

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VERAMYST Nasal Spray safely and effectively. See full prescribing information for VERAMYST Nasal Spray.

VERAMYST™ (fluticasone furoate) Nasal Spray

Initial U.S. Approval: 2007

INDICATIONS AND USAGE

VERAMYST Nasal Spray is a corticosteroid indicated for treatment of symptoms of seasonal and perennial allergic rhinitis in adults and children ≥ 2 years. (1.1)

DOSAGE AND ADMINISTRATION

For intranasal use only. Usual starting dosages:

- Adults and adolescents ≥ 12 years: 110 mcg (2 sprays per nostril) once daily. (2.1)
- Children 2-11 years: 55 mcg (1 spray per nostril) once daily. (2.2)
- Priming Information: Prime VERAMYST Nasal Spray before using for the first time, when not used for more than 30 days, or if the cap has been left off the bottle for 5 days or longer. (2)

DOSAGE FORMS AND STRENGTHS

Nasal spray: 27.5 mcg of fluticasone furoate in each 50-microliter spray. (3)
Supplied in 10 g bottle containing 120 sprays. (16)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Epistaxis, nasal ulceration, *Candida albicans* infection, nasal septal perforation, impaired wound healing. Monitor patients periodically for signs of adverse effects on the nasal mucosa. Avoid use in patients with recent nasal ulcers, nasal surgery, or nasal trauma. (5.1)

- Development of glaucoma or posterior subcapsular cataracts. Monitor patients closely with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts. (5.2)
- Potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. More serious or even fatal course of chickenpox or measles in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections. (5.3)
- Hypercorticism and adrenal suppression with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue VERAMYST Nasal Spray slowly. (5.4)
- Potential reduction in growth velocity in children. Monitor growth routinely in pediatric patients receiving VERAMYST Nasal Spray. (5.6, 8.4)

ADVERSE REACTIONS

The most common adverse reactions ($>1\%$ incidence) included headache, epistaxis, pharyngolaryngeal pain, nasal ulceration, back pain, pyrexia, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Potent inhibitors of CYP3A4 may increase exposure to fluticasone furoate.

- Co-administration of ritonavir is not recommended. (5.5, 7)
- Use caution with co-administration of other potent CYP3A4 inhibitors, such as ketoconazole. (5.5, 7)

USE IN SPECIFIC POPULATIONS

Hepatic impairment may increase exposure to fluticasone furoate. Use with caution in patients with severe hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 **1.1 Treatment of Allergic Rhinitis**

4 VERAMYST Nasal Spray is indicated for the treatment of the symptoms of seasonal and
5 perennial allergic rhinitis in patients 2 years of age and older.

6 **2 DOSAGE AND ADMINISTRATION**

7 Administer VERAMYST Nasal Spray by the intranasal route only. Prime VERAMYST
8 Nasal Spray before using for the first time by shaking the contents well and releasing 6 test
9 sprays into the air away from the face. When VERAMYST Nasal Spray has not been used for
10 more than 30 days or if the cap has been left off the bottle for 5 days or longer, prime the pump
11 again until a fine mist appears. Shake VERAMYST Nasal Spray well before each use.

12 **2.1 Adults and Adolescents 12 Years of Age and Older**

13 The recommended starting dosage is 110 mcg once daily administered as 2 sprays
14 (27.5 mcg/spray) in each nostril. Titrate an individual patient to the minimum effective dosage to
15 reduce the possibility of side effects. When the maximum benefit has been achieved and
16 symptoms have been controlled, reducing the dosage to 55 mcg (1 spray in each nostril) once
17 daily may be effective in maintaining control of allergic rhinitis symptoms.

18 **2.2 Children 2 to 11 Years of Age**

19 The recommended starting dosage in children is 55 mcg once daily administered as
20 1 spray (27.5 mcg/spray) in each nostril. Children not adequately responding to 55 mcg may use
21 110 mcg (2 sprays in each nostril) once daily. Once symptoms have been controlled, the dosage
22 may be decreased to 55 mcg once daily.

23 **3 DOSAGE FORMS AND STRENGTHS**

24 VERAMYST Nasal Spray is a nasal spray suspension. Each spray (50 microliters)
25 delivers 27.5 mcg of fluticasone furoate.

26 **4 CONTRAINDICATIONS**

27 None.

28 **5 WARNINGS AND PRECAUTIONS**

29 **5.1 Local Nasal Effects**

30 Epistaxis and Nasal Ulceration: In clinical studies of 2 to 52 weeks' duration, epistaxis
31 and nasal ulcerations were observed more frequently and some epistaxis events were more
32 severe in patients treated with VERAMYST Nasal Spray than those who received placebo [*see*
33 *Adverse Reactions (6)*].

34 Candida Infection: Evidence of localized infections of the nose with *Candida albicans*
35 was seen on nasal exams in 7 of 2,745 patients treated with VERAMYST Nasal Spray during
36 clinical trials and was reported as an adverse event in 3 patients. When such an infection

37 develops, it may require treatment with appropriate local therapy and discontinuation of
38 VERAMYST Nasal Spray. Therefore, patients using VERAMYST Nasal Spray over several
39 months or longer should be examined periodically for evidence of *Candida* infection or other
40 signs of adverse effects on the nasal mucosa.

41 Nasal Septal Perforation: Instances of nasal septal perforation have been reported in
42 patients following the intranasal application of corticosteroids. There were no instances of nasal
43 septal perforation observed in clinical studies with VERAMYST Nasal Spray.

44 Impaired Wound Healing: Because of the inhibitory effect of corticosteroids on wound
45 healing, patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should
46 not use VERAMYST Nasal Spray until healing has occurred.

47 **5.2 Glaucoma and Cataracts**

48 Nasal and inhaled corticosteroids may result in the development of glaucoma and/or
49 cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a
50 history of increased intraocular pressure, glaucoma, and/or cataracts.

51 Glaucoma and cataract formation was evaluated with intraocular pressure measurements
52 and slit lamp examinations in 1 controlled 12-month study in 806 adolescent and adult patients
53 aged 12 years and older and in 1 controlled 12-week study in 558 children aged 2 to 11 years.
54 The patients had perennial allergic rhinitis and were treated with either VERAMYST Nasal
55 Spray (110 mcg once daily in adult and adolescent patients and 55 or 110 mcg once daily in
56 pediatric patients) or placebo. Intraocular pressure remained within the normal range
57 (<21 mmHg) in ≥98% of the patients in any treatment group in both studies. However, in the
58 12-month study in adolescents and adults, 12 patients, all treated with VERAMYST Nasal Spray
59 110 mcg once daily, had intraocular pressure measurements that increased above normal levels
60 (≥21mmHg). In the same study, 7 patients (6 treated with VERAMYST Nasal Spray 110 mcg
61 once daily and 1 patient treated with placebo) had cataracts identified during the study that were
62 not present at baseline.

63 **5.3 Immunosuppression**

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

76 Corticosteroids should be used with caution, if at all, in patients with active or quiescent

77 tuberculous infections of the respiratory tract; untreated local or systemic fungal or bacterial
78 infections; systemic viral or parasitic infections; or ocular herpes simplex because of the
79 potential for worsening of these infections.

80 **5.4 Hypothalamic-Pituitary-Adrenal Axis Effects**

81 Hypercorticism and Adrenal Suppression: When intranasal steroids are used at higher
82 than recommended dosages or in susceptible individuals at recommended dosages, systemic
83 corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such
84 changes occur, the dosage of VERAMYST Nasal Spray should be discontinued slowly,
85 consistent with accepted procedures for discontinuing oral corticosteroid therapy.

86 The replacement of a systemic corticosteroid with a topical corticosteroid can be
87 accompanied by signs of adrenal insufficiency. In addition, some patients may experience
88 symptoms of corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and
89 depression. Patients previously treated for prolonged periods with systemic corticosteroids and
90 transferred to topical corticosteroids should be carefully monitored for acute adrenal
91 insufficiency in response to stress. In those patients who have asthma or other clinical conditions
92 requiring long-term systemic corticosteroid treatment, rapid decreases in systemic corticosteroid
93 dosages may cause a severe exacerbation of their symptoms.

94 **5.5 Use of CYP3A Inhibitors**

95 Co-administration with ritonavir is not recommended because of the risk of systemic
96 effects secondary to increased exposure to fluticasone furoate. Use caution with the
97 co-administration of VERAMYST Nasal Spray and other potent CYP3A4 inhibitors, such as
98 ketoconazole [see *Drug Interactions (7)*].

99 **5.6 Effect on Growth**

100 Corticosteroids may cause a reduction in growth velocity when administered to pediatric
101 patients. Monitor the growth routinely of pediatric patients receiving VERAMYST Nasal Spray.
102 To minimize the systemic effects of intranasal corticosteroids, including VERAMYST Nasal
103 Spray, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms
104 [see *Use in Specific Populations (8.4)*].

105 **6 ADVERSE REACTIONS**

106 Systemic and local corticosteroid use may result in the following:

- 107 • Epistaxis, ulcerations, *Candida albicans* infection, impaired wound healing [see
108 *Warnings and Precautions (5.1)*]
- 109 • Cataracts and glaucoma [see *Warnings and Precautions (5.2)*]
- 110 • Immunosuppression [see *Warnings and Precautions (5.3)*]
- 111 • Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction [see
112 *Warnings and Precautions (5.4, 5.6), Use in Specific Populations (8.4)*]

113 **6.1 Clinical Trials Experience**

114 The safety data described below reflect exposure to VERAMYST Nasal Spray in
115 1,563 patients with seasonal or perennial allergic rhinitis in 9 controlled clinical trials of 2 to

116 12 weeks' duration. The data from adults and adolescents are based upon 6 clinical trials in
 117 which 768 patients with seasonal or perennial allergic rhinitis (473 females and 295 males
 118 12 years of age and older) were treated with VERAMYST Nasal Spray 110 mcg once daily for 2
 119 to 6 weeks. The racial distribution of adult and adolescent patients receiving VERAMYST Nasal
 120 Spray was 82% white, 5% black, 13% other. The data from pediatric patients are based upon
 121 3 clinical trials in which 795 children with seasonal or perennial rhinitis (352 females and
 122 443 males 2 to 11 years of age) were treated with VERAMYST Nasal Spray 55 or 110 mcg once
 123 daily for 2 to 12 weeks. The racial distribution of pediatric patients receiving VERAMYST
 124 Nasal Spray was 75% white, 11% black, 14% other.

125 Because clinical trials are conducted under widely varying conditions, adverse reaction
 126 rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical
 127 trials of another drug and may not reflect the rates observed in practice.

128 Adults and Adolescents 12 Years of Age and Older: Overall adverse reactions were
 129 reported with approximately the same frequency by patients treated with VERAMYST Nasal
 130 Spray and those receiving placebo. Less than 3% of patients in clinical trials discontinued
 131 treatment because of adverse reactions. The rate of withdrawal among patients receiving
 132 VERAMYST Nasal Spray was similar or lower than the rate among patients receiving placebo.

133 Table 1 displays the common adverse reactions (>1% in any patient group receiving
 134 VERAMYST Nasal Spray) that occurred more frequently in patients 12 years of age and older
 135 treated with VERAMYST Nasal Spray compared with placebo-treated patients.

136

137 **Table 1. Adverse Reactions With >1% Incidence in Controlled Clinical**
 138 **Trials of 2 to 6 Weeks' Duration With VERAMYST Nasal Spray in Adult**
 139 **and Adolescent Patients With Seasonal or Perennial Allergic Rhinitis**

Adverse Event	Adult and Adolescent Patients 12 Years of Age and Older	
	Vehicle Placebo (n = 774)	VERAMYST Nasal Spray 110 mcg Once Daily (n = 768)
Headache	54 (7%)	72 (9%)
Epistaxis	32 (4%)	45 (6%)
Pharynolaryngeal pain	8 (1%)	15 (2%)
Nasal ulceration	3 (<1%)	11 (1%)
Back pain	7 (<1%)	9 (1%)

140

141 There were no differences in the incidence of adverse reactions based on gender or race.
 142 Clinical trials did not include sufficient numbers of patients 65 years of age and older to
 143 determine whether they respond differently from younger subjects.

144 Pediatric Patients 2 to 11 Years of Age: In the 3 clinical trials in pediatric patients 2
 145 to <12 years of age, overall adverse reactions were reported with approximately the same

146 frequency by patients treated with VERAMYST Nasal Spray and those receiving placebo. Table
 147 2 displays the common adverse reactions (>3% in any patient group receiving VERAMYST
 148 Nasal Spray), that occurred more frequently in patients 2 to 11 years of age treated with
 149 VERAMYST Nasal Spray compared with placebo-treated patients.

150

151 **Table 2. Adverse Reactions With >3% Incidence in Controlled Clinical Trials of 2 to**
 152 **12 Weeks' Duration With VERAMYST Nasal Spray in Pediatric Patients With Seasonal**
 153 **or Perennial Allergic Rhinitis**

Adverse Event	Pediatric Patients 2 to <12 Years of Age		
	Vehicle Placebo (n = 429)	VERAMYST Nasal Spray 55 mcg Once Daily (n = 369)	VERAMYST Nasal Spray 110 mcg Once Daily (n = 426)
Headache	31 (7%)	28 (8%)	33 (8%)
Nasopharyngitis	21 (5%)	20 (5%)	21 (5%)
Epistaxis	19 (4%)	17 (5%)	17 (4%)
Pyrexia	7 (2%)	17 (5%)	19 (4%)
Pharynolaryngeal pain	14 (3%)	16 (4%)	12 (3%)
Cough	12 (3%)	12 (3%)	16 (4%)

154

155 There were no differences in the incidence of adverse reactions based on gender or race.
 156 Pyrexia occurred more frequently in children 2 to <6 years of age compared with children 6 to
 157 <12 years.

158 Long-Term (52-Week) Safety Trial: In a 52-week, placebo-controlled, long-term safety
 159 trial, 605 patients (307 females and 298 males aged 12 years of age and older) with perennial
 160 allergic rhinitis were treated with VERAMYST Nasal Spray 110 mcg once daily for 12 months
 161 and 201 were treated with placebo nasal spray. While most adverse reactions were similar in type
 162 and rate between the treatment groups, epistaxis occurred more frequently in patients who
 163 received VERAMYST Nasal Spray (123/605, 20%) than in patients who received placebo
 164 (17/201, 8%). Epistaxis tended to be more severe in patients treated with VERAMYST Nasal
 165 Spray. All 17 reports of epistaxis that occurred in patients who received placebo were of mild
 166 intensity, while 83, 39, and 1 of the total 123 epistaxis events in patients treated with
 167 VERAMYST Nasal Spray were of mild, moderate, and severe intensity, respectively. No patient
 168 experienced a nasal septal perforation during this trial.

169 **7 DRUG INTERACTIONS**

170 Fluticasone furoate is cleared by extensive first-pass metabolism mediated by the
 171 cytochrome P450 isozyme CYP3A4. In a drug interaction study of intranasal fluticasone furoate
 172 and the CYP3A4 inhibitor ketoconazole given as a 200-mg once-daily dose for 7 days, 6 of
 173 20 subjects receiving fluticasone furoate and ketoconazole had measurable but low levels of
 174 fluticasone furoate compared with 1 of 20 receiving fluticasone furoate and placebo. Based on

175 this study and the low systemic exposure, there was a 5% reduction in 24-hour serum cortisol
176 levels with ketoconazole compared to placebo. The data from this study should be carefully
177 interpreted because the study was conducted with ketoconazole 200 mg once daily rather than
178 400 mg, which is the maximum recommended dosage. Therefore, caution is required with the
179 co-administration of VERAMYST Nasal Spray and ketoconazole or other potent CYP3A4
180 inhibitors.

181 Based on data with another glucocorticoid, fluticasone propionate, metabolized by
182 CYP3A4, co-administration of VERAMYST Nasal Spray with the potent CYP3A4 inhibitor
183 ritonavir is not recommended because of the risk of systemic effects secondary to increased
184 exposure to fluticasone furoate. High exposure to corticosteroids increases the potential for
185 systemic side effects, such as cortisol suppression.

186 Enzyme induction and inhibition data suggest that fluticasone furoate is unlikely to
187 significantly alter the cytochrome P450-mediated metabolism of other compounds at clinically
188 relevant intranasal dosages.

189 **8 USE IN SPECIFIC POPULATIONS**

190 **8.1 Pregnancy**

191 Teratogenic Effects: Pregnancy Category C. Corticosteroids have been shown to be
192 teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

193 There were no teratogenic effects in rats and rabbits at inhaled fluticasone furoate
194 dosages of up to 91 and 8 mcg/kg/day, respectively (approximately 7 and 1 times, respectively,
195 the maximum recommended daily intranasal dose in adults on a mcg/m² basis). There was also
196 no effect on pre- or post-natal development in rats treated with up to 27 mcg/kg/day by
197 inhalation during gestation and lactation (approximately 2 times the maximum recommended
198 daily intranasal dose in adults on a mcg/m² basis).

199 There are no adequate and well-controlled studies in pregnant women. VERAMYST
200 Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential
201 risk to the fetus.

202 Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers
203 receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

204 **8.3 Nursing Mothers**

205 It is not known whether fluticasone furoate is excreted in human breast milk. However,
206 other corticosteroids have been detected in human milk. Since there are no data from controlled
207 trials on the use of intranasal fluticasone furoate by nursing mothers, caution should be exercised
208 when VERAMYST Nasal Spray is administered to a nursing woman.

209 **8.4 Pediatric Use**

210 Controlled clinical trials with VERAMYST Nasal Spray included 1,224 patients aged 2
211 to 11 years and 344 adolescent patients aged 12 to 17 years [see *Clinical Studies (14)*]. The
212 safety and effectiveness of VERAMYST Nasal Spray in children below 2 years of age have not
213 been established.

214 Controlled clinical studies have shown that intranasal corticosteroids may cause a
215 reduction in growth velocity in pediatric patients. This effect has been observed in the absence of
216 laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive
217 indicator of systemic corticosteroid exposure in pediatric patients than some commonly used
218 tests of HPA axis function. The long-term effects of reduction in growth velocity associated with
219 intranasal corticosteroids, including the impact on final adult height, are unknown. The potential
220 for “catch-up” growth following discontinuation of treatment with intranasal corticosteroids has
221 not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids,
222 including VERAMYST Nasal Spray, should be monitored routinely (e.g., via stadiometry). The
223 potential growth effects of prolonged treatment should be weighed against the clinical benefits
224 obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of
225 intranasal corticosteroids, including VERAMYST Nasal Spray, each patient’s dose should be
226 titrated to the lowest dosage that effectively controls his/her symptoms.

227 The potential for VERAMYST Nasal Spray to cause growth suppression in susceptible
228 patients or when given at higher than recommended dosages cannot be ruled out.

229 **8.5 Geriatric Use**

230 Clinical studies of VERAMYST Nasal Spray did not include sufficient numbers of
231 subjects aged 65 years and older to determine whether they respond differently from younger
232 subjects. Other reported clinical experience has not identified differences in responses between
233 the elderly and younger patients. In general, dose selection for an elderly patient should be
234 cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of
235 decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

236 **8.6 Hepatic Impairment**

237 Use VERAMYST Nasal Spray with caution in patients with severe hepatic impairment
238 [*see Pharmacokinetics (12.3)*].

239 **8.7 Renal Impairment**

240 No dosage adjustment is required in patients with renal impairment [*see*
241 *Pharmacokinetics (12.3)*].

242 **10 OVERDOSAGE**

243 Chronic overdosage may result in signs/symptoms of hypercorticism [*see Warnings and*
244 *Precautions (5.4)*]. There are no data on the effects of acute or chronic overdosage with
245 VERAMYST Nasal Spray. Because of low systemic bioavailability and an absence of acute
246 drug-related systemic findings in clinical studies (with dosages of up to 440 mcg/day for 2 weeks
247 [4 times the maximum recommended daily dose]), overdose is unlikely to require any therapy
248 other than observation.

249 Intranasal administration of up to 2,640 mcg/day (24 times the recommended adult dose)
250 of fluticasone furoate was administered to healthy human volunteers for 3 days. Single- and
251 repeat-dose studies with orally inhaled fluticasone furoate doses of 50 to 4,000 mcg have shown
252 decreased mean serum cortisol at doses of 500 mcg or higher. The oral median lethal dose in

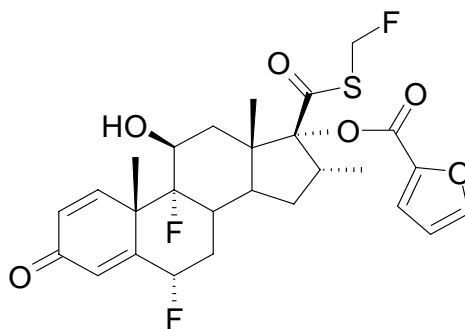
253 mice and rats was >2,000 mg/kg (approximately 74,000 and 147,000 times, respectively, the
254 maximum recommended daily intranasal dose in adults and 52,000 and 105,000 times,
255 respectively, the maximum recommended daily intranasal dose in children, on a mcg/m² basis).

256 Acute overdosage with the intranasal dosage form is unlikely since 1 bottle of
257 VERAMYST Nasal Spray contains approximately 3 mg of fluticasone furoate, and the
258 bioavailability of fluticasone furoate is <1% for 2.64 mg/day given intranasally and 1% for
259 2 mg/day given as an oral solution.

260 11 DESCRIPTION

261 Fluticasone furoate, the active component of VERAMYST Nasal Spray, is a synthetic
262 fluorinated corticosteroid having the chemical name (6 α ,11 β ,16 α ,17 α)-6,9-difluoro-17-
263 [(fluoro-methyl)thio]carbonyl]-11-hydroxy-16-methyl-3-oxoandrost-1,4-dien-17-yl 2-
264 furancarboxylate and the following chemical structure:

265



266

267

268 Fluticasone furoate is a white powder with a molecular weight of 538.6, and the empirical
269 formula is C₂₇H₂₉F₃O₆S. It is practically insoluble in water.

270 VERAMYST Nasal Spray is an aqueous suspension of micronized fluticasone furoate for
271 topical administration to the nasal mucosa by means of a metering (50 microliters), atomizing
272 spray pump. After initial priming [see Dosage and Administration (2)], each actuation delivers
273 27.5 mcg of fluticasone furoate in a volume of 50 microliters of nasal spray suspension.

274 VERAMYST Nasal Spray also contains 0.015% w/w benzalkonium chloride, dextrose
275 anhydrous, edetate disodium, microcrystalline cellulose and carboxymethylcellulose sodium,
276 polysorbate 80, and purified water. It has a pH of approximately 6.

277 12 CLINICAL PHARMACOLOGY

278 12.1 Mechanism of Action

279 Fluticasone furoate is a synthetic trifluorinated corticosteroid with potent
280 anti-inflammatory activity. The precise mechanism through which fluticasone furoate affects
281 rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of
282 actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages,
283 lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in
284 inflammation. Specific effects of fluticasone furoate demonstrated in in vitro and in vivo models

285 included activation of the glucocorticoid response element, inhibition of pro-inflammatory
286 transcription factors such as NFκB, and inhibition of antigen-induced lung eosinophilia in
287 sensitized rats.

288 Fluticasone furoate has been shown in vitro to exhibit a binding affinity for the human
289 glucocorticoid receptor that is approximately 29.9 times that of dexamethasone and 1.7 times
290 that of fluticasone propionate. The clinical relevance of these findings is unknown.

291 **12.2 Pharmacodynamics**

292 Adrenal Function: The effects of VERAMYST Nasal Spray on adrenal function have
293 been evaluated in 4 controlled clinical trials in patients with perennial allergic rhinitis. Two
294 6-week clinical trials were designed specifically to assess the effect of VERAMYST Nasal Spray
295 on the HPA axis with assessments of both 24-hour urinary cortisol excretion and serum cortisol
296 levels in domiciled patients. In addition, one 52-week safety study and one 12-week safety and
297 efficacy study included assessments of 24-hour urinary cortisol excretion. Details of the studies
298 and results are described below. In all 4 studies, since serum fluticasone determinations were
299 generally below the limit of quantification, compliance was assured by efficacy assessments.

300 *Clinical Trials Specifically Designed to Assess Hypothalamic-Pituitary-Adrenal*
301 *Axis Effect:* In a 6-week randomized, double-blind, parallel-group study in adult and adolescent
302 patients 12 years of age and older with perennial allergic rhinitis, VERAMYST Nasal Spray
303 110 mcg was compared to both placebo nasal spray and prednisone as a positive-control group
304 that received prednisone 10 mg orally once daily for the final 7 days of the treatment period.
305 Adrenal function was assessed by 24-hour urinary cortisol excretion before and after 6 weeks of
306 treatment and by serial serum cortisol levels. Patients were domiciled for collection of 24-hour
307 urinary cortisol. After 6 weeks of treatment, there was a change from baseline in the mean
308 24-hour urinary cortisol excretion in the group treated with VERAMYST Nasal Spray (n = 43)
309 of -1.16 mcg/day compared to -3.48 mcg/day in the placebo group (n = 42). The difference from
310 placebo in the group treated with VERAMYST Nasal Spray was 2.32 mcg/day (95% CI: -6.76,
311 11.39). Urinary cortisol data were not available for the positive-control (prednisone) treatment
312 group. For serum cortisol levels, after 6 weeks of treatment there was a change from baseline in
313 the mean (0-24 hours) of -0.38 and 0.08 mcg/dL for the group treated with VERAMYST Nasal
314 Spray (n = 43) and the placebo group (n = 44), respectively, with a difference between the group
315 treated with VERAMYST Nasal Spray and the placebo group of -0.47 mcg/dL (95% CI: -1.31,
316 0.37). For comparison, in the positive-control (prednisone, n = 12) treatment group, there was a
317 change in mean serum cortisol (0-24 hours) from baseline of -4.49 mcg/dL with a difference
318 between the prednisone and placebo group of -4.57 mcg/dL (95% CI: -5.83, -3.31).

319 The second 6-week study conducted in children 2 to 11 years of age was of similar design
320 to the adult study, including adrenal function assessments, but did not include a prednisone
321 positive-control arm. Patients were treated once daily with VERAMYST Nasal Spray 110 mcg
322 or placebo nasal spray. After 6 weeks of treatment, there was a change in the mean 24-hour
323 urinary cortisol excretion in the group treated with VERAMYST Nasal Spray (n = 43) of
324 0.49 mcg/day compared to 1.92 mcg/day in the placebo group (n = 41), with a difference

325 between the group treated with VERAMYST Nasal Spray and the placebo group of
326 -1.43 mcg/day (95% CI: -5.21, 2.35). For serum cortisol levels, after 6 weeks, there was a change
327 from baseline in mean (0-24 hours) of -0.34 and -0.23 mcg/dL for the group treated with
328 VERAMYST Nasal Spray (n = 48) and for the placebo group (n = 47), respectively, with a
329 difference between the group treated with VERAMYST Nasal Spray and the placebo group of
330 -0.11 mcg/dL (95% CI: -0.88, 0.66).

331 Additional Hypothalamic-Pituitary-Adrenal Axis Assessments: In the 52-week
332 safety trial in adolescents and adults 12 years of age and older with perennial allergic rhinitis,
333 VERAMYST Nasal Spray 110 mcg (n = 605) was compared to placebo nasal spray (n = 201).
334 Adrenal function was assessed by 24-hour urinary cortisol excretion in a subset of patients who
335 received VERAMYST Nasal Spray (n = 370) or placebo (n = 120) before and after 52 weeks of
336 treatment. After 52 weeks of treatment, the mean change from baseline 24-hour urinary cortisol
337 excretion was 5.84 mcg/day in the group treated with VERAMYST Nasal Spray and
338 3.34 mcg/day in the placebo group. The difference from placebo in mean change from baseline
339 24-hour urinary cortisol excretion was 2.50 mcg/day (95% CI: -5.49, 10.49).

340 In the 12-week safety and efficacy trial in children 2 to 11 years of age with perennial
341 allergic rhinitis, VERAMYST Nasal Spray 55 mcg (n = 185) and VERAMYST Nasal Spray
342 110 mcg (n = 185) were compared to placebo nasal spray (n = 188). Adrenal function was
343 assessed by measurement of 24-hour urinary free cortisol in a subset of patients who were 6 to
344 11 years of age (103 to 109 patients per group) before and after 12 weeks of treatment. After
345 12 weeks of treatment, there was a decrease in mean 24-hour urinary cortisol excretion from
346 baseline in the group treated with VERAMYST Nasal Spray 55 mcg (n = 109) of -2.93 mcg/day
347 and in the group treated with VERAMYST Nasal Spray 110 mcg (n = 103) of -2.07 mcg/day
348 compared to an increase in the placebo group (n = 107) of 0.08 mcg/day. The difference from
349 placebo in mean change from baseline in 24-hour urinary cortisol excretion for the group treated
350 with VERAMYST Nasal Spray 55 mcg was -3.01 mcg/day (95% CI: -6.16, 0.13) and
351 -2.14 mcg/day (95% CI: -5.33, 1.04) for the group treated with VERAMYST Nasal Spray
352 110 mcg.

353 When the results of the HPA axis assessments described above are taken as a whole, an
354 effect of intranasal fluticasone furoate on adrenal function cannot be ruled out, especially in
355 pediatric patients.

356 Cardiac Effects: A QT/QTc study did not demonstrate an effect of fluticasone furoate
357 administration on the QTc interval. The effect of a single dose of 4,000 mcg of orally inhaled
358 fluticasone furoate on the QTc interval was evaluated over 24 hours in 40 healthy male and
359 female subjects in a placebo and positive (a single dose of 400 mg oral moxifloxacin) controlled
360 cross-over study. The QTcF maximal mean change from baseline following fluticasone furoate
361 was similar to that observed with placebo with a treatment difference of 0.788 msec, 90% CI:
362 -1.802, 3.378. In contrast, moxifloxacin resulted in prolongation of the QTcF maximal mean
363 change from baseline compared with placebo with a treatment difference of 9.929 msec, 90% CI
364 7.339,12.520. While a single dose of fluticasone furoate had no effect on the QTc interval, the

365 effects of fluticasone furoate may not be at steady state following single dose. The effect of
366 fluticasone furoate on the QTc interval following multiple dose administration is unknown.

367 **12.3 Pharmacokinetics**

368 Absorption: Following intranasal administration of fluticasone furoate, most of the dose
369 is eventually swallowed and undergoes incomplete absorption and extensive first-pass
370 metabolism in the liver and gut, resulting in negligible systemic exposure. At the highest
371 recommended intranasal dosage of 110 mcg once daily for up to 12 months in adults and up to
372 12 weeks in children, plasma concentrations of fluticasone furoate are typically not quantifiable
373 despite the use of a sensitive HPLC-MS/MS assay with a lower limit of quantification (LOQ) of
374 10 pg/mL. However, in a few isolated cases (<0.3%) fluticasone furoate was detected in high
375 concentrations above 500 pg/mL, and in a single case the concentration was as high as
376 1,430 pg/mL in the 52-week study. There was no relationship between these concentrations and
377 cortisol levels in these subjects. The reasons for these high concentrations are unknown.

378 Absolute bioavailability was evaluated in 16 male and female subjects following
379 supratherapeutic dosages of fluticasone furoate (880 mcg given intranasally at 8-hour intervals
380 for 10 doses, or 2,640 mcg/day). The average absolute bioavailability was 0.50% (90% CI:
381 0.34%, 0.74%).

382 Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic
383 data was obtained via other routes of administration. Studies using oral solution and intravenous
384 dosing of radiolabeled drug have demonstrated that at least 30% of fluticasone furoate is
385 absorbed and then rapidly cleared from plasma. Oral bioavailability is on average 1.26%, and the
386 majority of the circulating radioactivity is due to inactive metabolites.

387 Distribution: Following intravenous administration, the mean volume of distribution at
388 steady state is 608 L.

389 Binding of fluticasone furoate to human plasma proteins is greater than 99%.

390 Metabolism: In vivo studies have revealed no evidence of cleavage of the furoate moiety
391 to form fluticasone. Fluticasone furoate is cleared (total plasma clearance of 58.7 L/h) from
392 systemic circulation principally by hepatic metabolism via the cytochrome P450 isozyme
393 CYP3A4. The principal route of metabolism is hydrolysis of the S-fluoromethyl carbothioate
394 function to form the inactive 17 β -carboxylic acid metabolite.

395 Elimination: Fluticasone furoate and its metabolites are eliminated primarily in the feces,
396 accounting for approximately 101% and 90% of the orally and intravenously administered dose,
397 respectively. Urinary excretion accounted for approximately 1% and 2% of the orally and
398 intravenously administered dose, respectively. The elimination phase half-life averaged
399 15.1 hours following intravenous administration.

400 Population Pharmacokinetics: Fluticasone furoate is typically not quantifiable in
401 plasma following intranasal dosing of 110 mcg once daily with the exception of isolated cases of
402 very high plasma levels (see Absorption). Overall, quantifiable levels (>10 pg/mL) were
403 observed in <31% of patients aged 12 years and older and in <16% of children (aged 2 to
404 11 years) following intranasal dosing of 110 mcg once daily and in <7% of children following

405 intranasal dosing of 55 mcg once daily. There was no evidence to suggest that the presence or
406 absence of detectable levels of fluticasone furoate was related to gender, age, or race.

407 Hepatic Impairment: Reduced liver function may affect the elimination of
408 corticosteroids. Since fluticasone furoate undergoes extensive first-pass metabolism by the
409 hepatic cytochrome P450 isozyme CYP3A4, the pharmacokinetics of fluticasone furoate may be
410 altered in patients with hepatic impairment. A study of a single 400-mcg dose of orally inhaled
411 fluticasone furoate in patients with moderate hepatic impairment (Child-Pugh Class B) resulted
412 in increased C_{max} (42%) and $AUC_{(0-\infty)}$ (172%), resulting in an approximately 20% reduction in
413 serum cortisol level in patients with hepatic impairment compared to healthy subjects. The
414 systemic exposure would be expected to be higher than that observed had the study been
415 conducted after multiple doses and/or in patients with severe hepatic impairment. Therefore, use
416 VERAMYST Nasal Spray with caution in patients with severe hepatic impairment.

417 Renal Impairment: Fluticasone furoate is not detectable in urine from healthy subjects
418 following intranasal dosing. Less than 1% of dose-related material is excreted in urine. No
419 dosage adjustment is required in patients with renal impairment.

420 **13 NONCLINICAL TOXICOLOGY**

421 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

422 Fluticasone furoate produced no treatment-related increases in the incidence of tumors in
423 2-year inhalation studies in rats and mice at doses of up to 9 and 19 mcg/kg/day, respectively
424 (less than the maximum recommended daily intranasal dose in adults and children on a mcg/m^2
425 basis).

426 Fluticasone furoate did not induce gene mutation in bacteria or chromosomal damage in a
427 mammalian cell mutation test in mouse lymphoma L5178Y cells in vitro. There was also no
428 evidence of genotoxicity in the in vivo micronucleus test in rats.

429 No evidence of impairment of fertility was observed in reproductive studies conducted in
430 male and female rats at inhaled fluticasone furoate doses of up to 24 and 91 mcg/kg/day,
431 respectively (approximately 2 and 7 times, respectively, the maximum recommended daily
432 intranasal dose in adults on a mcg/m^2 basis).

433 **14 CLINICAL STUDIES**

434 **14.1 Seasonal and Perennial Allergic Rhinitis**

435 Adult and Adolescent Patients 12 Years of Age and Older: The efficacy and safety
436 of VERAMYST Nasal Spray was evaluated in 5 randomized, double-blind, parallel-group,
437 multicenter, placebo-controlled clinical trials of 2 to 4 weeks' duration in adult and adolescent
438 patients 12 years of age and older with symptoms of seasonal or perennial allergic rhinitis. The
439 5 clinical trials included one 2-week dose-ranging trial in patients with seasonal allergic rhinitis,
440 three 2-week confirmatory efficacy trials in patients with seasonal allergic rhinitis, and one
441 4-week efficacy trial in patients with perennial allergic rhinitis. These trials included
442 1,829 patients (697 males and 1,132 females). About 75% of patients were Caucasian, and the
443 mean age was 36 years. Of these patients, 722 received VERAMYST Nasal Spray 110 mcg once

444 daily administered as 2 sprays in each nostril.

445 Assessment of efficacy was based on total nasal symptom score (TNSS). TNSS is
446 calculated as the sum of the patients' scoring of the 4 individual nasal symptoms (rhinorrhea,
447 nasal congestion, sneezing, and nasal itching) on a 0 to 3 categorical severity scale (0 = absent,
448 1 = mild, 2 = moderate, 3 = severe) as reflective or instantaneous. Reflective TNSS (rTNSS)
449 required the patients to record symptom severity over the previous 12 hours; the instantaneous
450 TNSS (iTNSS) required patients to record symptom severity at the time immediately prior to the
451 next dose. Morning and evening rTNSS scores were averaged over the treatment period and the
452 difference from placebo in the change from baseline rTNSS was the primary efficacy endpoint.
453 The morning iTNSS (AM iTNSS) reflects the TNSS at the end of the 24-hour dosing interval
454 and is an indication of whether the effect was maintained over the 24-hour dosing interval.

455 Additional secondary efficacy variables were assessed, including the total ocular
456 symptom score (TOSS) and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).
457 TOSS is calculated as the sum of the patients' scoring of the 3 individual ocular symptoms
458 (itching/burning, tearing/watering, and redness) on a 0 to 3 categorical severity scale (0 = absent,
459 1 = mild, 2 = moderate, 3 = severe) as reflective or instantaneous scores. To assess efficacy,
460 rTOSS and AM iTOSS were evaluated as described above for the TNSS. Patients' perceptions of
461 disease-specific quality of life was evaluated through use of the RQLQ, which assesses the
462 impact of allergic rhinitis treatment through 28 items in 7 domains (activities, sleep,
463 non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional) on
464 a 7-point scale where 0 = no impairment and 6 = maximum impairment. An overall RQLQ score
465 is calculated from the mean of all items in the instrument. An absolute difference of ≥ 0.5 in
466 mean change from baseline over placebo is considered the minimally important difference (MID)
467 for the RQLQ.

468 *Dose-Ranging Trial:* The dose-ranging trial was a 2-week trial that evaluated the
469 efficacy of 4 dosages of fluticasone furoate nasal spray (440, 220, 110, and 55 mcg) in patients
470 with seasonal allergic rhinitis. In this trial, each of the 4 dosages of fluticasone furoate nasal
471 spray demonstrated greater decreases in the rTNSS than placebo, and the difference was
472 statistically significant (Table 3).

473

474 **Table 3. Mean Change From Baseline in Reflective Total Nasal Symptom Score Over**
 475 **2 Weeks in Patients With Seasonal Allergic Rhinitis**

Treatment	n	Baseline (AM + PM)	Change From Baseline	Difference From Placebo		
				LS Mean	95% CI	P value
Fluticasone furoate 440 mcg	130	9.6	-4.02	-2.19	-2.75, -1.62	<0.001
Fluticasone furoate 220 mcg	129	9.5	-3.19	-1.36	-1.93, -0.79	<0.001
Fluticasone furoate 110 mcg	127	9.5	-3.84	-2.01	-2.58, -1.44	<0.001
Fluticasone furoate 55 mcg	125	9.6	-3.50	-1.68	-2.25, -1.10	<0.001
Placebo	128	9.6	-1.83			

476
 477 Each of the 4 dosages of fluticasone furoate nasal spray also demonstrated greater
 478 decreases in the AM iTNSS than placebo, and the difference between each of the 4 fluticasone
 479 furoate treatment groups and placebo was statistically significant, indicating that the effect was
 480 maintained over the 24-hour dosing interval.

481 **Seasonal Allergic Rhinitis Trials:** Three clinical trials were designed to evaluate the
 482 efficacy of VERAMYST Nasal Spray 110 mcg once daily compared with placebo in patients
 483 with seasonal allergic rhinitis over a 2-week treatment period. In all 3 trials, VERAMYST Nasal
 484 Spray 110 mcg demonstrated a greater decrease from baseline in the rTNSS and AM iTNSS than
 485 placebo, and the difference from placebo was statistically significant. In terms of ocular
 486 symptoms, in all 3 seasonal allergic rhinitis trials, VERAMYST Nasal Spray 110 mcg
 487 demonstrated a greater decrease from baseline in the rTOSS than placebo and the difference
 488 from placebo was statistically significant. For the RQLQ in all 3 seasonal allergic rhinitis trials,
 489 VERAMYST Nasal Spray 110 mcg demonstrated greater decrease from baseline in the overall
 490 RQLQ than placebo, and the difference from placebo was statistically significant. The difference
 491 in the overall RQLQ score mean change from baseline between the groups treated with
 492 VERAMYST Nasal Spray and placebo ranged from -0.60 to -0.70 in the 3 trials, meeting the
 493 minimally important difference criterion. Table 4 displays the efficacy results from a
 494 representative trial in patients with seasonal allergic rhinitis.

495 **Perennial Allergic Rhinitis Trials:** One clinical trial was designed to evaluate the
 496 efficacy of VERAMYST Nasal Spray 110 mcg once daily compared to placebo in patients with
 497 perennial allergic rhinitis over a 4-week treatment period. VERAMYST Nasal Spray 110 mcg
 498 demonstrated a greater decrease from baseline in the rTNSS and AM iTNSS than placebo, and
 499 the difference from placebo was statistically significant. Similar to patients with seasonal allergic
 500 rhinitis, the improvement of nasal symptoms with VERAMYST Nasal Spray in patients with
 501 perennial allergic rhinitis persisted for a full 24 hours, as evaluated by AM iTNSS immediately
 502 prior to the next dose. However, unlike the trials in patients with seasonal allergic rhinitis,
 503 patients with perennial allergic rhinitis who were treated with VERAMYST Nasal Spray
 504 110 mcg did not demonstrate statistically significant improvement from baseline in total ocular
 505 symptom scores (rTOSS) or in disease-specific quality of life as measured by the RQLQ

506 compared with placebo. In addition, the overall RQLQ score mean change from baseline
 507 difference between the group treated with VERAMYST Nasal Spray and the placebo group was
 508 -0.23, which did not meet the minimally important difference of ≥ 0.5 . Table 4 displays the
 509 efficacy results from the clinical trial in patients with perennial allergic rhinitis.
 510

511 **Table 4. Mean Changes in Efficacy Variables in Adult and Adolescent Patients With**
 512 **Seasonal or Perennial Allergic Rhinitis**

Treatment	n	Baseline	Change From Baseline – LS Mean	Difference From Placebo		
				LS Mean	95% CI	P value
Reflective Total Nasal Symptom Scores						
Seasonal Allergic Rhinitis Trial						
Fluticasone furoate 110 mcg	151	9.6	-3.55	-1.47	-2.01, -0.94	<0.001
Placebo	147	9.9	-2.07			
Perennial Allergic Rhinitis Trial						
Fluticasone furoate 110 mcg	149	8.6	-2.78	-0.71	-1.20, -0.21	0.005
Placebo	153	8.7	-2.08			
Instantaneous Total Nasal Symptom Scores						
Seasonal Allergic Rhinitis Trial						
Fluticasone furoate 110 mcg	151	9.4	-2.90	-1.38	-1.90, -0.85	<0.001
Placebo	147	9.3	-1.53			
Perennial Allergic Rhinitis Trial						
Fluticasone furoate 110 mcg	149	8.2	-2.45	-0.71	-1.20, -0.21	0.006
Placebo	153	8.3	-1.75			
Reflective Total Ocular Symptom Scores						
Seasonal Allergic Rhinitis Trial						
Fluticasone furoate 110 mcg	151	6.6	-2.23	-0.60	-1.01, -0.19	0.004
Placebo	147	6.5	-1.63			
Perennial Allergic Rhinitis Trial						

Fluticasone furoate 110 mcg	149	4.8	-1.39	-0.15	-0.52, 0.22	0.428
Placebo	153	5.0	-1.24			
Rhinoconjunctivitis Quality of Life Questionnaire						
Seasonal Allergic Rhinitis Trial						
Fluticasone furoate 110 mcg	144	3.9	-1.77	-0.60	-0.93, -0.28	<0.001
Placebo	144	3.9	-1.16			
Perennial Allergic Rhinitis Trial						
Fluticasone furoate 110 mcg	143	3.5	-1.41	-0.23	-0.59, 0.13	0.214
Placebo	151	3.4	-1.18			

513

514 Onset of action was evaluated by frequent instantaneous TNSS assessments after the first
515 dose in the clinical trials in patients with seasonal allergic rhinitis and perennial allergic rhinitis.

516 Onset of action was generally observed within 24 hours in patients with seasonal allergic rhinitis.

517 In patients with perennial rhinitis, onset of action was observed after 4 days of treatment.

518 Continued improvement in symptoms was observed over approximately 1 and 3 weeks in
519 patients with seasonal or perennial allergic rhinitis, respectively.

520 Pediatric Patients 2 to 11 Years of Age: The efficacy and safety of VERAMYST

521 Nasal Spray were evaluated in 1,112 children (633 boys and 479 girls), mean age of 8 years with

522 seasonal or perennial allergic rhinitis in 2 controlled clinical trials. The pediatric patients were

523 treated with VERAMYST Nasal Spray 55 or 110 mcg once daily for 2 to 12 weeks (n = 369 for

524 each dose). The trials were similar in design to the trials conducted in adolescents and adults,

525 however, the efficacy determination was made from patient- or parent/guardian-reported TNSS

526 for children aged 6 to <12 years. Children treated with VERAMYST Nasal Spray generally

527 exhibited greater decreases in nasal symptoms than placebo-treated patients. In seasonal allergic

528 rhinitis, the difference in rTNSS was statistically significant only for the 110-mcg dose. In

529 perennial allergic rhinitis, the difference in rTNSS was statistically significant only for the 55

530 mcg dose. Changes in ocular symptoms scores (rTOSS) in the seasonal allergic rhinitis trial were

531 not statistically significant compared with placebo for either dose. rTOSS was not assessed in the

532 perennial allergic rhinitis trial. Table 5 displays the efficacy results from the clinical trials in

533 patients with perennial allergic rhinitis and seasonal allergic rhinitis in children 6 to <12 years of

534 age. Efficacy in children 2 to <6 years of age was supported by a numerical decrease in the

535 rTNSS.

536

537 **Table 5. Mean Changes in Efficacy Variables in Pediatric Patients 6 to <12 Years of Age**
538 **With Seasonal or Perennial Allergic Rhinitis**

Treatment	n	Baseline	Change From Baseline – LS Mean	Difference From Placebo		
				LS Mean	95% CI	P value
Reflective Total Nasal Symptom Scores						
Seasonal Allergic Rhinitis Trial						
Fluticasone furoate 55 mcg	151	8.6	-2.71	-0.16	-0.69, 0.37	0.553
Fluticasone furoate 110 mcg	146	8.5	-3.16	-0.62	-1.15, -0.08	0.025
Placebo	149	8.4	-2.54			
Perennial Allergic Rhinitis Trial						
Fluticasone furoate 55 mcg	144	8.5	-4.16	-0.75	-1.24, -0.27	0.003
Fluticasone furoate 110 mcg	140	8.6	-3.86	-0.45	-0.95, 0.04	0.073
Placebo	147	8.5	-3.41			
Instantaneous Total Nasal Symptom Scores						
Seasonal Allergic Rhinitis Trial						
Fluticasone furoate 55 mcg	151	8.4	-2.37	-0.23	-0.77, 0.30	0.389
Fluticasone furoate 110 mcg	146	8.3	-2.80	-0.67	-1.21, -0.13	0.015
Placebo	149	8.4	-2.13			
Perennial Allergic Rhinitis Trial						
Fluticasone furoate 55 mcg	144	8.3	-3.62	-0.75	-1.24, -0.27	0.002
Fluticasone furoate 110 mcg	140	8.3	-3.52	-0.65	-1.14, -0.16	0.009
Placebo	147	8.3	-2.87			
Reflective Total Ocular Symptom Scores						
Seasonal Allergic Rhinitis Trial						
Fluticasone furoate 55 mcg	151	4.4	-1.26	0.04	-0.33, 0.41	0.826

Fluticasone furoate 110 mcg	146	4.1	-1.45	-0.15	-0.52, 0.22	0.426
Placebo	149	3.8	-1.30			

539 **16 HOW SUPPLIED/STORAGE AND HANDLING**

540 VERAMYST Nasal Spray, 27.5 mcg per spray, is supplied in a brown glass bottle
541 enclosed in a nasal device with a nozzle and a mist-release button to actuate the spray in a box of
542 1 (NDC 0173-0753-00) with FDA-Approved Patient Labeling (see Patient Instructions for Use
543 for proper actuation of the device). Each bottle contains a net fill weight of 10 g of white, liquid
544 suspension and will provide 120 metered sprays. After priming [see *Dosage and Administration*
545 (2)], each spray delivers a fine mist containing 27.5 mcg of fluticasone furoate in 50 microliters
546 of formulation through the nozzle. The contents of the bottle can be viewed through an indicator
547 window. Shake the contents well before each use. The correct amount of medication in each
548 spray cannot be assured before the initial priming and after 120 sprays have been used, even
549 though the bottle is not completely empty. The nasal device should be discarded after 120 sprays
550 have been used.

551 **Store the device in the upright position with the cap in place between 15° and 30°C**
552 **(59° and 86°F). Do not freeze or refrigerate.**

553 **17 PATIENT COUNSELING INFORMATION**

554 See FDA-Approved Patient Labeling accompanying the product.

555 **17.1 Local Nasal Effects**

556 Patients should be informed that treatment with VERAMYST Nasal Spray may lead to
557 adverse reactions, which include epistaxis and nasal ulceration. *Candida* infection may also
558 occur with treatment with VERAMYST Nasal Spray. In addition, nasal corticosteroids are
559 associated with nasal septal perforation and impaired wound healing. Patients who have
560 experienced recent nasal ulcers, nasal surgery, or nasal trauma should not use VERAMYST
561 Nasal Spray until healing has occurred [see *Warnings and Precautions (5.1)*].

562 **17.2 Cataracts and Glaucoma**

563 Patients should be informed that glaucoma and cataracts are associated with nasal and
564 inhaled corticosteroid use. Patients should inform his/her health care provider if a change in
565 vision is noted while using VERAMYST Nasal Spray [see *Warnings and Precautions (5.2)*].

566 **17.3 Immunosuppression**

567 Patients who are on immunosuppressant doses of corticosteroids should be warned to
568 avoid exposure to chickenpox or measles and, if exposed, to consult their physician without
569 delay. Patients should be informed of potential worsening of existing tuberculosis, fungal,
570 bacterial, viral or parasitic infections, or ocular herpes simplex [see *Warnings and Precautions*
571 (5.3)].

572 **17.4 Use Daily for Best Effect**

573 Patients should use VERAMYST Nasal Spray on a regular once-daily basis for optimal

574 effect. VERAMYST Nasal Spray, like other corticosteroids, does not have an immediate effect
575 on rhinitis symptoms. Although significant improvement is usually achieved within 24 hours in
576 patients with seasonal allergic rhinitis and 4 days in patients with perennial allergic rhinitis,
577 maximum benefit may not be reached for several days. The patient should not increase the
578 prescribed dosage but should contact the physician if symptoms do not improve or if the
579 condition worsens.

580 **17.5 Keep Spray Out of Eyes**

581 Patients should be informed to avoid spraying VERAMYST Nasal Spray in their eyes.

582 **17.6 Potential Drug Interactions**

583 Patients should be advised that co-administration of VERAMYST Nasal Spray and
584 ritonavir is not recommended and to be cautious if co-administrating with ketoconazole.
585
586



587
588 GlaxoSmithKline
589 Research Triangle Park, NC 27709
590
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PATIENT INFORMATION

VERAMYST™ [*VAIR-uh-mist*] (fluticasone furoate) Nasal Spray

FOR INTRANASAL USE ONLY

Read the Patient Information that comes with VERAMYST Nasal Spray carefully before you start using it and each time you get a refill. There may be new information. Keep the leaflet for reference because it gives you a summary of important information about VERAMYST Nasal Spray. This leaflet does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is VERAMYST Nasal Spray?

VERAMYST is a medicine that treats seasonal and year-round allergy symptoms in adults and children 2 years old and older.

VERAMYST contains fluticasone furoate, which is a man-made (synthetic) corticosteroid. Corticosteroids are natural substances found in the body that reduce inflammation. When you spray VERAMYST into your nose, it helps reduce the nasal symptoms of allergic rhinitis (inflammation of the lining of the nose), such as stuffy nose, runny nose, itching, and sneezing. VERAMYST may also help red, itchy, and watery eyes in adults and teenagers with seasonal allergic rhinitis.

Your healthcare provider has prescribed VERAMYST to treat your symptoms of allergic rhinitis.

What should I tell my healthcare provider before taking VERAMYST Nasal Spray?

Tell your healthcare provider about all of your medical conditions, including if you are:

- pregnant (or planning to become pregnant).
- breastfeeding a baby.
- allergic to any of the ingredients in VERAMYST or any other nasal corticosteroid. See “**What are the ingredients in VERAMYST Nasal Spray?**” below for a complete list of ingredients.
- exposed to chickenpox or measles.
- feeling unwell or have any symptoms that you do not understand.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal products. VERAMYST and other medicines may affect each other, causing side effects. **Be certain to tell your healthcare provider if you are taking a medicine that contains ritonavir (commonly used to treat HIV infection or AIDS).**

How should I use VERAMYST Nasal Spray?

- 39 • This medicine is for use in the nose only. Do not spray it in your eyes or mouth.
- 40 • An adult should help a young child use this medicine.
- 41 • This medicine has been prescribed for you by your healthcare provider. DO NOT give
- 42 this medicine to anyone else.
- 43 • Use VERAMYST exactly as your healthcare provider tells you to. DO NOT take more of
- 44 your medicine or take it more often than your healthcare provider tells you. The
- 45 prescription label will usually tell you how many sprays to take and how often. If it does
- 46 not or if you are not sure, ask your healthcare provider or pharmacist.
- 47 • **For people aged 12 years and older**, the usual starting dosage is **2 sprays in each**
- 48 **nostril, once a day**. After you begin to feel better, your healthcare provider may tell you
- 49 that 1 spray in each nostril once a day may be enough for you.
- 50 • **For children aged 2 to 11 years**, the usual starting dosage is **1 spray in each nostril,**
- 51 **once a day**. Your healthcare provider may tell you to take 2 sprays in each nostril once a
- 52 day. After you begin to feel better, your healthcare provider may change the dosage to 1
- 53 spray in each nostril once a day. An adult should help a young child use this medicine.
- 54 • Do not use VERAMYST after 120 sprays (plus the initial priming sprays) have been used
- 55 or after the expiration date, whichever comes first. The bottle may not be completely
- 56 empty. The expiration date is printed as “EXP” on the product label and box. Before you
- 57 throw away VERAMYST, talk to your healthcare provider to see if you need a refill of
- 58 your prescription. If your healthcare provider tells you to continue using VERAMYST,
- 59 throw away the empty or expired bottle and use a new bottle of VERAMYST. Follow the
- 60 **Patient Instructions for Use** below.
- 61 • Do not take extra doses or stop taking VERAMYST without telling your healthcare
- 62 provider.
- 63 • VERAMYST may begin to work within 24 hours after you take your first dose. It may
- 64 take several days before it has its greatest effect.
- 65 • You will get the best results if you keep using VERAMYST regularly each day without
- 66 missing a dose. If you miss a dose by several hours, just take your next dose at the usual
- 67 time. DO NOT take an extra dose.

68 **What are the possible side effects of VERAMYST Nasal Spray?**

69 Some patients taking VERAMYST had nosebleeds or nasal sores. These are not all of the
70 possible side effects of VERAMYST. For more information, ask your healthcare provider or
71 pharmacist.

72 **What are other risks of using VERAMYST?**

- 73 • Some patients may get a nasal fungal infection. This happened in about 1 out of 1,000
- 74 patients in clinical studies with VERAMYST.
- 75 • Corticosteroids can slow the healing of wounds. Do not use VERAMYST until your nose
- 76 has healed if you have a sore in your nose, if you have surgery on your nose, or if your
- 77 nose has been injured.

- 78 • Some patients may have eye problems, including glaucoma and cataracts. You should
79 have regular eye exams.
- 80 • Immune system effects may increase the risk of infections.
- 81 • Corticosteroids may slow growth in children. A child taking VERAMYST should have
82 his/her growth checked regularly.

83 **What should I know about allergic rhinitis?**

84 “Rhinitis” means inflammation of the lining of the nose. It is sometimes called “hay fever.”
85 Allergic rhinitis can be caused by allergies to pollen, animal dander, house dust mite, and mold
86 spores. If you have allergic rhinitis, your nose becomes stuffy, runny, and itchy. You may also
87 sneeze a lot. You may also have red, itchy, watery eyes, and itchy throat, or blocked itchy ears.

88 **What are the ingredients in VERAMYST Nasal Spray?**

89 Active ingredient: fluticasone furoate.

90 Inactive ingredients: 0.015% w/w benzalkonium chloride, dextrose anhydrous, edetate
91 disodium, microcrystalline cellulose, carboxymethylcellulose, polysorbate 80, and purified
92 water.

93 **Patient Instructions for Use**

94 Read this leaflet carefully before you start to use VERAMYST Nasal Spray. If you have any
95 questions, ask your healthcare provider.


96 **The parts of the VERAMYST Nasal Spray**

97 VERAMYST Nasal Spray comes in a brown glass bottle inside a nasal device.

	<p>The Cap has a tab that keeps the Mist-Release Button from being pressed accidentally. It also helps keep the nozzle clean. Do not throw the cap away. Always keep the cap on the device when you are not using it.</p> <p>The Nozzle is small and short, so it will fit inside your nose. The medicine comes out of the nozzle.</p> <p>Pressing the Mist-Release Button sprays a measured amount of medicine from the nozzle as a gentle, fine mist. Because the button is on the side of the device, you can keep the nozzle in the right place in your nose while you press the button.</p> <p>The Window lets you see if there is medicine left in the bottle.</p>
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98 **How to prime your VERAMYST Nasal Spray**

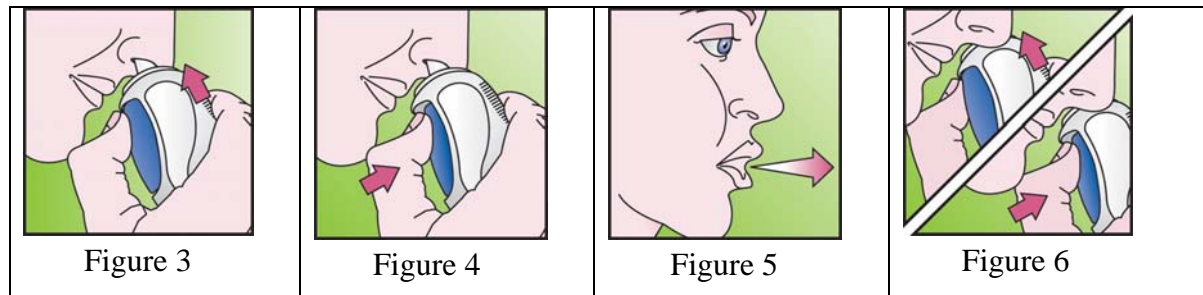
	<p>You need to prime VERAMYST Nasal Spray:</p> <ul style="list-style-type: none"> • Before you use a new bottle for the first time. • If you have not used your VERAMYST Nasal Spray for 30 days or longer. • If the cap has been left off the bottle for 5 days or longer.
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<p>Figure 1</p>  <p>Figure 2</p>	<p>Priming helps to make sure you always get the same full dose of medicine. To prime VERAMYST Nasal Spray:</p> <ol style="list-style-type: none"> 1. With the cap on, shake the device well. 2. Take the cap off by squeezing the finger grips and pulling it straight off (Figure 1). Do not press the button while you take off the cap. 3. Hold the device with the nozzle pointing up and away from you. Place your thumb on the button. Then firmly press and release the button 6 times or until a fine mist is sprayed from the nozzle (Figure 2). Your VERAMYST Nasal Spray is now ready to use. <p>VERAMYST Nasal Spray comes in a glass bottle. Be careful not to drop it. If you accidentally drop the device, check it for damage. If the device is damaged, return it to your pharmacist.</p>
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99 **How to use your VERAMYST Nasal Spray**

100 Follow the instructions below. If you have any questions, ask your healthcare provider or
101 pharmacist.

102 Before taking a dose of VERAMYST Nasal Spray, gently blow your nose to clear your nostrils.
103 Then do these 3 simple steps: **Place, Press, Repeat.**



104 **1. PLACE**

105 Tilt your head forward a little bit. Hold the device upright. **PLACE** the nozzle in one of your
106 nostrils (Figure 3).

107 Point the end of the nozzle toward the side of your nose, away from the center of your nose
108 (septum). This helps get the medicine to the right part of your nose.

109 **2. PRESS**

110 **Firmly PRESS** the button 1 time to spray the medicine in your nose while you are breathing
111 in (Figure 4).

112 **Do not get any spray in your eyes.** If you do, rinse your eyes well with water.

113 Take the nozzle out of your nose. Breathe out through your mouth (Figure 5).



114 **3. REPEAT**

115 To deliver the medicine to the other nostril, **REPEAT** Steps 1 and 2 in the other nostril
116 (Figure 6).

117 If your healthcare provider has told you to take 2 sprays in each nostril, do Steps 1-3 again.

118 Put the cap back on the device after you have finished taking your dose.

119 **How to clean your VERAMYST Nasal Spray**

		<p>After each use: wipe the nozzle with a clean, dry tissue (Figure 7). <u>Never</u> try to clean the nozzle with a pin or anything sharp because this may damage the nozzle.</p> <p>Once a week: clean the inside of the cap with a clean, dry tissue (Figure 8). This will help keep the nozzle from getting blocked.</p>
Figure 7	Figure 8	

120 **How to store your VERAMYST Nasal Spray**

- 121 • Keep your VERAMYST Nasal Spray and all medicines **out of the reach of children.**
- 122 • Store between 59° and 86°F (15° and 30°C). Do not refrigerate or freeze.
- 123 • Store with the cap on.
- 124 • Store in an upright position.

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126



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