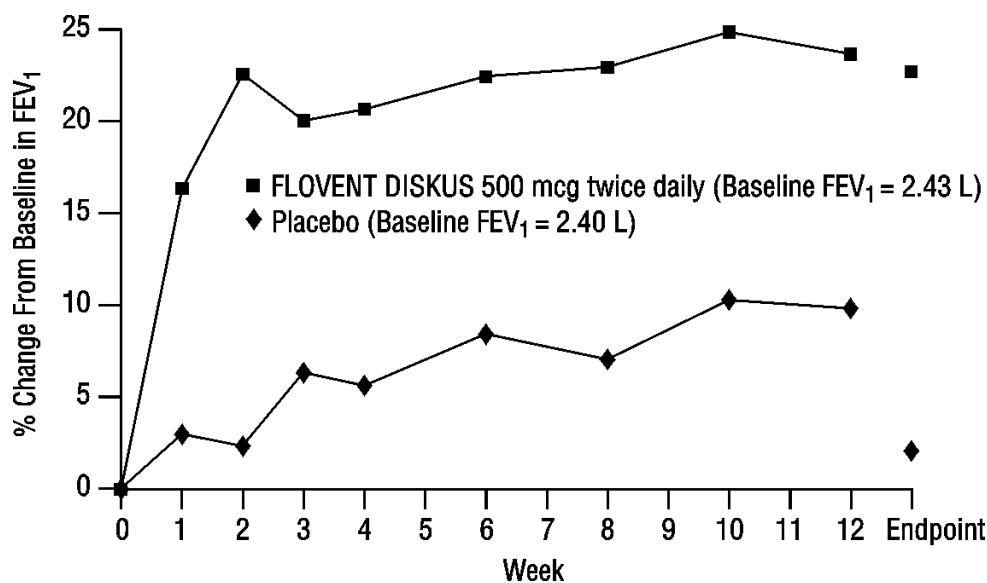
Figure 3: A 12-Week Clinical Trial Evaluating FLOVENT DISKUS 250 mcg Twice Daily in Adolescents and Adults Receiving Inhaled Corticosteroids or Bronchodilators Alone



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Figure 4: A 12-Week Clinical Trial Evaluating FLOVENT DISKUS 500 mcg Twice Daily in Adolescents and Adults Receiving Inhaled Corticosteroids or Bronchodilators Alone



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195 In all efficacy trials, measures of pulmonary function (FEV₁) and morning peak expiratory
196 flow rate (AM PEFr) were statistically significantly improved as compared with placebo at all
197 twice-daily doses. Patients on all fluticasone propionate dosages were also significantly less
198 likely to discontinue study participation due to asthma deterioration (as defined by
199 predetermined criteria for lack of efficacy including lung function and patient-recorded variables
200 such as AM PEFr, albuterol use and nighttime awakenings due to asthma) compared with
201 placebo.

202 In a clinical trial of 111 patients with severe asthma requiring chronic oral prednisone therapy
203 (average baseline daily prednisone dose was 14 mg), fluticasone propionate given by inhalation
204 powder at doses of 500 and 1000 mcg twice daily was evaluated. Both doses enabled a
205 statistically significantly larger percentage of patients to wean successfully from oral prednisone
206 as compared with placebo (75% of the patients on 500 mcg twice daily and 89% of the patients
207 on 1000 mcg twice daily as compared with 9% of patients on placebo). Accompanying the
208 reduction in oral corticosteroid use, patients treated with fluticasone propionate had significantly
209 improved lung function and fewer asthma symptoms as compared with the placebo group.

210 **Pediatric Experience:** A 12-week, placebo-controlled clinical trial was conducted in 437
211 patients (177 on fluticasone propionate via DISKUS) aged 4 to 11 years, approximately half of
212 whom were receiving inhaled corticosteroids at baseline. In this study, doses of fluticasone
213 propionate inhalation powder 50 and 100 mcg twice daily significantly improved FEV₁ (15% and
214 18% change from baseline at Endpoint, respectively) compared to placebo (7% change). Morning
215 peak expiratory flow rate was also significantly improved with doses of fluticasone propionate 50
216 and 100 mcg twice daily (26% and 27% change from baseline at Endpoint, respectively)

217 compared to placebo (14% change). In this study, patients on active treatment were significantly
218 less likely to discontinue treatment due to asthma deterioration (as defined by predetermined
219 criteria for lack of efficacy including lung function and patient recorded variables such as AM
220 PEFR, albuterol use, and nighttime awakenings due to asthma).

221 Two other 12-week placebo-controlled clinical trials were conducted in 504 pediatric patients
222 with asthma, approximately half of whom were receiving inhaled corticosteroids at baseline. In
223 these studies, fluticasone propionate inhalation powder was efficacious at doses of 50 and
224 100 mcg twice daily when compared to placebo on major endpoints including lung function and
225 symptom scores. Pulmonary function improved significantly compared with placebo by the first
226 week of treatment, and patients treated with fluticasone propionate were also less likely to
227 discontinue study participation due to asthma deterioration. One hundred ninety-two (192)
228 patients received fluticasone propionate for up to 1 year during an open-label extension. Data
229 from this open-label extension suggested that lung function improvements could be maintained
230 up to 1 year.

231
232 **INDICATIONS AND USAGE:** FLOVENT DISKUS is indicated for the maintenance treatment
233 of asthma as prophylactic therapy in adult and pediatric patients 4 years of age and older. It is
234 also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these
235 patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

236 FLOVENT DISKUS is NOT indicated for the relief of acute bronchospasm.

237
238 **CONTRAINDICATIONS:** FLOVENT DISKUS is contraindicated in the primary treatment of
239 status asthmaticus or other acute episodes of asthma where intensive measures are required.

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

241
242 **WARNINGS:** Particular care is needed for patients who are transferred from systemically active
243 corticosteroids to FLOVENT DISKUS because deaths due to adrenal insufficiency have
244 occurred in patients with asthma during and after transfer from systemic corticosteroids to less
245 systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a
246 number of months are required for recovery of HPA function.

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

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

261 Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid
262 use after transferring to fluticasone propionate inhalation powder. In a clinical trial of 111
263 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone
264 dose by 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive
265 reduction of prednisone dose was allowed only when lung function, symptoms, and as-needed
266 beta-agonist use were better than or comparable to that seen before initiation of prednisone dose
267 reduction. Lung function (FEV₁ or AM PEFr), beta-agonist use, and asthma symptoms should
268 be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring
269 asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal
270 insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

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

274 Persons who are using drugs that suppress the immune system are more susceptible to
275 infections than healthy individuals. Chickenpox and measles, for example, can have a more
276 serious or even fatal course in susceptible children or adults using corticosteroids. In such
277 children or adults who have not had these diseases or been properly immunized, particular care
278 should be taken to avoid exposure. How the dose, route, and duration of corticosteroid
279 administration affect the risk of developing a disseminated infection is not known. The
280 contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not
281 known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG)
282 may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin
283 (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing
284 information.) If chickenpox develops, treatment with antiviral agents may be considered.

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

287 As with other inhaled asthma medications, bronchospasm may occur with an immediate
288 increase in wheezing after dosing. If bronchospasm occurs following dosing with FLOVENT
289 DISKUS, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment
290 with FLOVENT DISKUS should be discontinued and alternative therapy instituted.

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

295

296 **PRECAUTIONS:**

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

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

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

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

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

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 tuberculosis 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 DISKUS should receive the
349 following information and instructions. This information is intended to aid them in the safe and
350 effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

351 It is important that patients understand how to use the DISKUS inhalation device
352 appropriately and how it should be used in relation to other asthma medications they are taking.
353 Patients should be given the following information:

- 354 1. Patients should use FLOVENT DISKUS at regular intervals as directed. Results of clinical
355 trials indicated significant improvement may occur within the first day or two of treatment;
356 however, the full benefit may not be achieved until treatment has been administered for 1 to
357 2 weeks or longer. The patient should not increase the prescribed dosage but should contact the
358 physician if symptoms do not improve or if the condition worsens.
- 359 2. FLOVENT DISKUS should not be used with a spacer device.
- 360 3. If you are pregnant or nursing, contact your physician about the use of FLOVENT DISKUS.
- 361 4. Effective and safe use of FLOVENT DISKUS includes an understanding of the way that it
362 should be used:
 - 363 • Never exhale into the DISKUS.
 - 364 • Never attempt to take the DISKUS apart.
 - 365 • Always activate and use the DISKUS in a level, horizontal position.
 - 366 • Never wash the mouthpiece or any part of the DISKUS. KEEP IT DRY.
 - 367 • Always keep the DISKUS in a dry place.
 - 368 • Discard **6 weeks (50-mcg strength) or 2 months (100- and 250-mcg strengths)** after
369 removal from the moisture-protective foil overwrap pouch or after all blisters have been used
370 (when the dose indicator reads “0”), whichever comes first.
- 371 5. Patients should be warned to avoid exposure to chickenpox or measles and, if they are
372 exposed, to consult their physicians without delay.
- 373 6. For the proper use of FLOVENT DISKUS and to attain maximum improvement, the patient
374 should read and follow carefully the Patient's Instructions for Use accompanying the product.

375 **Drug Interactions:** In a placebo-controlled, crossover study in 8 healthy volunteers,
376 coadministration of a single dose of fluticasone propionate (1,000 mcg) with multiple doses of
377 ketoconazole (200 mg) to steady state resulted in increased mean fluticasone propionate
378 concentrations, a reduction in plasma cortisol AUC, and no effect on urinary excretion of
379 cortisol. This interaction may be due to an inhibition of cytochrome P450 3A4 by ketoconazole,
380 which is also the route of metabolism of fluticasone propionate. Care should be exercised when
381 FLOVENT is coadministered with long-term ketoconazole and other known cytochrome P450
382 3A4 inhibitors.

383 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Fluticasone propionate
384 demonstrated no tumorigenic potential in mice at oral doses up to 1000 mcg/kg (approximately 2
385 times the maximum recommended daily inhalation dose in adults and approximately 10 times the
386 maximum recommended daily inhalation dose in children on a mcg/m² basis) for 78 weeks or in
387 rats at inhalation doses up to 57 mcg/kg (less than the maximum recommended daily inhalation
388 dose in adults and approximately equal to the maximum recommended daily inhalation dose in
389 children on a mcg/m² basis) for 104 weeks.

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

393 No evidence of impairment of fertility was observed in reproductive studies conducted in male
394 and female rats at subcutaneous doses up to 50 mcg/kg (less than the maximum recommended
395 daily inhalation dose in adults on a mcg/m² basis). Prostate weight was significantly reduced at a
396 subcutaneous dose of 50 mcg/kg.

397 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Subcutaneous studies in the
398 mouse and rat at 45 and 100 mcg/kg, respectively, (less than the maximum recommended daily
399 inhalation dose in adults on a mcg/m² basis) revealed fetal toxicity characteristic of potent
400 corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate,
401 and retarded cranial ossification.

402 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of
403 4 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m²
404 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg
405 (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m²
406 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this
407 study, consistent with the established low bioavailability following oral administration (see
408 CLINICAL PHARMACOLOGY).

409 Fluticasone propionate crossed the placenta following administration of a subcutaneous dose
410 of 100 mcg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a
411 mcg/m² basis), a subcutaneous or an oral dose of 100 mcg/kg to rats (less than the maximum
412 recommended daily inhalation dose in adults on a mcg/m² basis), and an oral dose of 300 mcg/kg
413 to rabbits (approximately 3 times the maximum recommended daily inhalation dose in adults on
414 a mcg/m² basis).

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

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

423 **Nursing Mothers:** It is not known whether fluticasone propionate is excreted in human breast
424 milk. However, other corticosteroids have been detected in human milk. Subcutaneous
425 administration to lactating rats of 10 mcg/kg of tritiated fluticasone propionate (less than the
426 maximum recommended daily inhalation dose in adults on a mcg/m² basis) resulted in
427 measurable radioactivity in the milk. Since there are no data from controlled trials on the use of
428 FLOVENT DISKUS by nursing mothers, a decision should be made whether to discontinue
429 nursing or to discontinue FLOVENT DISKUS, taking into account the importance of FLOVENT
430 DISKUS to the mother.

431 **Pediatric Use:** Five hundred twenty (520) patients 4 to 11 years of age and 66 patients 12 to
432 16 years of age were treated with FLOVENT DISKUS in US pivotal clinical trials. The safety
433 and effectiveness of FLOVENT DISKUS in children below 4 years of age have not been
434 established.

435 Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in
436 growth in pediatric patients. In these studies, the mean reduction in growth velocity was
437 approximately 1 cm/year (range, 0.3 to 1.8 cm/year) and appears to depend upon the dose and
438 duration of exposure. The specific growth effects of inhaled fluticasone propionate have also
439 been studied in a controlled clinical trial (see data below). This effect was observed in the
440 absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a
441 more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some
442 commonly used tests of HPA axis function. The long-term effects of this reduction in growth
443 velocity associated with orally inhaled corticosteroids, including the impact on final adult height,
444 are unknown. The potential for “catch-up” growth following discontinuation of treatment with
445 orally inhaled corticosteroids has not been adequately studied. The growth of children and
446 adolescents receiving orally inhaled corticosteroids, including FLOVENT DISKUS, should be
447 monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment
448 should be weighed against the clinical benefits obtained and the risks associated with alternative
449 therapies. To minimize the systemic effects of orally inhaled corticosteroids, including
450 FLOVENT DISKUS, each patient should be titrated to the lowest dose that effectively controls
451 his/her symptoms.

452 A 52-week, placebo-controlled study to assess the potential growth effects of fluticasone
453 propionate inhalation powder at 50 and 100 mcg twice daily was conducted in the US in 325
454 prepubescent children (244 males and 81 females) 4 to 11 years of age. The mean growth

455 velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the
 456 placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and 5.66 cm/year in the
 457 100-mcg group (n = 89). An imbalance in the proportion of children entering puberty between
 458 groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be
 459 confounding factors in interpreting these data. A separate subset analysis of children who
 460 remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the
 461 placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the
 462 100-mcg group (n = 79). The clinical significance of these growth data is not certain. In children
 463 8.5 years of age, the mean age of children in this study, the range for expected growth velocity
 464 is: boys – 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th
 465 percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and
 466 97th percentile = 7.3 cm/year.

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

475
 476 **ADVERSE REACTIONS:** The following incidence of common adverse experiences is based
 477 upon 7 placebo-controlled US clinical trials in which 1176 pediatric, adolescent, and adult
 478 patients (466 females and 710 males) previously treated with as-needed bronchodilators and/or
 479 inhaled corticosteroids were treated with fluticasone propionate inhalation powder (doses of 50
 480 to 500 mcg twice daily for up to 12 weeks) or placebo.

481
 482 **Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate**
 483 **in US Controlled Clinical Trials With FLOVENT DISKUS**
 484 **in Patients Previously Receiving Bronchodilators and/or Inhaled Corticosteroids**

Adverse Event	Placebo (n = 543) %	FLOVENT 50 mcg Twice Daily (n = 178) %	FLOVENT 100 mcg Twice Daily (n = 305) %	FLOVENT 250 mcg Twice Daily (n = 86) %	FLOVEN T 500 mcg Twice Daily (n = 64) %
Ear, nose, and throat Upper respiratory tract infection	16	20	18	21	14

Throat irritation	8	13	13	3	22
Sinusitis/sinus infection	6	9	10	6	6
Upper respiratory inflammation	3	5	5	0	5
Rhinitis	2	4	3	1	2
Oral candidiasis	7	<1	9	6	5
Gastrointestinal					
Nausea and vomiting	4	8	4	1	2
Gastrointestinal discomfort and pain	3	4	3	2	2
Viral gastrointestinal infection	1	4	3	3	5
Non-site specific					
Fever	4	7	7	1	2
Viral infection	2	2	2	0	5
Lower respiratory					
Viral respiratory infection	4	4	5	1	2
Cough	4	3	5	1	5
Bronchitis	1	2	3	0	8
Neurological					
Headache	7	12	12	2	14
Musculoskeletal and trauma					
Muscle injury	1	2	0	1	5
Musculoskeletal pain	2	4	3	2	5
Injury	<1	2	<1	0	5
Average duration of exposure (days)	56	76	73	79	78

485
486 The table above includes all events (whether considered drug-related or nondrug-related by
487 the investigator) that occurred at a rate of over 3% in any of the fluticasone propionate inhalation
488 powder groups and were more common than in the placebo group. In considering these data,
489 differences in average duration of exposure should be taken into account.

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

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

497 **Cardiovascular:** Palpitations.

498 **Drug Interaction, Overdose, and Trauma:** Soft tissue injuries, contusions and
499 hematomas, wounds and lacerations, postoperative complications, burns, poisoning and toxicity,
500 pressure-induced disorders.

501 **Ear, Nose, and Throat:** Ear signs and symptoms; rhinorrhea/postnasal drip;
502 hoarseness/dysphonia; epistaxis; tonsillitis; nasal signs and symptoms; laryngitis; unspecified
503 oropharyngeal plaques; otitis; ear, nose, throat, and tonsil signs and symptoms; ear, nose, and
504 throat polyps; allergic ear, nose, and throat disorders; throat constriction.

505 **Endocrine and Metabolic:** Fluid disturbances, weight gain, goiter, disorders of uric acid
506 metabolism, appetite disturbances.

507 **Eye:** Keratitis and conjunctivitis, blepharoconjunctivitis.

508 **Gastrointestinal:** Diarrhea, gastrointestinal signs and symptoms, oral ulcerations, dental
509 discomfort and pain, gastroenteritis, gastrointestinal infections, abdominal discomfort and pain,
510 oral erythema and rashes, mouth and tongue disorders, oral discomfort and pain, tooth decay.

511 **Hepatobiliary Tract and Pancreas:** Cholecystitis.

512 **Lower Respiratory:** Lower respiratory infections.

513 **Musculoskeletal:** Muscle pain, arthralgia and articular rheumatism, muscle cramps and
514 spasms, musculoskeletal inflammation.

515 **Neurological:** Dizziness, sleep disorders, migraines, paralysis of cranial nerves.

516 **Non-Site Specific:** Chest symptoms; malaise and fatigue; pain; edema and swelling;
517 bacterial infections; fungal infections; mobility disorders; cysts, lumps, and masses.

518 **Psychiatry:** Mood disorders.

519 **Reproduction:** Bacterial reproductive infections.

520 **Skin:** Skin rashes, urticaria, photodermatitis, dermatitis and dermatosis, viral skin infections,
521 eczema, fungal skin infections, pruritus, acne and folliculitis.

522 **Urology:** Urinary infections.

523 Three of the 7 placebo-controlled US clinical trials were pediatric studies. A total of 592
524 patients 4 to 11 years were treated with FLOVENT DISKUS (doses of 50 or 100 mcg twice
525 daily) or placebo; an additional 174 patients 4 to 11 years received FLOVENT[®] ROTADISK[®]
526 (fluticasone propionate inhalation powder) at the same doses. There were no clinically relevant
527 differences in the pattern or severity of adverse events in children compared with those reported
528 in adults.

529 In the first 16 weeks of a 52-week clinical trial in adult asthma patients who previously
530 required oral corticosteroids (daily doses of 5 to 40 mg oral prednisone), the effects of
531 FLOVENT DISKUS 500 mcg twice daily (n = 41) and 1000 mcg twice daily (n = 36) were
532 compared with placebo (n = 34) for the frequency of reported adverse events. Adverse events,
533 whether or not considered drug related by the investigators, reported in more than five patients in

534 the group taking FLOVENT DISKUS and that occurred more frequently with FLOVENT
535 DISKUS than with placebo are shown below (percent FLOVENT DISKUS and percent
536 placebo). In considering these data, the increased average duration of exposure for patients
537 taking FLOVENT DISKUS (105 days for FLOVENT DISKUS versus 75 days for placebo)
538 should be taken into account.

539 **Ear, Nose, and Throat:** Hoarseness/dysphonia (9% and 0%), nasal congestion/blockage
540 (16% and 0%), oral candidiasis (31% and 21%), rhinitis (13% and 9%), sinusitis/sinus infection
541 (33% and 12%), throat irritation (10% and 9%), and upper respiratory tract infection (31% and
542 24%).

543 **Gastrointestinal:** Nausea and vomiting (9% and 0%).

544 **Lower Respiratory:** Cough (9% and 3%) and viral respiratory infections (9% and 6%).

545 **Musculoskeletal:** Arthralgia and articular rheumatism (17% and 3%) and muscle pain
546 (12% and 0%).

547 **Non-Site Specific:** Malaise and fatigue (16% and 9%) and pain (10% and 3%).

548 **Skin:** Pruritus (6% and 0%) and skin rashes (8% and 3%).

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

555 **Ear, Nose, and Throat:** Aphonia and throat soreness.

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

558 **Eye:** Cataracts.

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

560 **Respiratory:** Asthma exacerbation, bronchospasm, chest tightness, cough, dyspnea,
561 immediate bronchospasm, wheeze, and pneumonia.

562 **Skin:** Contusions and ecchymoses.

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

573

574 **OVERDOSAGE:** Chronic overdosage may result in signs/symptoms of hypercorticism (see
575 PRECAUTIONS). Inhalation by healthy volunteers of a single dose of 4000 mcg of fluticasone
576 propionate inhalation powder or single doses of 1760 or 3520 mcg of fluticasone propionate
577 inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses
578 of 1320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated.
579 Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to
580 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or
581 moderate severity, and incidences were similar in active and placebo treatment groups. The oral
582 and subcutaneous median lethal doses in mice and rats were >1000 mg/kg (>2200 and >4400
583 times, respectively, the maximum recommended daily inhalation dose in adults and >10,000 and
584 >20,000 times, respectively, the maximum recommended daily inhalation dose in children on a
585 mg/m² basis).

586
587 **DOSAGE AND ADMINISTRATION:** FLOVENT DISKUS should be administered by the
588 orally inhaled route in patients 4 years of age and older. Individual patients will experience a
589 variable time to onset and degree of symptom relief. Generally, fluticasone propionate inhalation
590 powder has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in
591 asthma control following inhaled administration of fluticasone propionate can occur within
592 24 hours of beginning treatment, although maximum benefit may not be achieved for 1 to
593 2 weeks or longer after starting treatment.

594 After asthma stability has been achieved, it is always desirable to titrate to the lowest effective
595 dose to reduce the possibility of side effects. For patients who do not respond adequately to the
596 starting dose after 2 weeks of therapy, higher doses may provide additional asthma control. The
597 safety and efficacy of FLOVENT DISKUS when administered in excess of recommended doses
598 have not been established.

599 Rinsing the mouth after inhalation is advised.

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

602

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

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 [†]	500-1000 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

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

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

615 ‡ The choice of starting dose should be made on the basis of individual patient assessment. A
 616 controlled clinical study of 111 oral corticosteroid-dependent patients with asthma showed
 617 few significant differences between the 2 doses of FLOVENT DISKUS on safety and efficacy
 618 endpoints. However, inability to decrease the dose of oral corticosteroids further during
 619 corticosteroid reduction may be indicative of the need to increase the dose of fluticasone
 620 propionate up to the maximum of 1000 mcg twice daily.

621
 622 **Pediatric Use:** Because individual responses may vary, children previously maintained on
 623 fluticasone propionate ROTADISK[®] 50 or 100 mcg twice daily may require dosage adjustments
 624 upon transfer to FLOVENT DISKUS.

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

629 **Directions for Use:** Illustrated Patient's Instructions for Use accompany each package of
 630 FLOVENT DISKUS.

631
 632 **HOW SUPPLIED:** FLOVENT DISKUS 50 mcg is supplied as a disposable, orange-colored
 633 device containing 60 blisters. The DISKUS inhalation device is packaged within an

634 orange-colored, plastic-coated, moisture-protective foil pouch (NDC 0173-0600-02). FLOVENT
635 DISKUS 50 mcg is also supplied in an institutional pack of one orange-colored, disposable
636 DISKUS inhalation device containing 28 blisters. The DISKUS inhalation device is packaged
637 within an orange-colored, plastic-coated foil pouch (NDC 0173-0600-00).

638 FLOVENT DISKUS 100 mcg is supplied as a disposable, orange-colored device containing
639 60 blisters. The DISKUS inhalation device is packaged within an orange-colored, plastic-coated,
640 moisture-protective foil pouch (NDC 0173-0602-02). FLOVENT DISKUS 100 mcg is also
641 supplied in an institutional pack of one orange-colored, disposable DISKUS inhalation device
642 containing 28 blisters. The DISKUS inhalation device is packaged within an orange-colored,
643 plastic-coated foil pouch (NDC 0173-0602-00).

644 FLOVENT DISKUS 250 mcg is supplied as a disposable, orange-colored device containing
645 60 blisters. The DISKUS inhalation device is packaged within an orange-colored, plastic-coated,
646 moisture-protective foil pouch (NDC 0173-0601-02). FLOVENT DISKUS 250 mcg is also
647 supplied in an institutional pack of one orange-colored, disposable DISKUS inhalation device
648 containing 28 blisters. The DISKUS inhalation device is packaged within an orange-colored,
649 plastic-coated foil pouch (NDC 0173-0601-00).

650 **Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place**
651 **away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation**
652 **device is not reusable. The device should be discarded 6 weeks (50-mcg strength) or**
653 **2 months (100- and 250-mcg strengths) after removal from the moisture-protective foil**
654 **overwrap pouch or after all blisters have been used (when the dose indicator reads “0”),**
655 **whichever comes first. Do not attempt to take the device apart.**

656
657

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661
662 US Patent Nos. 4,335,121; D 342,994; 5,590,645; 5,860,419; and 5,873,360

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