

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

Hypersensitivity to ingredients. (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)
- Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and

urticaria, may occur after administration of VERAMYST Nasal Spray. (5.3)

- 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. (5.4)
- 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. (5.5)
- Potential reduction in growth velocity in children. Monitor growth routinely in pediatric patients receiving VERAMYST Nasal Spray. (5.7, 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 cytochrome P450 3A4 (CYP3A4) may increase exposure to fluticasone furoate.
- Coadministration of ritonavir is not recommended. (5.6, 7)
- Use caution with coadministration of other potent CYP3A4 inhibitors, such as ketoconazole. (5.6, 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.

Revised: 10/2011

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

3 1.1 Treatment of Allergic Rhinitis

4 VERAMYST® (fluticasone furoate) Nasal Spray is indicated for the treatment of the
5 symptoms of seasonal and perennial allergic rhinitis in patients aged 2 years 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 sprays
9 into the air away from the face. When VERAMYST Nasal Spray has not been used for more
10 than 30 days or if the cap has been left off the bottle for 5 days or longer, prime the pump again
11 until a fine mist appears. Shake VERAMYST Nasal Spray well before each use.

12 **2.1 Adults and Adolescents Aged 12 Years 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 Aged 2 to 11 Years**

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 VERAMYST Nasal Spray is contraindicated in patients with hypersensitivity to any of its
28 ingredients [*see Warnings and Precautions (5.3)*].

29 **5 WARNINGS AND PRECAUTIONS**

30 **5.1 Local Nasal Effects**

31 Epistaxis and Nasal Ulceration: In clinical studies of 2 to 52 weeks' duration, epistaxis
32 and nasal ulcerations were observed more frequently and some epistaxis events were more
33 severe in patients treated with VERAMYST Nasal Spray than those who received placebo [*see*
34 *Adverse Reactions (6.1)*].

35 Candida Infection: Evidence of localized infections of the nose with *Candida albicans*
36 was seen on nasal exams in 7 of 2,745 patients treated with VERAMYST Nasal Spray during
37 clinical trials and was reported as an adverse event in 3 patients. When such an infection
38 develops, it may require treatment with appropriate local therapy and discontinuation of
39 VERAMYST Nasal Spray. Therefore, patients using VERAMYST Nasal Spray over several
40 months or longer should be examined periodically for evidence of *Candida* infection or other

41 signs of adverse effects on the nasal mucosa.

42 **Nasal Septal Perforation:** Postmarketing cases of nasal septal perforation have been
43 reported in patients following the intranasal application of VERAMYST Nasal Spray [*see*
44 *Adverse Reactions (6.2)*].

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

48 **5.2 Glaucoma and Cataracts**

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

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

64 **5.3 Hypersensitivity Reactions, Including Anaphylaxis**

65 Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria, may
66 occur after administration of VERAMYST Nasal Spray. Discontinue VERAMYST Nasal Spray
67 if such reactions occur [*see Contraindications (4)*].

68 **5.4 Immunosuppression**

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

81 Corticosteroids should be used with caution, if at all, in patients with active or quiescent
82 tuberculous infections of the respiratory tract, untreated local or systemic fungal or bacterial
83 infections, systemic viral or parasitic infections, or ocular herpes simplex because of the
84 potential for worsening of these infections.

85 **5.5 Hypothalamic-Pituitary-Adrenal Axis Effects**

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

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

99 **5.6 Use of Cytochrome P450 3A4 Inhibitors**

100 Coadministration with ritonavir is not recommended because of the risk of systemic
101 effects secondary to increased exposure to fluticasone furoate. Use caution with the
102 coadministration of VERAMYST Nasal Spray and other potent cytochrome P450 3A4
103 (CYP3A4) inhibitors, such as ketoconazole [*see Drug Interactions (7)*].

104 **5.7 Effect on Growth**

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

110 **6 ADVERSE REACTIONS**

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

- 112 • Epistaxis, ulcerations, *Candida albicans* infection, impaired wound healing, and nasal septal
113 perforation [*see Warnings and Precautions (5.1)*]
- 114 • Cataracts and glaucoma [*see Warnings and Precautions (5.2)*]
- 115 • Immunosuppression [*see Warnings and Precautions (5.4)*]
- 116 • Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction [*see*
117 *Warnings and Precautions (5.5), Use in Specific Populations (8.4)*]

118 **6.1 Clinical Trials Experience**

119 The safety data described below reflect exposure to VERAMYST Nasal Spray in 1,563

120 patients with seasonal or perennial allergic rhinitis in 9 controlled clinical trials of 2 to 12 weeks’
 121 duration. The data from adults and adolescents are based upon 6 clinical trials in which
 122 768 patients with seasonal or perennial allergic rhinitis (473 females and 295 males aged
 123 12 years and older) were treated with VERAMYST Nasal Spray 110 mcg once daily for 2 to
 124 6 weeks. The racial distribution of adult and adolescent patients receiving VERAMYST Nasal
 125 Spray was 82% white, 5% black, and 13% other. The data from pediatric patients are based upon
 126 3 clinical trials in which 795 children with seasonal or perennial rhinitis (352 females and 443
 127 males aged 2 to 11 years) were treated with VERAMYST Nasal Spray 55 or 110 mcg once daily
 128 for 2 to 12 weeks. The racial distribution of pediatric patients receiving VERAMYST Nasal
 129 Spray was 75% white, 11% black, and 14% other.

130 Because clinical trials are conducted under widely varying conditions, adverse reaction
 131 rates observed in the clinical trials of a drug cannot be directly compared with rates in the
 132 clinical trials of another drug and may not reflect the rates observed in practice.

133 Adults and Adolescents Aged 12 Years and Older: Overall adverse reactions were
 134 reported with approximately the same frequency by patients treated with VERAMYST Nasal
 135 Spray and those receiving placebo. Less than 3% of patients in clinical trials discontinued
 136 treatment because of adverse reactions. The rate of withdrawal among patients receiving
 137 VERAMYST Nasal Spray was similar or lower than the rate among patients receiving placebo.

138 Table 1 displays the common adverse reactions (>1% in any patient group receiving
 139 VERAMYST Nasal Spray) that occurred more frequently in patients aged 12 years and older
 140 treated with VERAMYST Nasal Spray compared with placebo-treated patients.

141

142 **Table 1. Adverse Reactions With >1% Incidence in Controlled Clinical Trials of**
 143 **2 to 6 Weeks’ Duration With VERAMYST Nasal Spray in Adult and Adolescent**
 144 **Patients With Seasonal or Perennial Allergic Rhinitis**

| Adverse Event | Adult and Adolescent Patients Aged 12 Years 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%) |
| Pharyngolaryngeal pain | 8 (1%) | 15 (2%) |
| Nasal ulceration | 3 (<1%) | 11 (1%) |
| Back pain | 7 (<1%) | 9 (1%) |

145

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

149 Pediatric Patients Aged 2 to 11 Years: In the 3 clinical trials in pediatric patients aged

150 2 to <12 years, overall adverse reactions were reported with approximately the same frequency
 151 by patients treated with VERAMYST Nasal Spray and those receiving placebo. Table 2 displays
 152 the common adverse reactions (>3% in any patient group receiving VERAMYST Nasal Spray),
 153 that occurred more frequently in patients aged 2 to 11 years treated with VERAMYST Nasal
 154 Spray compared with placebo-treated patients.

155

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

| Adverse Event | Pediatric Patients Aged 2 to <12 Years | | |
|------------------------|--|---|--|
| | 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%) |
| Pharyngolaryngeal pain | 14 (3%) | 16 (4%) | 12 (3%) |
| Cough | 12 (3%) | 12 (3%) | 16 (4%) |

159

160 There were no differences in the incidence of adverse reactions based on gender or race.
 161 Pyrexia occurred more frequently in children aged 2 to <6 years compared with children aged 6
 162 to <12 years.

163 Long-Term (52-Week) Safety Trial: In a 52-week, placebo-controlled, long-term safety
 164 trial, 605 patients (307 females and 298 males aged 12 years and older) with perennial allergic
 165 rhinitis were treated with VERAMYST Nasal Spray 110 mcg once daily for 12 months and 201
 166 were treated with placebo nasal spray. While most adverse reactions were similar in type and rate
 167 between the treatment groups, epistaxis occurred more frequently in patients who received
 168 VERAMYST Nasal Spray (123/605, 20%) than in patients who received placebo (17/201, 8%).
 169 Epistaxis tended to be more severe in patients treated with VERAMYST Nasal Spray. All 17
 170 reports of epistaxis that occurred in patients who received placebo were of mild intensity, while
 171 83, 39, and 1 of the total 123 epistaxis events in patients treated with VERAMYST Nasal Spray
 172 were of mild, moderate, and severe intensity, respectively. No patient experienced a nasal septal
 173 perforation during this trial.

174 **6.2 Postmarketing Experience**

175 In addition to adverse reactions reported from clinical trials, the following adverse
 176 reactions have been identified during postmarketing use of VERAMYST Nasal Spray. Because
 177 these reactions are reported voluntarily from a population of uncertain size, it is not always
 178 possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

179 These events have been chosen for inclusion due to either their seriousness, frequency of
180 reporting, or causal connection to fluticasone furoate or a combination of these factors.

181 Immune System Disorders: Hypersensitivity reactions, including anaphylaxis,
182 angioedema, rash, and urticaria.

183 Respiratory, Thoracic, and Mediastinal Disorders: Rhinalgia, nasal discomfort
184 (including nasal burning, nasal irritation, and nasal soreness), nasal dryness, and nasal septal
185 perforation.

186 **7 DRUG INTERACTIONS**

187 Fluticasone furoate is cleared by extensive first-pass metabolism mediated by CYP3A4.
188 In a drug interaction study of intranasal fluticasone furoate and the CYP3A4 inhibitor
189 ketoconazole given as a 200-mg once-daily dose for 7 days, 6 of 20 subjects receiving
190 fluticasone furoate and ketoconazole had measurable but low levels of fluticasone furoate
191 compared with 1 of 20 receiving fluticasone furoate and placebo. Based on this study and the
192 low systemic exposure, there was a 5% reduction in 24-hour serum cortisol levels with
193 ketoconazole compared with placebo. The data from this study should be carefully interpreted
194 because the study was conducted with ketoconazole 200 mg once daily rather than 400 mg,
195 which is the maximum recommended dosage. Therefore, caution is required with the
196 coadministration of VERAMYST Nasal Spray and ketoconazole or other potent CYP3A4
197 inhibitors.

198 Based on data with another glucocorticoid, fluticasone propionate, metabolized by
199 CYP3A4, coadministration of VERAMYST Nasal Spray with the potent CYP3A4 inhibitor
200 ritonavir is not recommended because of the risk of systemic effects secondary to increased
201 exposure to fluticasone furoate. High exposure to corticosteroids increases the potential for
202 systemic side effects, such as cortisol suppression.

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

206 **8 USE IN SPECIFIC POPULATIONS**

207 **8.1 Pregnancy**

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

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

216 There are no adequate and well-controlled studies in pregnant women. VERAMYST
217 Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential

218 risk to the fetus.

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

221 **8.3 Nursing Mothers**

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

226 **8.4 Pediatric Use**

227 Controlled clinical trials with VERAMYST Nasal Spray included 1,224 patients aged 2
228 to 11 years and 344 adolescent patients aged 12 to 17 years [see *Clinical Studies (14)*]. The
229 safety and effectiveness of VERAMYST Nasal Spray in children younger than 2 years have not
230 been established.

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

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

246 **8.5 Geriatric Use**

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

253 **8.6 Hepatic Impairment**

254 Use VERAMYST Nasal Spray with caution in patients with severe hepatic impairment
255 [see *Clinical Pharmacology (12.3)*].

256 **8.7 Renal Impairment**

257 No dosage adjustment is required in patients with renal impairment [see *Clinical*

258 *Pharmacology (12.3)].*

259 **10 OVERDOSAGE**

260 Chronic overdosage may result in signs/symptoms of hypercorticism [*see Warnings and*
261 *Precautions (5.4)].* There are no data on the effects of acute or chronic overdosage with
262 VERAMYST Nasal Spray. Because of low systemic bioavailability and an absence of acute
263 drug-related systemic findings in clinical studies (with dosages of up to 440 mcg/day for 2 weeks
264 [4 times the maximum recommended daily dose]), overdose is unlikely to require any therapy
265 other than observation.

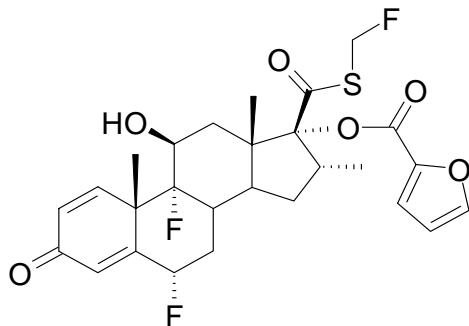
266 Intranasal administration of up to 2,640 mcg/day (24 times the recommended adult dose)
267 of fluticasone furoate was administered to healthy human volunteers for 3 days. Single- and
268 repeat-dose studies with orally inhaled fluticasone furoate doses of 50 to 4,000 mcg have shown
269 decreased mean serum cortisol at doses of 500 mcg or higher. The oral median lethal dose in
270 mice and rats was >2,000 mg/kg (approximately 74,000 and 147,000 times, respectively, the
271 maximum recommended daily intranasal dose in adults and 52,000 and 105,000 times,
272 respectively, the maximum recommended daily intranasal dose in children, on a mcg/m² basis).

273 Acute overdosage with the intranasal dosage form is unlikely since 1 bottle of
274 VERAMYST Nasal Spray contains approximately 3 mg of fluticasone furoate, and the
275 bioavailability of fluticasone furoate is <1% for 2.64 mg/day given intranasally and 1% for
276 2 mg/day given as an oral solution.

277 **11 DESCRIPTION**

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

282



283

284

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

287 VERAMYST Nasal Spray is an aqueous suspension of micronized fluticasone furoate for
288 topical administration to the nasal mucosa by means of a metering (50 microliters), atomizing
289 spray pump. After initial priming [*see Dosage and Administration (2)*], each actuation delivers

290 27.5 mcg of fluticasone furoate in a volume of 50 microliters of nasal spray suspension.
291 VERAMYST Nasal Spray also contains 0.015% w/w benzalkonium chloride, dextrose
292 anhydrous, edetate disodium, microcrystalline cellulose and carboxymethylcellulose sodium,
293 polysorbate 80, and purified water. It has a pH of approximately 6.

294 **12 CLINICAL PHARMACOLOGY**

295 **12.1 Mechanism of Action**

296 Fluticasone furoate is a synthetic trifluorinated corticosteroid with potent anti-
297 inflammatory activity. The precise mechanism through which fluticasone furoate affects rhinitis
298 symptoms is not known. Corticosteroids have been shown to have a wide range of actions on
299 multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and
300 mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation.
301 Specific effects of fluticasone furoate demonstrated in in vitro and in vivo models included
302 activation of the glucocorticoid response element, inhibition of pro-inflammatory transcription
303 factors such as NFκB, and inhibition of antigen-induced lung eosinophilia in sensitized rats.

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

307 **12.2 Pharmacodynamics**

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

316 *Clinical Trials Specifically Designed to Assess Hypothalamic-Pituitary-Adrenal*
317 *Axis Effect:* In a 6-week randomized, double-blind, parallel-group study in adult and adolescent
318 patients aged 12 years and older with perennial allergic rhinitis, VERAMYST Nasal Spray 110
319 mcg was compared with both placebo nasal spray and prednisone as a positive-control group that
320 received prednisone 10 mg orally once daily for the final 7 days of the treatment period. Adrenal
321 function was assessed by 24-hour urinary cortisol excretion before and after 6 weeks of treatment
322 and by serial serum cortisol levels. Patients were domiciled for collection of 24-hour urinary
323 cortisol. After 6 weeks of treatment, there was a change from baseline in the mean 24-hour
324 urinary cortisol excretion in the group treated with VERAMYST Nasal Spray (n = 43) of -1.16
325 mcg/day compared with -3.48 mcg/day in the placebo group (n = 42). The difference from
326 placebo in the group treated with VERAMYST Nasal Spray was 2.32 mcg/day (95% CI: -6.76,
327 11.39). Urinary cortisol data were not available for the positive-control (prednisone) treatment
328 group. For serum cortisol levels, after 6 weeks of treatment there was a change from baseline in

329 the mean (0-24 hours) of -0.38 and 0.08 mcg/dL for the group treated with VERAMYST Nasal
330 Spray (n = 43) and the placebo group (n = 44), respectively, with a difference between the group
331 treated with VERAMYST Nasal Spray and the placebo group of -0.47 mcg/dL (95% CI: -1.31,
332 0.37). For comparison, in the positive-control (prednisone, n = 12) treatment group, there was a
333 change in mean serum cortisol (0-24 hours) from baseline of -4.49 mcg/dL with a difference
334 between the prednisone and placebo group of -4.57 mcg/dL (95% CI: -5.83, -3.31).

335 The second 6-week study conducted in children aged 2 to 11 years was of similar design
336 to the adult study, including adrenal function assessments, but did not include a prednisone
337 positive-control arm. Patients were treated once daily with VERAMYST Nasal Spray 110 mcg
338 or placebo nasal spray. After 6 weeks of treatment, there was a change in the mean 24-hour
339 urinary cortisol excretion in the group treated with VERAMYST Nasal Spray (n = 43) of
340 0.49 mcg/day compared with 1.92 mcg/day in the placebo group (n = 41), with a difference
341 between the group treated with VERAMYST Nasal Spray and the placebo group of
342 -1.43 mcg/day (95% CI: -5.21, 2.35). For serum cortisol levels, after 6 weeks, there was a change
343 from baseline in mean (0-24 hours) of -0.34 and -0.23 mcg/dL for the group treated with
344 VERAMYST Nasal Spray (n = 48) and for the placebo group (n = 47), respectively, with a
345 difference between the group treated with VERAMYST Nasal Spray and the placebo group of
346 -0.11 mcg/dL (95% CI: -0.88, 0.66).

347 Additional Hypothalamic-Pituitary-Adrenal Axis Assessments: In the 52-week
348 safety trial in adolescents and adults aged 12 years and older with perennial allergic rhinitis,
349 VERAMYST Nasal Spray 110 mcg (n = 605) was compared with placebo nasal spray (n = 201).
350 Adrenal function was assessed by 24-hour urinary cortisol excretion in a subset of patients who
351 received VERAMYST Nasal Spray (n = 370) or placebo (n = 120) before and after 52 weeks of
352 treatment. After 52 weeks of treatment, the mean change from baseline 24-hour urinary cortisol
353 excretion was 5.84 mcg/day in the group treated with VERAMYST Nasal Spray and
354 3.34 mcg/day in the placebo group. The difference from placebo in mean change from baseline
355 24-hour urinary cortisol excretion was 2.50 mcg/day (95% CI: -5.49, 10.49).

356 In the 12-week safety and efficacy trial in children aged 2 to 11 years with perennial
357 allergic rhinitis, VERAMYST Nasal Spray 55 mcg (n = 185) and VERAMYST Nasal Spray
358 110 mcg (n = 185) were compared with placebo nasal spray (n = 188). Adrenal function was
359 assessed by measurement of 24-hour urinary free cortisol in a subset of patients who were aged 6
360 to 11 years (103 to 109 patients per group) before and after 12 weeks of treatment. After
361 12 weeks of treatment, there was a decrease in mean 24-hour urinary cortisol excretion from
362 baseline in the group treated with VERAMYST Nasal Spray 55 mcg (n = 109) of -2.93 mcg/day
363 and in the group treated with VERAMYST Nasal Spray 110 mcg (n = 103) of -2.07 mcg/day
364 compared with an increase in the placebo group (n = 107) of 0.08 mcg/day. The difference from
365 placebo in mean change from baseline in 24-hour urinary cortisol excretion for the group treated
366 with VERAMYST Nasal Spray 55 mcg was -3.01 mcg/day (95% CI: -6.16, 0.13) and
367 -2.14 mcg/day (95% CI: -5.33, 1.04) for the group treated with VERAMYST Nasal Spray
368 110 mcg.

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

372 **Cardiac Effects:** A QT/QTc study did not demonstrate an effect of fluticasone furoate
373 administration on the QTc interval. The effect of a single dose of 4,000 mcg of orally inhaled
374 fluticasone furoate on the QTc interval was evaluated over 24 hours in 40 healthy male and
375 female subjects in a placebo and positive (a single dose of 400 mg oral moxifloxacin) controlled
376 cross-over study. The QTcF maximal mean change from baseline following fluticasone furoate
377 was similar to that observed with placebo with a treatment difference of 0.788 msec (90% CI:
378 -1.802, 3.378). In contrast, moxifloxacin given as a 400-mg tablet resulted in prolongation of the
379 QTcF maximal mean change from baseline compared with placebo with a treatment difference
380 of 9.929 msec (90% CI: 7.339, 12.520). While a single dose of fluticasone furoate had no effect
381 on the QTc interval, the effects of fluticasone furoate may not be at steady state following single
382 dose. The effect of fluticasone furoate on the QTc interval following multiple dose
383 administration is unknown.

384 **12.3 Pharmacokinetics**

385 **Absorption:** Following intranasal administration of fluticasone furoate, most of the dose
386 is eventually swallowed and undergoes incomplete absorption and extensive first-pass
387 metabolism in the liver and gut, resulting in negligible systemic exposure. At the highest
388 recommended intranasal dosage of 110 mcg once daily for up to 12 months in adults and up to
389 12 weeks in children, plasma concentrations of fluticasone furoate are typically not quantifiable
390 despite the use of a sensitive HPLC-MS/MS assay with a lower limit of quantification (LOQ) of
391 10 pg/mL. However, in a few isolated cases (<0.3%) fluticasone furoate was detected in high
392 concentrations above 500 pg/mL, and in a single case the concentration was as high as
393 1,430 pg/mL in the 52-week study. There was no relationship between these concentrations and
394 cortisol levels in these subjects. The reasons for these high concentrations are unknown.

395 Absolute bioavailability was evaluated in 16 male and female subjects following
396 supratherapeutic dosages of fluticasone furoate (880 mcg given intranasally at 8-hour intervals
397 for 10 doses, or 2,640 mcg/day). The average absolute bioavailability was 0.50% (90% CI:
398 0.34%, 0.74%).

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

404 **Distribution:** Following intravenous administration, the mean volume of distribution at
405 steady state is 608 L.

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

407 **Metabolism:** In vivo studies have revealed no evidence of cleavage of the furoate moiety
408 to form fluticasone. Fluticasone furoate is cleared (total plasma clearance of 58.7 L/h) from

409 systemic circulation principally by hepatic metabolism via CYP3A4. The principal route of
410 metabolism is hydrolysis of the S-fluoromethyl carbothioate function to form the inactive
411 17 β -carboxylic acid metabolite.

412 Elimination: Fluticasone furoate and its metabolites are eliminated primarily in the feces,
413 accounting for approximately 101% and 90% of the orally and intravenously administered dose,
414 respectively. Urinary excretion accounted for approximately 1% and 2% of the orally and
415 intravenously administered dose, respectively. The elimination phase half-life averaged
416 15.1 hours following intravenous administration.

417 Population Pharmacokinetics: Fluticasone furoate is typically not quantifiable in
418 plasma following intranasal dosing of 110 mcg once daily with the exception of isolated cases of
419 very high plasma levels (see Absorption). Overall, quantifiable levels (>10 pg/mL) were
420 observed in <31% of patients aged 12 years and older and in <16% of children (aged 2 to
421 11 years) following intranasal dosing of 110 mcg once daily and in <7% of children following
422 intranasal dosing of 55 mcg once daily. There was no evidence to suggest that the presence or
423 absence of detectable levels of fluticasone furoate was related to gender, age, or race.

424 Hepatic Impairment: Reduced liver function may affect the elimination of
425 corticosteroids. Since fluticasone furoate undergoes extensive first-pass metabolism by the
426 hepatic CYP3A4, the pharmacokinetics of fluticasone furoate may be altered in patients with
427 hepatic impairment. A study of a single 400-mcg dose of orally inhaled fluticasone furoate in
428 patients with moderate hepatic impairment (Child-Pugh Class B) resulted in increased C_{max}
429 (42%) and AUC_(0- ∞) (172%), resulting in an approximately 20% reduction in serum cortisol level
430 in patients with hepatic impairment compared with healthy subjects. The systemic exposure
431 would be expected to be higher than that observed had the study been conducted after multiple
432 doses and/or in patients with severe hepatic impairment. Therefore, use VERAMYST Nasal
433 Spray with caution in patients with severe hepatic impairment.

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

437 **13 NONCLINICAL TOXICOLOGY**

438 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

439 Fluticasone furoate produced no treatment-related increases in the incidence of tumors in
440 2-year inhalation studies in rats and mice at doses of up to 9 and 19 mcg/kg/day, respectively
441 (less than the maximum recommended daily intranasal dose in adults and children on a mcg/m²
442 basis).

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

446 No evidence of impairment of fertility was observed in reproductive studies conducted in
447 male and female rats at inhaled fluticasone furoate doses of up to 24 and 91 mcg/kg/day,

448 respectively (approximately 2 and 7 times, respectively, the maximum recommended daily
449 intranasal dose in adults on a mcg/m² basis).

450 **14 CLINICAL STUDIES**

451 **14.1 Seasonal and Perennial Allergic Rhinitis**

452 Adult and Adolescent Patients Aged 12 Years and Older: The efficacy and safety of
453 VERAMYST Nasal Spray was evaluated in 5 randomized, double-blind, parallel-group,
454 multicenter, placebo-controlled clinical trials of 2 to 4 weeks' duration in adult and adolescent
455 patients aged 12 years and older with symptoms of seasonal or perennial allergic rhinitis. The 5
456 clinical trials included one 2-week dose-ranging trial in patients with seasonal allergic rhinitis,
457 three 2-week confirmatory efficacy trials in patients with seasonal allergic rhinitis, and one
458 4-week efficacy trial in patients with perennial allergic rhinitis. These trials included 1,829
459 patients (697 males and 1,132 females). About 75% of patients were Caucasian, and the mean
460 age was 36 years. Of these patients, 722 received VERAMYST Nasal Spray 110 mcg once daily
461 administered as 2 sprays in each nostril.

462 Assessment of efficacy was based on total nasal symptom score (TNSS). TNSS is
463 calculated as the sum of the patients' scoring of the 4 individual nasal symptoms (rhinorrhea,
464 nasal congestion, sneezing, and nasal itching) on a 0 to 3 categorical severity scale (0 = absent,
465 1 = mild, 2 = moderate, 3 = severe) as reflective (rTNSS) or instantaneous (iTNSS). rTNSS
466 required the patients to record symptom severity over the previous 12 hours; iTNSS required
467 patients to record symptom severity at the time immediately prior to the next dose. Morning and
468 evening rTNSS scores were averaged over the treatment period and the difference from placebo
469 in the change from baseline rTNSS was the primary efficacy endpoint. The morning iTNSS (AM
470 iTNSS) reflects the TNSS at the end of the 24-hour dosing interval and is an indication of
471 whether the effect was maintained over the 24-hour dosing interval.

472 Additional secondary efficacy variables were assessed, including the total ocular
473 symptom score (TOSS) and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).
474 TOSS is calculated as the sum of the patients' scoring of the 3 individual ocular symptoms
475 (itching/burning, tearing/watering, and redness) on a 0 to 3 categorical severity scale (0 = absent,
476 1 = mild, 2 = moderate, 3 = severe) as reflective (rTOSS) or instantaneous scores (iTOSS). To
477 assess efficacy, rTOSS and AM iTOSS were evaluated as described above for the TNSS.
478 Patients' perceptions of disease-specific quality of life were evaluated through use of the RQLQ,
479 which assesses the impact of allergic rhinitis treatment through 28 items in 7 domains (activities,
480 sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and
481 emotional) on a 7-point scale where 0 = no impairment and 6 = maximum impairment. An
482 overall RQLQ score is calculated from the mean of all items in the instrument. An absolute
483 difference of ≥ 0.5 in mean change from baseline over placebo is considered the minimally
484 important difference (MID) for the RQLQ.

485 *Dose-Ranging Trial:* The dose-ranging trial was a 2-week trial that evaluated the
486 efficacy of 4 dosages of fluticasone furoate nasal spray (440, 220, 110, and 55 mcg) in patients

487 with seasonal allergic rhinitis. In this trial, each of the 4 dosages of fluticasone furoate nasal
 488 spray demonstrated greater decreases in the rTNSS than placebo, and the difference was
 489 statistically significant (Table 3).

490

491 **Table 3. Mean Change From Baseline in Reflective Total Nasal Symptom Score Over 2**
 492 **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 | | | |

493

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

498 *Seasonal Allergic Rhinitis Trials:* Three clinical trials were designed to evaluate the
 499 efficacy of VERAMYST Nasal Spray 110 mcg once daily compared with placebo in patients
 500 with seasonal allergic rhinitis over a 2-week treatment period. In all 3 trials, VERAMYST Nasal
 501 Spray 110 mcg demonstrated a greater decrease from baseline in the rTNSS and AM iTNSS than
 502 placebo, and the difference from placebo was statistically significant. In terms of ocular
 503 symptoms, in all 3 seasonal allergic rhinitis trials, VERAMYST Nasal Spray 110 mcg
 504 demonstrated a greater decrease from baseline in the rTOSS than placebo and the difference
 505 from placebo was statistically significant. For the RQLQ in all 3 seasonal allergic rhinitis trials,
 506 VERAMYST Nasal Spray 110 mcg demonstrated greater decrease from baseline in the overall
 507 RQLQ than placebo, and the difference from placebo was statistically significant. The difference
 508 in the overall RQLQ score mean change from baseline between the groups treated with
 509 VERAMYST Nasal Spray and placebo ranged from -0.60 to -0.70 in the 3 trials, meeting the
 510 minimally important difference criterion. Table 4 displays the efficacy results from a
 511 representative trial in patients with seasonal allergic rhinitis.

512 *Perennial Allergic Rhinitis Trials:* One clinical trial was designed to evaluate the
 513 efficacy of VERAMYST Nasal Spray 110 mcg once daily compared with placebo in patients
 514 with perennial allergic rhinitis over a 4-week treatment period. VERAMYST Nasal Spray
 515 110 mcg demonstrated a greater decrease from baseline in the rTNSS and AM iTNSS than
 516 placebo, and the difference from placebo was statistically significant. Similar to patients with
 517 seasonal allergic rhinitis, the improvement of nasal symptoms with VERAMYST Nasal Spray in
 518 patients with perennial allergic rhinitis persisted for a full 24 hours, as evaluated by AM iTNSS

519 immediately prior to the next dose. However, unlike the trials in patients with seasonal allergic
 520 rhinitis, patients with perennial allergic rhinitis who were treated with VERAMYST Nasal Spray
 521 110 mcg did not demonstrate statistically significant improvement from baseline in rTOSS or in
 522 disease-specific quality of life as measured by the RQLQ compared with placebo. In addition,
 523 the overall RQLQ score mean change from baseline difference between the group treated with
 524 VERAMYST Nasal Spray and the placebo group was -0.23, which did not meet the minimally
 525 important difference of ≥ 0.5 . Table 4 displays the efficacy results from the clinical trial in
 526 patients with perennial allergic rhinitis.

527

528 **Table 4. Mean Changes in Efficacy Variables in Adult and Adolescent Patients With**
 529 **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 | 151 | 6.6 | -2.23 | -0.60 | -1.01, -0.19 | 0.004 |

| | | | | | | |
|--|-----|-----|-------|-------|--------------|--------|
| furoate 110 mcg 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 | | | |

530

531 Onset of action was evaluated by frequent instantaneous TNSS assessments after the first
532 dose in the clinical trials in patients with seasonal allergic rhinitis and perennial allergic rhinitis.
533 Onset of action was generally observed within 24 hours in patients with seasonal allergic rhinitis.
534 In patients with perennial rhinitis, onset of action was observed after 4 days of treatment.
535 Continued improvement in symptoms was observed over approximately 1 and 3 weeks in
536 patients with seasonal or perennial allergic rhinitis, respectively.

537 **Pediatric Patients Aged 2 to 11 Years:** The efficacy and safety of VERAMYST Nasal
538 Spray were evaluated in 1,112 children (633 boys and 479 girls), mean age of 8 years with
539 seasonal or perennial allergic rhinitis in 2 controlled clinical trials. The pediatric patients were
540 treated with VERAMYST Nasal Spray 55 or 110 mcg once daily for 2 to 12 weeks (n = 369 for
541 each dose). The trials were similar in design to the trials conducted in adolescents and adults;
542 however, the efficacy determination was made from patient- or parent/guardian-reported TNSS
543 for children aged 6 to <12 years. Children treated with VERAMYST Nasal Spray generally
544 exhibited greater decreases in nasal symptoms than placebo-treated patients. In seasonal allergic
545 rhinitis, the difference in rTNSS was statistically significant only for the 110-mcg dose. In
546 perennial allergic rhinitis, the difference in rTNSS was statistically significant only for the
547 55-mcg dose. Changes in rTOSS in the seasonal allergic rhinitis trial were not statistically
548 significant compared with placebo for either dose. rTOSS was not assessed in the perennial
549 allergic rhinitis trial. Table 5 displays the efficacy results from the clinical trials in patients with
550 perennial allergic rhinitis and seasonal allergic rhinitis in children aged 6 to <12 years. Efficacy
551 in children aged 2 to <6 years was supported by a numerical decrease in the rTNSS.

552
553
554

Table 5. Mean Changes in Efficacy Variables in Pediatric Patients Aged 6 to <12 Years 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 | 151 | 4.4 | -1.26 | 0.04 | -0.33, 0.41 | 0.826 |

| | | | | | | |
|-----------------|-----|-----|-------|-------|-------------|-------|
| furoate 55 mcg | | | | | | |
| Fluticasone | 146 | 4.1 | -1.45 | -0.15 | -0.52, 0.22 | 0.426 |
| furoate 110 mcg | | | | | | |
| Placebo | 149 | 3.8 | -1.30 | | | |

555 **16 HOW SUPPLIED/STORAGE AND HANDLING**

556 VERAMYST Nasal Spray, 27.5 mcg per spray, is supplied in a brown glass bottle
557 enclosed in a nasal device with a nozzle and a mist-release button to actuate the spray in a box of
558 1 (NDC 0173-0753-00) with FDA-Approved Patient Labeling (see Patient Instructions for Use
559 for proper actuation of the device). Each bottle contains a net fill weight of 10 g of white, liquid
560 suspension and will provide 120 metered sprays. After priming [see *Dosage and Administration*
561 (2)], each spray delivers a fine mist containing 27.5 mcg of fluticasone furoate in 50 microliters
562 of formulation through the nozzle. The contents of the bottle can be viewed through an indicator
563 window. Shake the contents well before each use. The correct amount of medication in each
564 spray cannot be assured before the initial priming and after 120 sprays have been used, even
565 though the bottle is not completely empty. The nasal device should be discarded after 120 sprays
566 have been used.

567 **Store the device in the upright position with the cap in place between 15° and 30°C**
568 **(59° and 86°F). Do not freeze or refrigerate.**

569 **17 PATIENT COUNSELING INFORMATION**

570 See FDA-Approved Patient Labeling.

571 **17.1 Local Nasal Effects**

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

578 **17.2 Cataracts and Glaucoma**

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

582 **17.3 Hypersensitivity Reactions, Including Anaphylaxis**

583 Patients should be aware that hypersensitivity reactions, including anaphylaxis,
584 angioedema, rash, and urticaria, may occur after administration of VERAMYST Nasal Spray. If
585 such reactions occur, patients should discontinue use of VERAMYST Nasal Spray [see
586 *Warnings and Precautions (5.3)*].

587 **17.4 Immunosuppression**

588 Patients who are on immunosuppressant doses of corticosteroids should be warned to

589 avoid exposure to chickenpox or measles and, if exposed, to consult their physician without
590 delay. Patients should be informed of potential worsening of existing tuberculosis, fungal,
591 bacterial, viral or parasitic infections, or ocular herpes simplex [see *Warnings and Precautions*
592 (5.4)].

593 **17.5 Use Daily for Best Effect**

594 Patients should use VERAMYST Nasal Spray on a regular once-daily basis for optimal
595 effect. VERAMYST Nasal Spray, like other corticosteroids, does not have an immediate effect
596 on rhinitis symptoms. Although significant improvement is usually achieved within 24 hours in
597 patients with seasonal allergic rhinitis and 4 days in patients with perennial allergic rhinitis,
598 maximum benefit may not be reached for several days. The patient should not increase the
599 prescribed dosage but should contact the physician if symptoms do not improve or if the
600 condition worsens.

601 **17.6 Keep Spray Out of Eyes**

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

603 **17.7 Potential Drug Interactions**

604 Patients should be advised that coadministration of VERAMYST Nasal Spray and
605 ritonavir is not recommended and to be cautious if coadministrating with ketoconazole.
606
607



608 **GlaxoSmithKline**

608

609 GlaxoSmithKline

610 Research Triangle Park, NC 27709

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