

**PRESCRIBING INFORMATION**

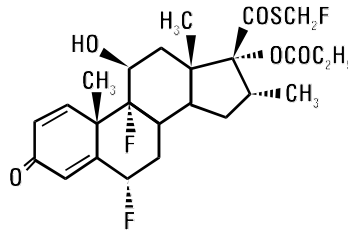
**FLONASE<sup>®</sup>**  
**(fluticasone propionate)**  
**Nasal Spray, 50 mcg**

**SHAKE GENTLY  
BEFORE USE.**

**For Intranasal Use Only.**

**DESCRIPTION**

Fluticasone propionate, the active component of FLONASE Nasal Spray, is a synthetic corticosteroid having the chemical name S-(fluoromethyl)6 $\alpha$ ,9-difluoro-11 $\beta$ -17-dihydroxy-16 $\alpha$ -methyl-3-oxoandrost-1,4-diene-17 $\beta$ -carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is C<sub>25</sub>H<sub>31</sub>F<sub>3</sub>O<sub>5</sub>S. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FLONASE Nasal Spray, 50 mcg is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. FLONASE Nasal Spray also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol, and has a pH between 5 and 7.

It is necessary to prime the pump before first use or after a period of non-use (1 week or more). After initial priming (6 actuations), each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. Each 16-g bottle of FLONASE Nasal Spray provides 120 metered sprays. After 120 metered sprays, the amount of fluticasone propionate delivered per actuation may not be consistent and the unit should be discarded.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action:** Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity. In vitro dose response studies on a cloned human glucocorticoid receptor system involving binding and gene expression afforded 50% responses at 1.25 and 0.17 nM concentrations, respectively. Fluticasone propionate was 3-fold to 5-fold more potent

35 than dexamethasone in these assays. Data from the McKenzie vasoconstrictor assay in man also  
36 support its potent glucocorticoid activity.

37 In preclinical studies, fluticasone propionate revealed progesterone-like activity similar to the  
38 natural hormone. However, the clinical significance of these findings in relation to the low  
39 plasma levels (see Pharmacokinetics) is not known.

40 The precise mechanism through which fluticasone propionate affects allergic rhinitis  
41 symptoms is not known. Corticosteroids have been shown to have a wide range of effects on  
42 multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and  
43 mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. In  
44 7 trials in adults, FLONASE Nasal Spray has decreased nasal mucosal eosinophils in 66% (35%  
45 for placebo) of patients and basophils in 39% (28% for placebo) of patients. The direct  
46 relationship of these findings to long-term symptom relief is not known.

47 FLONASE Nasal Spray, like other corticosteroids, is an agent that does not have an  
48 immediate effect on allergic symptoms. A decrease in nasal symptoms has been noted in some  
49 patients 12 hours after initial treatment with FLONASE Nasal Spray. Maximum benefit may not  
50 be reached for several days. Similarly, when corticosteroids are discontinued, symptoms may not  
51 return for several days.

52 **Pharmacokinetics: Absorption:** The activity of FLONASE Nasal Spray is due to the parent  
53 drug, fluticasone propionate. Indirect calculations indicate that fluticasone propionate delivered  
54 by the intranasal route has an absolute bioavailability averaging less than 2%. After intranasal  
55 treatment of patients with allergic rhinitis for 3 weeks, fluticasone propionate plasma  
56 concentrations were above the level of detection (50 pg/mL) only when recommended doses  
57 were exceeded and then only in occasional samples at low plasma levels. Due to the low  
58 bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via  
59 other routes of administration. Studies using oral dosing of radiolabeled drug have demonstrated  
60 that fluticasone propionate is highly extracted from plasma and absorption is low. Oral  
61 bioavailability is negligible, and the majority of the circulating radioactivity is due to an inactive  
62 metabolite.

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

66 The percentage of fluticasone propionate bound to human plasma proteins averaged 91% with  
67 no obvious concentration relationship. Fluticasone propionate is weakly and reversibly bound to  
68 erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propionate is  
69 not significantly bound to human transcortin.

70 **Metabolism:** The total blood clearance of fluticasone propionate is high (average,  
71 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only  
72 circulating metabolite detected in man is the 17 $\beta$ -carboxylic acid derivative of fluticasone  
73 propionate, which is formed through the cytochrome P450 3A4 pathway. This inactive  
74 metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid

75 receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies.  
76 Other metabolites detected in vitro using cultured human hepatoma cells have not been detected  
77 in man.

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

82 **Special Populations:** Fluticasone propionate nasal spray was not studied in any special  
83 populations, and no gender-specific pharmacokinetic data have been obtained.

84 **Drug-Drug Interactions:** In a multiple-dose drug interaction study, coadministration of orally  
85 inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily)  
86 did not affect fluticasone propionate pharmacokinetics. In another drug interaction study,  
87 coadministration of orally inhaled fluticasone propionate (1,000 mcg, 5 times the maximum daily  
88 intranasal dose) and ketoconazole (200 mg once daily) resulted in increased fluticasone  
89 propionate concentrations and reduced plasma cortisol area under the plasma concentration  
90 versus time curve (AUC), but had no effect on urinary excretion of cortisol. Due to very low  
91 plasma concentrations achieved after intranasal dosing, clinically significant drug interactions are  
92 unlikely; however, since fluticasone propionate is a substrate of cytochrome P450 3A4, caution  
93 should be exercised when known strong cytochrome P450 3A4 inhibitors (e.g., ritonavir,  
94 ketoconazole) are coadministered with fluticasone propionate as this could result in increased  
95 plasma concentrations of fluticasone propionate.

96 **Pharmacodynamics:** In a trial to evaluate the potential systemic and topical effects of  
97 FLONASE Nasal Spray on allergic rhinitis symptoms, the benefits of comparable drug blood  
98 levels produced by FLONASE Nasal Spray and oral fluticasone propionate were compared. The  
99 doses used were 200 mcg of FLONASE Nasal Spray, the nasal spray vehicle (plus oral placebo),  
100 and 5 and 10 mg of oral fluticasone propionate (plus nasal spray vehicle) per day for 14 days.  
101 Plasma levels were undetectable in the majority of patients after intranasal dosing, but present at  
102 low levels in the majority after oral dosing. FLONASE Nasal Spray was significantly more  
103 effective in reducing symptoms of allergic rhinitis than either the oral fluticasone propionate or  
104 the nasal vehicle. This trial demonstrated that the therapeutic effect of FLONASE Nasal Spray  
105 can be attributed to the topical effects of fluticasone propionate.

106 In another trial, the potential systemic effects of FLONASE Nasal Spray on the  
107 hypothalamic-pituitary-adrenal (HPA) axis were also studied in allergic patients. FLONASE  
108 Nasal Spray given as 200 mcg once daily or 400 mcg twice daily was compared with placebo or  
109 oral prednisone 7.5 or 15 mg given in the morning. FLONASE Nasal Spray at either dose for 4  
110 weeks did not affect the adrenal response to 6-hour cosyntropin stimulation, while both doses of  
111 oral prednisone significantly reduced the response to cosyntropin.

112 **Clinical Trials:** A total of 13 randomized, double-blind, parallel-group, multicenter, vehicle  
113 placebo-controlled clinical trials were conducted in the United States in adults and pediatric  
114 patients (4 years of age and older) to investigate regular use of FLONASE Nasal Spray in

115 patients with seasonal or perennial allergic rhinitis. The trials included 2,633 adults (1,439 men  
116 and 1,194 women) with a mean age of 37 (range, 18 to 79 years). A total of 440 adolescents (405  
117 boys and 35 girls), mean age of 14 (range, 12 to 17 years), and 500 children (325 boys and 175  
118 girls), mean age of 9 (range, 4 to 11 years) were also studied. The overall racial distribution was  
119 89% white, 4% black, and 7% other. These trials evaluated the total nasal symptom scores  
120 (TNSS) that included rhinorrhea, nasal obstruction, sneezing, and nasal itching in known allergic  
121 patients who were treated for 2 to 24 weeks. Subjects treated with FLONASE Nasal Spray  
122 exhibited significantly greater decreases in TNSS than vehicle placebo-treated patients. Nasal  
123 mucosal basophils and eosinophils were also reduced at the end of treatment in adult studies;  
124 however, the clinical significance of this decrease is not known.

125 There were no significant differences between fluticasone propionate regimens whether  
126 administered as a single daily dose of 200 mcg (two 50-mcg sprays in each nostril) or as 100 mcg  
127 (one 50-mcg spray in each nostril) twice daily in 6 clinical trials. A clear dose response could not  
128 be identified in clinical trials. In 1 trial, 200 mcg/day was slightly more effective than 50 mcg/day  
129 during the first few days of treatment; thereafter, no difference was seen.

130 Two randomized, double-blind, parallel-group, multicenter, vehicle placebo-controlled 28-day  
131 trials were conducted in the United States in 732 patients (243 given FLONASE) 12 years of age  
132 and older to investigate “as-needed” use of FLONASE Nasal Spray (200 mcg) in patients with  
133 seasonal allergic rhinitis. Patients were instructed to take the study medication only on days when  
134 they thought they needed the medication for symptom control, not to exceed 2 sprays per nostril  
135 on any day, and not more than once daily. “As-needed” use was prospectively defined as average  
136 use of study medication no more than 75% of study days. Average use of study medications was  
137 57% to 70% of days for all treatment arms. The studies demonstrated significantly greater  
138 reduction in TNSS (sum of nasal congestion, rhinorrhea, sneezing, and nasal itching) with  
139 FLONASE Nasal Spray 200 mcg compared to placebo. The relative difference in efficacy with  
140 as-needed use as compared to regularly administered doses was not studied.

141 Three randomized, double-blind, parallel-group, vehicle placebo-controlled trials were  
142 conducted in 1,191 patients to investigate regular use of FLONASE Nasal Spray in patients with  
143 perennial nonallergic rhinitis. These trials evaluated the patient-rated TNSS (nasal obstruction,  
144 postnasal drip, rhinorrhea) in patients treated for 28 days of double-blind therapy and in 1 of the  
145 3 trials for 6 months of open-label treatment. Two of these trials demonstrated that patients  
146 treated with FLONASE Nasal Spray at a dose of 100 mcg twice daily exhibited statistically  
147 significant decreases in TNSS compared with patients treated with vehicle.

148 **Individualization of Dosage:** Patients should use FLONASE Nasal Spray at regular intervals  
149 for optimal effect.

150 Adult patients may be started on a 200-mcg once-daily regimen (two 50-mcg sprays in each  
151 nostril once daily). An alternative 200-mcg/day dosage regimen can be given as 100 mcg twice  
152 daily (one 50-mcg spray in each nostril twice daily).

153 Individual patients will experience a variable time to onset and different degree of symptom  
154 relief. In 4 randomized, double-blind, vehicle placebo-controlled, parallel-group allergic rhinitis

155 studies and 2 studies of patients in an outdoor “park” setting (park studies), a decrease in nasal  
156 symptoms in treated subjects compared to placebo was shown to occur as soon as 12 hours after  
157 treatment with a 200-mcg dose of FLONASE Nasal Spray. Maximum effect may take several  
158 days. Regular-use patients who have responded may be able to be maintained (after 4 to 7 days)  
159 on 100 mcg/day (1 spray in each nostril once daily).

160 Some patients (12 years of age and older) with seasonal allergic rhinitis may find as-needed  
161 use of FLONASE Nasal Spray (not to exceed 200 mcg daily) effective for symptom control (see  
162 Clinical Trials). Greater symptom control may be achieved with scheduled regular use. Efficacy  
163 of as-needed use of FLONASE Nasal Spray has not been studied in pediatric patients under 12  
164 years of age with seasonal allergic rhinitis, or patients with perennial allergic or nonallergic  
165 rhinitis.

166 Pediatric patients (4 years of age and older) should be started with 100 mcg (1 spray in each  
167 nostril once daily). Treatment with 200 mcg (2 sprays in each nostril once daily or 1 spray in each  
168 nostril twice daily) should be reserved for pediatric patients not adequately responding to  
169 100 mcg daily. Once adequate control is achieved, the dosage should be decreased to 100 mcg (1  
170 spray in each nostril) daily.

171 Maximum total daily doses should not exceed 2 sprays in each nostril (total dose,  
172 200 mcg/day). There is no evidence that exceeding the recommended dose is more effective.

173

## 174 **INDICATIONS AND USAGE**

175 FLONASE Nasal Spray is indicated for the management of the nasal symptoms of seasonal  
176 and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and  
177 older.

178 Safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not  
179 been adequately established.

180

## 181 **CONTRAINDICATIONS**

182 FLONASE Nasal Spray is contraindicated in patients with a hypersensitivity to any of its  
183 ingredients.

184

## 185 **WARNINGS**

186 The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied  
187 by signs of adrenal insufficiency, and in addition some patients may experience symptoms of  
188 withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated  
189 for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids  
190 should be carefully monitored for acute adrenal insufficiency in response to stress. In those  
191 patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid  
192 treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of  
193 their symptoms.

194 The concomitant use of intranasal corticosteroids with other inhaled corticosteroids could  
195 increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis.

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

207 Avoid spraying in eyes.

208

## 209 **PRECAUTIONS**

210 **General:** Intranasal corticosteroids may cause a reduction in growth velocity when administered  
211 to pediatric patients (see PRECAUTIONS: Pediatric Use).

212 Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the  
213 administration of FLONASE Nasal Spray. Rare instances of wheezing, nasal septum perforation,  
214 cataracts, glaucoma, and increased intraocular pressure have been reported following the  
215 intranasal application of corticosteroids, including fluticasone propionate.

216 Use of excessive doses of corticosteroids may lead to signs or symptoms of hypercorticism  
217 and/or suppression of HPA function.

218 Although systemic effects have been minimal with recommended doses of FLONASE Nasal  
219 Spray, potential risk increases with larger doses. Therefore, larger than recommended doses of  
220 FLONASE Nasal Spray should be avoided.

221 When used at higher than recommended doses or in rare individuals at recommended doses,  
222 systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If  
223 such changes occur, the dosage of FLONASE Nasal Spray should be discontinued slowly  
224 consistent with accepted procedures for discontinuing oral corticosteroid therapy.

225 In clinical studies with fluticasone propionate administered intranasally, the development of  
226 localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely.  
227 When such an infection develops, it may require treatment with appropriate local therapy and  
228 discontinuation of treatment with FLONASE Nasal Spray. Patients using FLONASE Nasal Spray  
229 over several months or longer should be examined periodically for evidence of *Candida* infection  
230 or other signs of adverse effects on the nasal mucosa.

231 Intranasal corticosteroids should be used with caution, if at all, in patients with active or  
232 quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal or  
233 bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex.

234 Because of the inhibitory effect of corticosteroids on wound healing, patients who have  
235 experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal  
236 corticosteroid until healing has occurred.

237 **Information for Patients:** Patients being treated with FLONASE Nasal Spray should receive  
238 the following information and instructions. This information is intended to aid them in the safe  
239 and effective use of this medication. It is not a disclosure of all possible adverse or intended  
240 effects.

241 Patients should be warned to avoid exposure to chickenpox or measles and, if exposed, to  
242 consult their physician without delay.

243 Patients should use FLONASE Nasal Spray at regular intervals for optimal effect. Some  
244 patients (12 years of age and older) with seasonal allergic rhinitis may find as-needed use of  
245 200 mcg once daily effective for symptom control (see Clinical Trials).

246 A decrease in nasal symptoms may occur as soon as 12 hours after starting therapy with  
247 FLONASE Nasal Spray. Results in several clinical trials indicate statistically significant  
248 improvement within the first day or two of treatment; however, the full benefit of FLONASE  
249 Nasal Spray may not be achieved until treatment has been administered for several days. The  
250 patient should not increase the prescribed dosage but should contact the physician if symptoms  
251 do not improve or if the condition worsens.

252 For the proper use of FLONASE Nasal Spray and to attain maximum improvement, the  
253 patient should read and follow carefully the patient's instructions accompanying the product.

254 **Drug Interactions:** In a placebo-controlled, crossover study in 8 healthy volunteers,  
255 coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg; 5 times the  
256 maximum daily intranasal dose) with multiple doses of ketoconazole (200 mg) to steady state  
257 resulted in increased mean fluticasone propionate concentrations, a reduction in plasma cortisol  
258 AUC, and no effect on urinary excretion of cortisol. This interaction may be due to an inhibition  
259 of cytochrome P450 3A4 by ketoconazole, which is also the route of metabolism of fluticasone  
260 propionate. No drug interaction studies have been conducted with FLONASE Nasal Spray;  
261 however, care should be exercised when fluticasone propionate is coadministered with long-term  
262 ketoconazole and other known cytochrome P450 3A4 inhibitors.

263 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Fluticasone propionate  
264 demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately  
265 20 times the maximum recommended daily intranasal dose in adults and approximately 10 times  
266 the maximum recommended daily intranasal dose in children on a mcg/m<sup>2</sup> basis) for 78 weeks or  
267 in rats at inhalation doses up to 57 mcg/kg (approximately 2 times the maximum recommended  
268 daily intranasal dose in adults and approximately equivalent to the maximum recommended daily  
269 intranasal dose in children on a mcg/m<sup>2</sup> basis) for 104 weeks.

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

273 No evidence of impairment of fertility was observed in reproductive studies conducted in male  
274 and female rats at subcutaneous doses up to 50 mcg/kg (approximately 2 times the maximum  
275 recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis). Prostate weight was  
276 significantly reduced at a subcutaneous dose of 50 mcg/kg.

277 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Subcutaneous studies in the  
278 mouse and rat at 45 and 100 mcg/kg, respectively (approximately equivalent to and 4 times the  
279 maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis, respectively) revealed  
280 fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth  
281 retardation, omphalocele, cleft palate, and retarded cranial ossification.

282 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of  
283 4 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup>  
284 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg  
285 (approximately 25 times the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup>  
286 basis) of fluticasone propionate to the rabbit. No fluticasone propionate was detected in the  
287 plasma in this study, consistent with the established low bioavailability following oral  
288 administration (see CLINICAL PHARMACOLOGY).

289 Fluticasone propionate crossed the placenta following oral administration of 100 mcg/kg to  
290 rats or 300 mcg/kg to rabbits (approximately 4 and 25 times, respectively, the maximum  
291 recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis).

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

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

300 **Nursing Mothers:** It is not known whether fluticasone propionate is excreted in human breast  
301 milk. However, other corticosteroids have been detected in human milk. Subcutaneous  
302 administration to lactating rats of 10 mcg/kg of tritiated fluticasone propionate (less than the  
303 maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis) resulted in  
304 measurable radioactivity in the milk. Since there are no data from controlled trials on the use of  
305 intranasal fluticasone propionate by nursing mothers, caution should be exercised when  
306 FLONASE Nasal Spray is administered to a nursing woman.

307 **Pediatric Use:** Six hundred fifty (650) patients aged 4 to 11 years and 440 patients aged 12 to  
308 17 years were studied in US clinical trials with fluticasone propionate nasal spray. The safety and  
309 effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been  
310 established.

311 Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in  
312 growth velocity in pediatric patients. This effect has been observed in the absence of laboratory



313 evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator  
314 of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA  
315 axis function. The long-term effects of this reduction in growth velocity associated with  
316 intranasal corticosteroids, including the impact on final adult height, are unknown. The potential  
317 for “catch-up” growth following discontinuation of treatment with intranasal corticosteroids has  
318 not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids,  
319 including FLONASE Nasal Spray, should be monitored routinely (e.g., via stadiometry). The  
320 potential growth effects of prolonged treatment should be weighed against the clinical benefits  
321 obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of  
322 intranasal corticosteroids, including FLONASE Nasal Spray, each patient should be titrated to  
323 the lowest dose that effectively controls his/her symptoms.

324 A 1-year placebo-controlled clinical growth study was conducted in 150 pediatric patients  
325 (ages 3 to 9 years) to assess the effect of FLONASE Nasal Spray (single daily dose of 200 mcg,  
326 the maximum approved dose) on growth velocity. From the primary population of 56 patients  
327 receiving FLONASE Nasal Sprays~~subjects~~ and 52 receiving placebo~~subjects~~, the point estimate  
328 for growth velocity with FLONASE Nasal Spray was 0.14 cm/year lower than that noted with  
329 placebo (95% confidence interval ranging from 0.54 cm/year lower than placebo to 0.27 cm/year  
330 higher than placebo). Thus, no statistically significant effect on growth was noted compared to  
331 placebo. No evidence of clinically relevant changes in HPA axis function or bone mineral density  
332 was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray  
333 absorptiometry, respectively.

334  
335 The potential for FLONASE Nasal Spray to cause growth suppression in susceptible patients  
336 or when given at higher doses cannot be ruled out.

337  
338 **Geriatric Use:** A limited number of patients 65 years of age and older (n = 129) or 75 years of  
339 age and older (n = 11) have been treated with FLONASE Nasal Spray in US and non-US clinical  
340 trials. While the number of patients is too small to permit separate analysis of efficacy and safety,  
341 the adverse reactions reported in this population were similar to those reported by younger  
342 patients.

### 343 344 **ADVERSE REACTIONS**

345 In controlled US studies, more than 3,300 patients with seasonal allergic, perennial allergic, or  
346 perennial nonallergic rhinitis received treatment with intranasal fluticasone propionate. In  
347 general, adverse reactions in clinical studies have been primarily associated with irritation of the  
348 nasal mucous membranes, and the adverse reactions were reported with approximately the same  
349 frequency by patients treated with the vehicle itself. The complaints did not usually interfere with  
350 treatment. Less than 2% of patients in clinical trials discontinued because of adverse events; this  
351 rate was similar for vehicle placebo and active comparators.

352 Systemic corticosteroid side effects were not reported during controlled clinical studies up to 6  
353 months' duration with FLONASE Nasal Spray. If recommended doses are exceeded, however, or  
354 if individuals are particularly sensitive or taking FLONASE Nasal Spray in conjunction with  
355 administration of other corticosteroids, symptoms of hypercorticism, e.g., Cushing syndrome,  
356 could occur.

357 The following incidence of common adverse reactions (>3%, where incidence in fluticasone  
358 propionate-treated subjects exceeded placebo) is based upon 7 controlled clinical trials in which  
359 536 patients (57 girls and 108 boys aged 4 to 11 years, 137 female and 234 male adolescents and  
360 adults) were treated with FLONASE Nasal Spray 200 mcg once daily over 2 to 4 weeks and 2  
361 controlled clinical trials in which 246 patients (119 female and 127 male adolescents and adults)  
362 were treated with FLONASE Nasal Spray 200 mcg once daily over 6 months. Also included in  
363 the table are adverse events from 2 studies in which 167 children (45 girls and 122 boys aged 4  
364 to 11 years) were treated with FLONASE Nasal Spray 100 mcg once daily for 2 to 4 weeks.

365  
366 **Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in Controlled**  
367 **Clinical Trials With FLONASE Nasal Spray in Patients ≥4 Years With Seasonal or**  
368 **Perennial Allergic Rhinitis**

Adverse Experience	Vehicle Placebo (n = 758) %	FLONASE 100 mcg Once Daily (n = 167) %	FLONASE 200 mcg Once Daily (n = 782) %
Headache	14.6	6.6	16.1
Pharyngitis	7.2	6.0	7.8
Epistaxis	5.4	6.0	6.9
Nasal burning/nasal irritation	2.6	2.4	3.2
Nausea/vomiting	2.0	4.8	2.6
Asthma symptoms	2.9	7.2	3.3
Cough	2.8	3.6	3.8

369  
370 Other adverse events that occurred in ≤3% but ≥1% of patients and that were more common  
371 with fluticasone propionate (with uncertain relationship to treatment) included: blood in nasal  
372 mucus, runny nose, abdominal pain, diarrhea, fever, flu-like symptoms, aches and pains,  
373 dizziness, bronchitis.

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

380 **General:** Hypersensitivity reactions, including angioedema, skin rash, edema of the face and  
381 tongue, pruritus, urticaria, bronchospasm, wheezing, dyspnea, and anaphylaxis/anaphylactoid  
382 reactions, which in rare instances were severe.

383 **Ear, Nose, and Throat:** Alteration or loss of sense of taste and/or smell and, rarely, nasal  
384 septal perforation, nasal ulcer, sore throat, throat irritation and dryness, cough, hoarseness, and  
385 voice changes.

386 **Eye:** Dryness and irritation, conjunctivitis, blurred vision, glaucoma, increased intraocular  
387 pressure, and cataracts.

388 Cases of growth suppression have been reported for intranasal corticosteroids, including  
389 FLONASE (see PRECAUTIONS: Pediatric Use).

390

### 391 **OVERDOSAGE**

392 Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS).  
393 Intranasal administration of 2 mg (10 times the recommended dose) of fluticasone propionate  
394 twice daily for 7 days to healthy human volunteers was well tolerated. Single oral doses up to  
395 16 mg have been studied in human volunteers with no acute toxic effects reported. Repeat oral  
396 doses up to 80 mg daily for 10 days in volunteers and repeat oral doses up to 10 mg daily for  
397 14 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and  
398 incidences were similar in active and placebo treatment groups. Acute overdosage with this  
399 dosage form is unlikely since 1 bottle of FLONASE Nasal Spray contains approximately 8 mg of  
400 fluticasone propionate.

401 The oral and subcutaneous median lethal doses in mice and rats were >1,000 mg/kg (>20,000  
402 and >41,000 times, respectively, the maximum recommended daily intranasal dose in adults and  
403 >10,000 and >20,000 times, respectively, the maximum recommended daily intranasal dose in  
404 children on a mg/m<sup>2</sup> basis).

405

### 406 **DOSAGE AND ADMINISTRATION**

407 Patients should use FLONASE Nasal Spray at regular intervals for optimal effect.

408 **Adults:** The recommended starting dosage in **adults** is 2 sprays (50 mcg of fluticasone  
409 propionate each) in each nostril once daily (total daily dose, 200 mcg). The same dosage divided  
410 into 100 mcg given twice daily (e.g., 8 a.m. and 8 p.m.) is also effective. After the first few days,  
411 patients may be able to reduce their dosage to 100 mcg (1 spray in each nostril) once daily for  
412 maintenance therapy. Some patients (12 years of age and older) with seasonal allergic rhinitis  
413 may find as-needed use of 200 mcg once daily effective for symptom control (see Clinical  
414 Trials). Greater symptom control may be achieved with scheduled regular use.

415 **Adolescents and Children (4 Years of Age and Older):** Patients should be started with  
416 100 mcg (1 spray in each nostril once daily). Patients not adequately responding to 100 mcg may  
417 use 200 mcg (2 sprays in each nostril). Once adequate control is achieved, the dosage should be  
418 decreased to 100 mcg (1 spray in each nostril) daily.

419 The maximum total daily dosage should not exceed 2 sprays in each nostril (200 mcg/day).  
420 (See Individualization of Dosage and Clinical Trials sections.)

421 FLONASE Nasal Spray is not recommended for children under 4 years of age.

422 **Directions for Use:** Illustrated patient's instructions for proper use accompany each package  
423 of FLONASE Nasal Spray.

424

#### 425 **HOW SUPPLIED**

426 FLONASE Nasal Spray 50 mcg is supplied in an amber glass bottle fitted with a white  
427 metering atomizing pump, white nasal adapter, and green dust cover in a box of 1 (NDC 0173-  
428 0453-01) with patient's instructions for use. Each bottle contains a net fill weight of 16 g and will  
429 provide 120 actuations. Each actuation delivers 50 mcg of fluticasone propionate in 100 mg of  
430 formulation through the nasal adapter. The correct amount of medication in each spray cannot be  
431 assured after 120 sprays even though the bottle is not completely empty. The bottle should be  
432 discarded when the labeled number of actuations has been used.

433 **Store between 4° and 30°C (39° and 86°F).**

434

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437 GlaxoSmithKline

438 Research Triangle Park, NC 27709

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