

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**DYMISTA (azelastine hydrochloride and fluticasone propionate) Nasal Spray**

Initial U.S. Approval: 2012

### INDICATIONS AND USAGE

Dymista Nasal Spray, containing an H<sub>1</sub>-receptor antagonist and a corticosteroid, is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief. (1.1)

### DOSAGE AND ADMINISTRATION

- For intranasal use only. (2.1)
- Recommended dose is 1 spray per nostril twice daily in adults and adolescents 12 years of age and older (2.1)
- Prime before initial use and when it has not been used for 14 or more days. (2.2)

### DOSAGE FORMS AND STRENGTHS

Dymista Nasal Spray: 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate (137 mcg/50 mcg) in each 0.137 mL spray. (3)

### CONTRAINDICATIONS

None.

### WARNINGS AND PRECAUTIONS

- Somnolence: Avoid engaging in hazardous occupations requiring complete mental alertness such as driving or operating machinery when taking Dymista Nasal Spray. (5.1)
- Avoid concurrent use of alcohol or other central nervous system (CNS) depressants with Dymista Nasal Spray because further decreased alertness and impairment of CNS performance may occur. (5.1)

- Epistaxis, nasal ulcerations, nasal septal perforation, impaired wound healing, *Candida albicans* infection. 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. (5.2)
- 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. (5.3)
- 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 Dymista Nasal Spray slowly. (5.5)
- Potential reduction in growth velocity in children. Monitor growth routinely in pediatric patients receiving Dymista Nasal Spray. (5.7, 8.4)

### ADVERSE REACTIONS

The most common adverse reactions (≥2% incidence) are: dysgeusia, epistaxis, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Meda Pharmaceuticals Inc. at 1-888-939-6478 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Potent inhibitors of cytochrome P450 (CYP) 3A4: May increase blood levels of fluticasone propionate.
- Ritanovir: Coadministration is not recommended. (5.6, 7.2)
- Other potent CYP3A4 inhibitors, such as ketoconazole: use caution with coadministration. (5.6, 7.2)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 4/2012

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\*Sections or subsections omitted from the full prescribing information are not listed.

1 FULL PRESCRIBING INFORMATION

2 **1 INDICATIONS AND USAGE**

3 Dymista Nasal Spray is indicated for the relief of symptoms of seasonal allergic rhinitis in  
4 patients 12 years of age and older who require treatment with both azelastine hydrochloride and  
5 fluticasone propionate for symptomatic relief.

6 **2 DOSAGE AND ADMINISTRATION**

7 **2.1 Dosing Information**

8 The recommended dose of Dymista Nasal Spray, 137 mcg/50 mcg, is 1 spray per nostril twice  
9 daily for seasonal allergic rhinitis. Each spray contains 137 mcg of azelastine hydrochloride and  
10 50 mcg of fluticasone propionate (137 mcg/50 mcg).

11

12 Administer Dymista Nasal Spray by the intranasal route only.

13

14 **2.2 Important Administration Instructions**

15 Shake the bottle gently before each use.

16 Priming: Prime Dymista Nasal Spray before initial use by releasing 6 sprays or until a fine mist  
17 appears. When Dymista Nasal Spray has not been used for 14 or more days, reprime with 1 spray  
18 or until a fine mist appears. Avoid spraying Dymista Nasal Spray into the eyes. If sprayed in the  
19 eyes, flush eyes with water for at least 10 minutes.

20 **3 DOSAGE FORMS AND STRENGTHS**

21 Dymista is a nasal spray suspension. Each spray delivers a volume of 0.137 mL suspension  
22 containing 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate (137  
23 mcg/50 mcg).

24 **4 CONTRAINDICATIONS**

25 None.

26 **5 WARNINGS AND PRECAUTIONS**

27 **5.1 Somnolence**

28 In clinical trials, the occurrence of somnolence has been reported in some patients (6 of 853  
29 patients) taking Dymista Nasal Spray [*see Adverse Reactions (6.1)*]. Patients should be cautioned  
30 against engaging in hazardous occupations requiring complete mental alertness and motor

31 coordination such as operating machinery or driving a motor vehicle after administration of  
32 Dymista Nasal Spray. Concurrent use of Dymista Nasal Spray with alcohol or other central  
33 nervous system depressants should be avoided because additional reductions in alertness and  
34 additional impairment of central nervous system performance may occur [*see Drug Interactions*  
35 (7.1)].

## 36 **5.2 Local Nasal Effects**

37 In clinical trials of 2 to 52 weeks' duration, epistaxis was observed more frequently in patients  
38 treated with Dymista Nasal Spray than those who received placebo [*see Adverse Reactions (6)*].

39 Instances of nasal ulceration and nasal septal perforation have been reported in patients  
40 following the intranasal application of corticosteroids. There were no instances of nasal  
41 ulceration or nasal septal perforation observed in clinical trials with Dymista Nasal Spray.

42 Because of the inhibitory effect of corticosteroids on wound healing, patients who have  
43 experienced recent nasal ulcers, nasal surgery, or nasal trauma should not use Dymista Nasal  
44 Spray until healing has occurred.

45 In clinical trials with fluticasone propionate administered intranasally, the development of  
46 localized infections of the nose and pharynx with *Candida albicans* has occurred. When such an  
47 infection develops, it may require treatment with appropriate local therapy and discontinuation of  
48 treatment with Dymista Nasal Spray. Patients using Dymista Nasal Spray over several months  
49 or longer should be examined periodically for evidence of *Candida* infection or other signs of  
50 adverse effects on the nasal mucosa.

## 51 **5.3 Glaucoma and Cataracts**

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

55 Glaucoma and cataract formation were evaluated with intraocular pressure measurements and slit  
56 lamp examinations in a controlled 12-month study in 612 adolescent and adult patients aged 12  
57 years and older with perennial allergic or vasomotor rhinitis (VMR). Of the 612 patients enrolled  
58 in the study, 405 were randomized to receive Dymista Nasal Spray (1 spray per nostril twice  
59 daily) and 207 were randomized to receive fluticasone propionate nasal spray (2 sprays per  
60 nostril once daily). In the Dymista Nasal Spray group, one patient had increased intraocular  
61 pressure at month 6. In addition, three patients had evidence of posterior subcapsular cataract at  
62 month 6 and one at month 12 (end of treatment). In the fluticasone propionate group, three  
63 patients had evidence of posterior subcapsular cataract at month 12 (end of treatment).

## 64 **5.4 Immunosuppression**

65 Persons who are using drugs, such as corticosteroids, that suppress the immune system are more  
66 susceptible to infections than healthy individuals. Chickenpox and measles, for example, can  
67 have a more serious or even fatal course in susceptible children or adults using corticosteroids. In  
68 children or adults who have not had these diseases or been properly immunized, particular care  
69 should be taken to avoid exposure. How the dose, route, and duration of corticosteroid  
70 administration affect the risk of developing a disseminated infection is not known. The

71 contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not  
72 known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG)  
73 may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin  
74 (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing  
75 information.) If chickenpox develops, treatment 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 **5.5 Hypothalamic-Pituitary-Adrenal (HPA) Axis Effects**

81 When intranasal steroids are used at higher than recommended dosages or in susceptible  
82 individuals at recommended dosages, systemic corticosteroid effects such as hypercorticism and  
83 adrenal suppression may appear. If such changes occur, the dosage of Dymista Nasal Spray  
84 should be discontinued slowly, consistent with accepted procedures for discontinuing oral  
85 corticosteroid therapy. The concomitant use of intranasal corticosteroids with other inhaled  
86 corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or  
87 suppression of the HPA axis.

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

## 96 **5.6 Use of Cytochrome P450 3A4 Inhibitors**

97 Ritonavir and other strong cytochrome P450 3A4 (CYP3A4) inhibitors can significantly increase  
98 plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol  
99 concentrations [*see Drug Interactions (7.2) and Clinical Pharmacology (12.3)*]. During  
100 postmarketing use, there have been reports of clinically significant drug interactions in patients  
101 receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects  
102 including Cushing syndrome and adrenal suppression. Therefore, coadministration of Dymista  
103 Nasal Spray and ritonavir is not recommended unless the potential benefit to the patient  
104 outweighs the risk of systemic corticosteroid side effects.

105 Use caution with the coadministration of Dymista Nasal Spray and other potent CYP3A4  
106 inhibitors, such as ketoconazole [*see Drug Interactions (7.2) and Clinical Pharmacology (12.3)*].

## 107 **5.7 Effect on Growth**

108 Corticosteroids may cause a reduction in growth velocity when administered to pediatric  
109 patients. Monitor the growth routinely of pediatric patients receiving Dymista Nasal Spray [*see*  
110 *Use in Specific Populations (8.4)*].

111 **6 ADVERSE REACTIONS**

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

- 113 • Somnolence [*see Warnings and Precautions (5.1)*]
- 114 • Local nasal effects, including epistaxis, nasal ulceration, nasal septal perforation,  
115 impaired wound healing, and *Candida albicans* infection [*see Warnings and*  
116 *Precautions (5.2)*]
- 117 • Cataracts and glaucoma [*see Warnings and Precautions (5.3)*]
- 118 • Immunosuppression [*see Warnings and Precautions (5.4)*]
- 119 • Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction [*see*  
120 *Warnings and Precautions (5.5 and 5.7), Use in Specific Populations (8.4)*]

121 **6.1 Clinical Trials Experience**

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

125 The safety data described below reflect exposure to Dymista Nasal Spray in 853 patients (12  
126 years of age and older; 36% male and 64% female) with seasonal allergic rhinitis in 3 double-  
127 blind, placebo-controlled clinical trials of 2-week duration. The racial distribution for the 3  
128 clinical trials was 80% white, 16% black, 2% Asian, and 1% other. In the 12-month open-label,  
129 active-controlled clinical trial, 404 Asian patients (240 males and 164 females) with perennial  
130 allergic rhinitis or vasomotor rhinitis were treated with Dymista Nasal Spray, 1 spray per nostril  
131 twice daily.

132 Adults and Adolescents 12 Years of Age and Older

133 In the 3 placebo controlled clinical trials of 2-week duration, 3411 patients with seasonal allergic  
134 rhinitis were treated with 1 spray per nostril of Dymista Nasal Spray, azelastine hydrochloride  
135 nasal spray, fluticasone propionate nasal spray, or placebo, twice daily. The azelastine  
136 hydrochloride and fluticasone propionate comparators use the same vehicle and device as  
137 Dymista Nasal Spray and are not commercially marketed. Overall, adverse reactions were 16%  
138 in the Dymista Nasal Spray treatment groups, 15% in the azelastine hydrochloride nasal spray  
139 groups, 13% in the fluticasone propionate nasal spray groups, and 12% in the placebo groups.  
140 Overall, 1% of patients in both the Dymista Nasal Spray and placebo groups discontinued due to  
141 adverse reactions.

142 Table 1 contains adverse reactions reported with frequencies greater than or equal to 2% and  
143 more frequently than placebo in patients treated with Dymista Nasal Spray in the seasonal  
144 allergic rhinitis controlled clinical trials.

145  
146

**Table 1. Adverse Reactions with  $\geq 2\%$  Incidence and More Frequently than Placebo in Placebo-Controlled Trials of 2 Weeks Duration with Dymista Nasal Spray in Adult and Adolescent Patients With Seasonal Allergic Rhinitis**

	1 spray per nostril twice daily			
	Dymista Nasal Spray (N=853)*	Azelastine Hydrochloride Nasal Spray <sup>†</sup> (N=851)	Fluticasone Propionate Nasal Spray <sup>†</sup> (N=846)	Vehicle Placebo (N=861)
Dysgeusia	30(4%)	44(5%)	4(1%)	2(<1%)
Headache	18(2%)	20(2%)	20(2%)	10(1%)
Epistaxis	16(2%)	14(2%)	14(2%)	15(2%)

147 \*Safety population N=853, intent-to-treat population N=848

148 <sup>†</sup> Not commercially marketed

149 In the above trials, somnolence was reported in <1% of patients treated with Dymista Nasal  
150 Spray (6 of 853) or vehicle placebo (1 of 861) [*see Warnings and Precautions (5.1)*].

151

#### 152 Long-Term (12-Month) Safety Trial:

153 In the 12-month, open-label, active-controlled, long-term safety trial, 404 patients (12 years of  
154 age and older) with perennial allergic rhinitis or vasomotor rhinitis were treated with Dymista  
155 Nasal Spray 1 spray per nostril twice daily and 207 patients were treated with fluticasone  
156 propionate nasal spray, 2 sprays per nostril once daily. Overall, adverse reactions were 47% in  
157 the Dymista Nasal Spray treatment group and 44% in the fluticasone propionate nasal spray  
158 group. The most frequently reported adverse reactions ( $\geq 2\%$ ) with Dymista Nasal Spray were  
159 headache, pyrexia, cough, nasal congestion, rhinitis, dysgeusia, viral infection, upper respiratory  
160 tract infection, pharyngitis, pain, diarrhea, and epistaxis. In the Dymista Nasal Spray treatment  
161 group, 7 patients (2%) had mild epistaxis and 1 patient (<1%) had moderate epistaxis. In the  
162 fluticasone propionate nasal spray treatment group 1 patient (<1%) had mild epistaxis. No  
163 patients had reports of severe epistaxis. Focused nasal examinations were performed and no  
164 nasal ulcerations or septal perforations were observed. Eleven of 404 patients (3%) treated with  
165 Dymista Nasal Spray and 6 of 207 patients (3%) treated with fluticasone propionate nasal spray  
166 discontinued from the trial due to adverse events.

167

## 168 **6.2 Postmarketing Experience**

169 Because these reactions are reported voluntarily from a population of uncertain size, it is not  
170 always possible to reliably estimate their frequency or establish a causal relationship to drug  
171 exposure.

172 The following spontaneous adverse events have been reported during the marketing of azelastine  
173 hydrochloride nasal spray and causal relationship with the drug is unknown: anaphylactoid  
174 reaction, application site irritation, atrial fibrillation, chest pain, confusion, dyspnea, facial  
175 edema, involuntary muscle contractions, nasal sores, palpitations, paresthesia, parosmia, pruritus,

176 rash, disturbance or loss of sense of smell and/or taste, tolerance, urinary retention, vision  
177 abnormal and xerophthalmia.

178 In addition, the following events have been identified during post-approval use of fluticasone  
179 propionate nasal spray. These events have been chosen for inclusion due to either their  
180 seriousness, frequency of reporting, or causal connection to fluticasone propionate or a  
181 combination of these factors.

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

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

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

190 Cases of growth suppression have been reported for intranasal corticosteroids, including  
191 fluticasone propionate [*see Use in Specific Populations (8.4)*].

## 192 **7 DRUG INTERACTIONS**

193 No formal drug interaction studies have been performed with Dymista Nasal Spray. The drug  
194 interactions of the combination are expected to reflect those of the individual components.

### 195 **7.1 Central Nervous System Depressants**

196 Concurrent use of Dymista Nasal Spray with alcohol or other central nervous system depressants  
197 should be avoided because somnolence and impairment of central nervous system performance  
198 may occur [*see Warnings and Precautions (5.1)*].

### 199 **7.2 Cytochrome P450 3A4**

200 Ritonavir (a strong CYP3A4 inhibitor) significantly increased plasma fluticasone propionate  
201 exposure following administration of fluticasone propionate aqueous nasal spray, resulting in  
202 significantly reduced serum cortisol concentrations [*see Clinical Pharmacology (12.3)*]. During  
203 postmarketing use, there have been reports of clinically significant drug interactions in patients  
204 receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects  
205 including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone  
206 propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs  
207 the risk of systemic corticosteroid side effects.

208 Ketoconazole (also a strong CYP3A4 inhibitor), administered in multiple 200 mg doses to  
209 steady-state, increased plasma exposure of fluticasone propionate, reduced plasma cortisol AUC,  
210 but had no effect on urinary excretion of cortisol, following administration of a single 1000 mcg  
211 dose of fluticasone propionate by oral inhalation route.

212 Caution should be exercised when Dymista Nasal Spray is coadministered with ketoconazole and  
213 other known strong CYP3A4 inhibitors.

## 214 8 USE IN SPECIFIC POPULATIONS

### 215 8.1 Pregnancy

#### 216 **Dymista Nasal Spray: Teratogenic Effects: Pregnancy Category C:**

217 There are no adequate and well-controlled clinical trials of Dymista Nasal Spray, azelastine  
218 hydrochloride only, or fluticasone propionate only in pregnant women. Animal reproductive  
219 studies of azelastine hydrochloride and fluticasone propionate in mice, rats, and/or rabbits  
220 revealed evidence of teratogenicity as well as other developmental toxic effects. Because animal  
221 reproduction studies are not always predictive of human response, Dymista Nasal Spray should  
222 be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

223 **Azelastine hydrochloride: Teratogenic Effects:** In mice, azelastine hydrochloride caused  
224 embryo-fetal death, malformations (cleft palate; short or absent tail; fused, absent or branched  
225 ribs), delayed ossification, and decreased fetal weight at an oral dose approximately 610 times  
226 the maximum recommended human daily intranasal dose (MRHDID) in adults (on a mg/m<sup>2</sup> basis  
227 at a maternal dose of 68.6 mg/kg). This dose also caused maternal toxicity as evidenced by  
228 decreased body weight. Neither fetal nor maternal effects occurred at a dose that was  
229 approximately 26 times the MRHDID (on a mg/m<sup>2</sup> basis at a maternal dose of 3 mg/kg).

230 In rats, azelastine hydrochloride caused malformations (oligo- and brachydactylia), delayed  
231 ossification and skeletal variations, in the absence of maternal toxicity, at an oral dose  
232 approximately 530 times the MRHDID in adults (on a mg/m<sup>2</sup> basis at a maternal dose of 30  
233 mg/kg). At a dose approximately 1200 times the MRHDID (on a mg/m<sup>2</sup> basis at a maternal dose  
234 of 68.6 mg/kg), azelastine hydrochloride also caused embryo-fetal death and decreased fetal  
235 weight; however, this dose caused severe maternal toxicity. Neither fetal nor maternal effects  
236 occurred at a dose approximately 53 times the MRHDID (on a mg/m<sup>2</sup> basis at a maternal dose of  
237 3 mg/kg).

238 In rabbits, azelastine hydrochloride caused abortion, delayed ossification, and decreased fetal  
239 weight at oral doses approximately 1100 times the MRHDID in adults (on a mg/m<sup>2</sup> basis at a  
240 maternal dose of 30 mg/kg); however, these doses also resulted in severe maternal toxicity.  
241 Neither fetal nor maternal effects occurred at a dose approximately 11 times the MRHDID (on a  
242 mg/m<sup>2</sup> basis at a maternal dose of 0.3 mg/kg).

243 **Fluticasone propionate: Teratogenic Effects:** Corticosteroids have been shown to be  
244 teratogenic in laboratory animals when administered systemically at relatively low dosage levels.  
245 Subcutaneous studies in the mouse and rat at doses approximately equivalent to and 4 times,  
246 respectively, the MRHDID in adults (on a mcg/m<sup>2</sup> basis at maternal doses of 45 and 100 mcg/kg,  
247 respectively), revealed fetal toxicity characteristic of potent corticosteroid compounds, including  
248 embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

249 In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose less  
250 than the MRHDID in adults (on a mcg/m<sup>2</sup> basis at a maternal dose of 4 mcg/kg). However, no  
251 teratogenic effects were reported at oral doses up to approximately 25 times the MRHDID in  
252 adults (on a mcg/m<sup>2</sup> basis at a maternal dose of 300 mcg/kg) of fluticasone propionate to the  
253 rabbit. No fluticasone propionate was detected in the plasma in this study, consistent with the  
254 established low bioavailability following oral administration [*see Clinical Pharmacology (12.3)*].



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

260 **Nonteratogenic Effects:** Fluticasone propionate crossed the placenta following oral  
261 administration of approximately 4 and 25 times the MRHDID in adults (on a mcg/m<sup>2</sup> basis at  
262 maternal doses of 100 mcg/kg and 300 mcg/kg to rats and rabbits, respectively).

### 263 **8.3 Nursing Mothers**

264 **Dymista Nasal Spray:** It is not known whether Dymista Nasal Spray is excreted in human  
265 breast milk. Because many drugs are excreted in human milk, caution should be exercised when  
266 Dymista Nasal Spray is administered to a nursing woman. Since there are no data from well-  
267 controlled human studies on the use of Dymista Nasal Spray by nursing mothers, based on data  
268 from the individual components, a decision should be made whether to discontinue nursing or to  
269 discontinue Dymista Nasal Spray, taking into account the importance of Dymista Nasal Spray to  
270 the mother.

271 **Azelastine hydrochloride:** It is not known if azelastine hydrochloride is excreted in human  
272 milk.

273 **Fluticasone propionate:** It is not known if fluticasone propionate is excreted in human milk.  
274 However, other corticosteroids are excreted in human milk. Subcutaneous administration to  
275 lactating rats of 10 mcg/kg of tritiated fluticasone propionate (less than the maximum  
276 recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis) resulted in measurable  
277 radioactivity in the milk.

### 278 **8.4 Pediatric Use**

279 Safety and effectiveness of Dymista Nasal Spray in pediatric patients below the age of 12 years  
280 have not been established.

281 Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in  
282 growth velocity in pediatric patients. This effect has been observed in the absence of laboratory  
283 evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator  
284 of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA  
285 axis function. The long-term effects of this reduction in growth velocity associated with  
286 intranasal corticosteroids, including the impact on final adult height, are unknown. The potential  
287 for “catch-up” growth following discontinuation of treatment with intranasal corticosteroids has  
288 not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids,  
289 including Dymista Nasal Spray, should be monitored routinely (e.g., via stadiometry). The  
290 potential growth effects of prolonged treatment should be weighed against the clinical benefits  
291 obtained and the risks/benefits of treatment alternatives.

### 292 **8.5 Geriatric Use**

293 Clinical trials of Dymista Nasal Spray did not include sufficient numbers of patients 65 years of  
294 age and older to determine whether they respond differently from younger patients. Other

295 reported clinical experience has not identified differences in responses between the elderly and  
296 younger patients. In general, dose selection for an elderly patient should be cautious, usually  
297 starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic,  
298 renal, or cardiac function, and of concomitant disease or other drug therapy.

## 299 **10 OVERDOSAGE**

300 **Dymista Nasal Spray:** Dymista Nasal Spray contains both azelastine hydrochloride and  
301 fluticasone propionate; therefore, the risks associated with overdosage for the individual  
302 components described below apply to Dymista Nasal Spray.

303 **Azelastine hydrochloride:** There have been no reported overdosages with azelastine  
304 hydrochloride. Acute azelastine hydrochloride overdosage by adults with this dosage form is  
305 unlikely to result in clinically significant adverse events, other than increased somnolence, since  
306 one (1) 23 g bottle of Dymista Nasal Spray contains approximately 23 mg of azelastine  
307 hydrochloride. Clinical trials in adults with single doses of the oral formulation of azelastine  
308 hydrochloride (up to 16 mg) have not resulted in increased incidence of serious adverse events.  
309 General supportive measures should be employed if overdosage occurs. There is no known  
310 antidote to Dymista Nasal Spray. Oral ingestion of antihistamines has the potential to cause  
311 serious adverse effects in children. Accordingly, Dymista Nasal Spray should be kept out of the  
312 reach of children

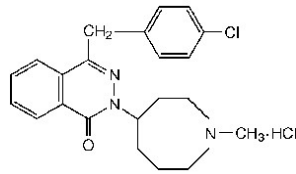
313 **Fluticasone propionate:** Chronic fluticasone propionate overdosage may result in  
314 signs/symptoms of hypercorticism [*see Warnings and Precautions (5.2)*]. Intranasal  
315 administration of 2 mg (10 times the recommended dose) of fluticasone propionate twice daily  
316 for 7 days to healthy human volunteers was well tolerated. Single oral fluticasone propionate  
317 doses up to 16 mg have been studied in human volunteers with no acute toxic effects reported.  
318 Repeat oral doses up to 80 mg daily for 10 days in volunteers and repeat oral doses up to 10 mg  
319 daily for 14 days in patients were well tolerated. Adverse reactions were of mild or moderate  
320 severity, and incidences were similar in active and placebo treatment groups. Acute overdosage  
321 with this dosage form is unlikely since one (1) 23 g bottle of Dymista Nasal Spray contains  
322 approximately 8.5 mg of fluticasone propionate.

## 323 **11 DESCRIPTION**

324 Dymista (azelastine hydrochloride and fluticasone propionate) Nasal Spray is formulated as a  
325 white, uniform metered-spray suspension for intranasal administration. It is a fixed dose  
326 combination product containing an antihistamine (H<sub>1</sub> receptor antagonist) and a corticosteroid as  
327 active ingredients.

328 Azelastine hydrochloride active ingredient occurs as a white, odorless, crystalline powder with a  
329 bitter taste. It has a molecular weight of 418.37. It is sparingly soluble in water, methanol, and  
330 propylene glycol and slightly soluble in ethanol, octanol, and glycerin. It has a melting point of  
331 225°C and the pH of 5.2. Its chemical name is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl)  
332 methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride. Its molecular formula is  
333 C<sub>22</sub>H<sub>24</sub>ClN<sub>3</sub>O•HCl with the following chemical structure:

334

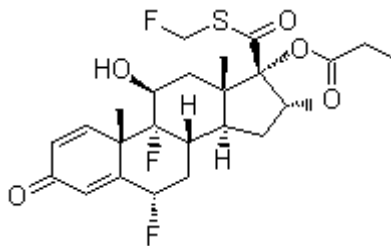


335

336

337 Fluticasone propionate active ingredient is a white powder with a melting point of 273°C, a  
338 molecular weight of 500.6, and the empirical formula is C<sub>25</sub>H<sub>31</sub>F<sub>3</sub>O<sub>5</sub>S. It is practically insoluble  
339 in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in  
340 methanol and 95% ethanol. Fluticasone propionate is a synthetic corticosteroid having the  
341 chemical name S-(fluoromethyl)-6α,9-difluoro-11β,-17-dihydroxy-16α-methyl-3-oxoandrosta-  
342 1,4-diene-17β-carbothioate, 17-propionate, and the following chemical structure:

343



344

345 Dymista (azelastine hydrochloride and fluticasone propionate) Nasal Spray, 137 mcg / 50 mcg  
346 contains 0.1% solution of azelastine hydrochloride and 0.037% suspension of micronized  
347 fluticasone propionate in an isotonic aqueous suspension containing glycerin, microcrystalline  
348 cellulose and carboxymethylcellulose sodium, phenylethyl alcohol (2.5 mg/g), edetate disodium,  
349 benzalkonium chloride (0.1 mg/g), polysorbate 80, and purified water. It has a pH of  
350 approximately 6.0.

351 After priming [*see Dosage and Administration (2.2)*], each metered spray delivers a 0.137 mL  
352 mean volume of suspension containing 137 mcg of azelastine hydrochloride (equivalent to 125  
353 mcg of azelastine base) and 50 mcg of fluticasone propionate. The 23 g bottle provides 120  
354 metered sprays, after priming.

## 355 12 CLINICAL PHARMACOLOGY

### 356 12.1 Mechanism of Action

357 **Dymista Nasal Spray:** Dymista Nasal Spray contains both azelastine hydrochloride and  
358 fluticasone propionate; therefore, the mechanisms of actions described below for the individual  
359 components apply to Dymista Nasal Spray. These drugs represent two different classes of  
360 medications (histamine H<sub>1</sub>-receptor antagonist and synthetic corticosteroid).

361 **Azelastine hydrochloride:** Azelastine hydrochloride, a phthalazinone derivative, exhibits  
362 histamine H<sub>1</sub>-receptor antagonist activity in isolated tissues, animal models, and humans.  
363 Azelastine hydrochloride in Dymista Nasal Spray is administered as a racemic mixture with no

364 difference in pharmacologic activity noted between the enantiomers in *in vitro* studies. The  
365 major metabolite, desmethylazelastine, also possesses H<sub>1</sub>-receptor antagonist activity.

366 **Fluticasone propionate:** Fluticasone propionate is a synthetic trifluorinated corticosteroid with  
367 anti-inflammatory activity. *In vitro* dose response studies on a cloned human glucocorticoid  
368 receptor system involving binding and gene expression afforded 50% responses at 1.25 and 0.17  
369 nM concentrations, respectively. Fluticasone propionate was 3-fold to 5-fold more potent than  
370 dexamethasone in these assays. Data from the McKenzie vasoconstrictor assay in man also  
371 support its potent glucocorticoid activity. The clinical relevance of these findings is unknown.

372 The precise mechanism through which fluticasone propionate affects allergic rhinitis symptoms  
373 is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell  
374 types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators  
375 (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

## 376 **12.2 Pharmacodynamics**

### 377 Cardiac Effects:

378 In a placebo-controlled trial (95 patients with allergic rhinitis), there was no evidence of an effect  
379 of azelastine hydrochloride nasal spray (2 sprays per nostril twice daily for 56 days) on cardiac  
380 repolarization as represented by the corrected QT interval (QTc) of the electrocardiogram.  
381 Following multiple dose oral administration of azelastine 4 mg or 8 mg twice daily, the mean  
382 change in QTc was 7.2 msec and 3.6 msec, respectively.

383 Interaction studies investigating the cardiac repolarization effects of concomitantly administered  
384 oral azelastine hydrochloride and erythromycin or ketoconazole were conducted. These drugs  
385 had no effect on QTc based on analysis of serial electrocardiograms.

## 386 **12.3 Pharmacokinetics**

387 *Absorption:* After intranasal administration of two sprays per nostril (548 mcg of azelastine  
388 hydrochloride and 200 mcg of fluticasone) of Dymista Nasal Spray, the mean ( $\pm$  standard  
389 deviation) peak plasma exposure ( $C_{max}$ ) was  $194.5 \pm 74.4$  pg/mL for azelastine and  $10.3 \pm 3.9$   
390 pg/mL for fluticasone propionate and the mean total exposure (AUC) was  $4217 \pm 2618$   
391 pg/mL\*hr for azelastine and  $97.7 \pm 43.1$  pg/mL\*hr for fluticasone. The median time to peak  
392 exposure ( $t_{max}$ ) from a single dose was 0.5 hours for azelastine and 1.0 hours for fluticasone.

393 Systemic bioavailability of azelastine from Dymista Nasal Spray following intranasal  
394 administration was comparable with monotherapy azelastine hydrochloride (Astelin<sup>®</sup>) nasal  
395 spray (i.e., approximately 40%). Systemic bioavailability of fluticasone from Dymista Nasal  
396 Spray following intranasal administration was 44-61% higher than monotherapy fluticasone  
397 propionate (bioavailability for monotherapy fluticasone nasal spray was less than 2%). Due to  
398 the low intranasal bioavailability, pharmacokinetic data for fluticasone propionate were obtained  
399 via other routes of administration. Studies using oral dosing of radiolabeled fluticasone  
400 propionate showed negligible oral bioavailability and high extraction from plasma. The majority  
401 of the circulating radioactivity was due to an inactive metabolite.

402 *Distribution:* Based on intravenous and oral administration, the steady-state volume of  
403 distribution of azelastine hydrochloride is 14.5 L/kg. *In vitro* studies with human plasma indicate

404 that the plasma protein binding of azelastine hydrochloride and its metabolite,  
405 desmethylazelastine, are approximately 88% and 97%, respectively.

406 Following intravenous administration, the initial disposition phase for fluticasone propionate was  
407 rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution  
408 averaged 4.2 L/kg.

409 The percentage of fluticasone propionate bound to human plasma proteins averaged 91% with no  
410 obvious concentration relationship. Fluticasone propionate is weakly and reversibly bound to  
411 erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propionate is  
412 not significantly bound to human transcortin.

413 *Metabolism:* Azelastine hydrochloride is oxidatively metabolized to the principal active  
414 metabolite, desmethylazelastine, by the cytochrome P450 enzyme system. The specific P450  
415 isoforms responsible for the biotransformation of azelastine have not been identified. The total  
416 clearance of azelastine is approximately 0.50 L/kg/hr.

417 For fluticasone propionate, the only circulating metabolite detected in man is the 17 $\beta$ -carboxylic  
418 acid derivative, which is formed through the CYP3A4 pathway. This inactive metabolite had less  
419 affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human  
420 lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites  
421 detected in vitro using cultured human hepatoma cells have not been detected in man. The  
422 average total clearance of fluticasone propionate is relatively high (approximately 66 L/hr).

423 *Elimination:* Following intranasal administration of Dymista Nasal Spray, the elimination half-  
424 life of azelastine hydrochloride is approximately 25 hours. Approximately 75% of an oral dose  
425 of radiolabeled azelastine hydrochloride was excreted in the feces with less than 10% as  
426 unchanged azelastine.

427 Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a  
428 terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral  
429 dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent  
430 drug and metabolites.

431 *Special Populations:*

432 Dymista Nasal Spray was not studied in any special populations, and no gender-specific  
433 pharmacokinetic data have been obtained.

434 *Hepatic Impairment:* Following oral administration of azelastine hydrochloride, pharmacokinetic  
435 parameters were not influenced by hepatic impairment.

436 *Renal Impairment:* Based on oral, single-dose studies of azelastine hydrochloride, renal  
437 impairment (creatinine clearance <50 mL/min) resulted in a 70-75% higher C<sub>max</sub> and AUC  
438 compared to healthy subjects. Time to maximum concentration was unchanged.

439 *Age:* Following oral administration of azelastine hydrochloride, pharmacokinetic parameters  
440 were not influenced by age.

441 *Gender:* Following oral administration of azelastine hydrochloride, pharmacokinetic parameters  
442 were not influenced by gender.

443 *Race:* The effect of race has not been evaluated.

444 *Drug-Drug Interactions:*

445 No formal drug interaction studies have been performed with Dymista Nasal Spray. The drug  
446 interactions of the combination are expected to reflect those of the individual components.

447 *Erythromycin:* Co-administration of orally administered azelastine (4 mg twice daily) with  
448 erythromycin (500 mg three times daily for 7 days) resulted in  $C_{\max}$  of  $5.36 \pm 2.6$  ng/mL and  
449 AUC of  $49.7 \pm 24$  ng•h/mL for azelastine, whereas, administration of azelastine alone resulted in  
450  $C_{\max}$  of  $5.57 \pm 2.7$  ng/mL and AUC of  $48.4 \pm 24$  ng•h/mL for azelastine.

451 In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone  
452 propionate (500 mcg twice daily) and erythromycin (333 mg three times daily) did not affect  
453 fluticasone propionate pharmacokinetics.

454 *Cimetidine and Ranitidine:* In a multiple-dose, steady-state drug interaction trial in healthy  
455 subjects, cimetidine (400 mg twice daily) increased orally administered mean azelastine  
456 hydrochloride (4 mg twice daily) concentrations by approximately 65%. Coadministration of  
457 orally administered azelastine hydrochloride (4 mg twice daily) with ranitidine hydrochloride  
458 (150 mg twice daily) resulted in  $C_{\max}$  of  $8.89 \pm 3.28$  ng/mL and AUC of  $88.22 \pm 40.43$  ng•h/mL  
459 for azelastine hydrochloride, whereas, administration of azelastine hydrochloride alone resulted  
460 in  $C_{\max}$  of  $7.83 \pm 4.06$  ng/mL and AUC of  $80.09 \pm 43.55$  ng•h/mL for azelastine hydrochloride.

461 *Theophylline:* No significant pharmacokinetic interaction was observed with the  
462 coadministration of an oral 4 mg dose of azelastine hydrochloride twice daily and theophylline  
463 300 mg or 400 mg twice daily.

464 *Ritonavir:* Coadministration of fluticasone propionate and the strong CYP3A4 inhibitor,  
465 ritonavir, is not recommended based upon a multiple-dose, crossover drug interaction study in 18  
466 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was  
467 coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate  
468 concentrations following fluticasone propionate aqueous nasal spray alone were undetectable  
469 (<10 pg/mL) in most subjects, and when concentrations were detectable, peak levels ( $C_{\max}$ )  
470 averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and AUC(0- $\tau$ ) averaged 8.43 pg•hr/mL (range,  
471 4.2 to 18.8 pg•hr/mL). Fluticasone propionate  $C_{\max}$  and AUC(0- $\tau$ ) increased to 318 pg/mL  
472 (range, 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL),  
473 respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray.  
474 This significant increase in plasma fluticasone propionate exposure resulted in a significant  
475 decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

476 Caution should be exercised when other strong CYP3A4 inhibitors are coadministered with  
477 fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone  
478 propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased fluticasone  
479 propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of  
480 cortisol. [see *Drug Interactions* (7.2)]

## 481 13 NONCLINICAL TOXICOLOGY

### 482 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

483 **Dymista Nasal Spray:** No studies of carcinogenicity, mutagenicity, or impairment of fertility  
484 were conducted with Dymista Nasal Spray; however, studies are available for the individual  
485 active components, azelastine hydrochloride and fluticasone propionate, as described below.

486 **Azelastine hydrochloride:** In 2-year carcinogenicity studies in rats and mice, azelastine  
487 hydrochloride did not show evidence of carcinogenicity at oral doses up to 30 mg/kg and 25  
488 mg/kg, respectively. These doses were approximately 530 and 220 times the maximum  
489 recommended human daily intranasal dose [MRHDID] on a mg/m<sup>2</sup> basis.

490 Azelastine hydrochloride showed no genotoxic effects in the Ames test, DNA repair test, mouse  
491 lymphoma forward mutation assay, mouse micronucleus test, or chromosomal aberration test in  
492 rat bone marrow.

493 Reproduction and fertility studies in rats showed no effects on male or female fertility at oral  
494 doses up to 30 mg/kg (approximately 530 times the MRHDID in adults on a mg/m<sup>2</sup> basis). At  
495 68.6 mg/kg (approximately 1200 times the MRHDID on a mg/m<sup>2</sup> basis), the duration of estrous  
496 cycles was prolonged and copulatory activity and the number of pregnancies were decreased.  
497 The numbers of corpora lutea and implantations were decreased; however, pre-implantation loss  
498 was not increased.

499 **Fluticasone propionate:** Fluticasone propionate demonstrated no tumorigenic potential in mice  
500 at oral doses up to 1,000 mcg/kg (approximately 20 times the maximum recommended daily  
501 intranasal dose in adults and approximately 10 times the maximum recommended daily  
502 intranasal dose in children on a mcg/m<sup>2</sup> basis) for 78 weeks or in rats at inhalation doses up to 57  
503 mcg/kg (approximately 2 times the MRHDID in adults on a mcg/m<sup>2</sup> basis) for 104 weeks.

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

507 No evidence of impairment of fertility was observed in reproductive studies conducted in male  
508 and female rats at subcutaneous doses up to 50 mcg/kg (approximately 2 times the MRHDID in  
509 adults on a mcg/m<sup>2</sup> basis). Prostate weight was significantly reduced at a subcutaneous dose of  
510 50 mcg/kg.

## 511 14 CLINICAL STUDIES

512 The efficacy and safety of Dymista Nasal Spray in seasonal allergic rhinitis was evaluated in 3  
513 randomized, multicenter, double-blind, placebo-controlled clinical trials in 853 adult and  
514 adolescent patients 12 years and older with seasonal allergic rhinitis. The population of the trials  
515 was 12 to 78 years of age (64% female, 36% male; 80% white, 16% black, 2% Asian, 1% other).

516 Patients were randomized to one of four treatment groups: one spray per nostril twice daily of  
517 Dymista Nasal Spray, azelastine hydrochloride nasal spray, fluticasone propionate nasal spray,  
518 and vehicle placebo. The azelastine hydrochloride and fluticasone propionate comparators use  
519 the same device and vehicle as Dymista Nasal Spray and are not commercially marketed.

520 Assessment of efficacy was based on the reflective total nasal symptom score (rTNSS), in  
521 addition to the instantaneous total nasal symptom score (iTNSS) and other supportive secondary  
522 efficacy variables. TNSS is calculated as the sum of the patients' scoring of the 4 individual  
523 nasal symptoms (rhinorrhea, nasal congestion, sneezing, and nasal itching) on a 0 to 3  
524 categorical severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Patients were  
525 required to record symptom severity daily reflecting over the previous 12 hours (morning, AM,  
526 and evening, PM). For the primary efficacy endpoint, the combined AM+PM rTNSS (maximum  
527 score of 24) was assessed as a change from baseline for each day and then averaged over a 2-  
528 week treatment period. The primary efficacy endpoint was the mean change from baseline in  
529 combined AM+PM rTNSS over 2 weeks. The iTNSS was recorded immediately prior to the next  
530 dose.

531 In these trials, Dymista Nasal Spray demonstrated statistically significant greater decreases in  
532 rTNSS as compared to azelastine hydrochloride and to fluticasone propionate, as well as to  
533 placebo. The differences between the monotherapies and placebo also were statistically  
534 significant. Representative results from one of the trials are shown below (Table 2).

535

536



<b>Table 2. Mean Change from Baseline in Reflective Total Nasal Symptom Scores over 2 Weeks* in Adults and Children ≥ 12 years with Seasonal Allergic Rhinitis</b>						
		Baseline	Change from Baseline	Difference From Dymista Nasal Spray		
Treatment (one spray /nostril twice daily)	N	LS Mean	LS Mean	LS Mean	95% CI	<i>P</i> -value
Dymista Nasal Spray	207	18.3	-5.6	--	--	--
Azelastine HCl Nasal Spray <sup>†</sup>	208	18.3	-4.3	-1.4	(-2.2, -0.5)	0.002
Fluticasone Propionate Nasal Spray <sup>†</sup>	207	18.2	-4.7	-1.0	(-1.8, -0.2)	0.022
Placebo	209	18.6	-2.9	-2.7	(-3.5, -1.9)	<0.001
* Sum of AM and PM rTNSS for each day (Maximum Score =24) and averaged over the 14 day treatment period						
<sup>†</sup> Not commercially marketed						
LS Mean, 95% CI, and p-value are obtained from the repeated-measures analysis of covariance model using observed data.						

538

539 In these trials, Dymista Nasal Spray also demonstrated statistically significant, greater decreases  
540 in iTNSS as compared to placebo, as did the azelastine hydrochloride and fluticasone propionate  
541 comparators. Representative results from one of the trials are shown below (Table 3).  
542  
543

<b>Table 3. Mean Change from Baseline in Instantaneous Total Nasal Symptom Scores over 2 Weeks* in Adults and Children ≥ 12 years with Seasonal Allergic Rhinitis</b>						
		Baseline	Change from Baseline	Difference From Placebo		
Treatment (one spray /nostril twice daily)	N	LS Mean	LS Mean	LS Mean	95% CI	<i>P</i> -value
Dymista Nasal Spray	207	17.2	-5.2	-2.6	(-3.4, -1.8)	<0.001
Azelastine HCl Nasal Spray <sup>†</sup>	208	16.8	-3.9	-1.3	(-2.0, -0.6)	<0.001
Fluticasone Propionate Nasal Spray <sup>†</sup>	207	16.8	-4.5	-1.9	(-2.6, -1.2)	<0.001
Placebo	209	17.3	-2.7	--	--	--
* Sum of AM and PM iTNSS for each day (Maximum Score =24) and averaged over the 14 day treatment period						
<sup>†</sup> Not commercially marketed						
LS Mean, 95% CI, and p-value are obtained from the repeated-measures analysis of covariance model using observed data.						

544

545 Onset of action, defined as the first timepoint at which Dymista Nasal Spray was statistically  
546 superior to placebo in the mean change from baseline in iTNSS and which was sustained  
547 thereafter, was assessed in each of the three trials. Onset of action was observed as early as 30  
548 minutes following the initial dose of Dymista Nasal Spray.

549 The subjective impact of seasonal allergic rhinitis on patient's health-related quality of life was  
550 evaluated by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (28 items in 7  
551 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye  
552 symptoms, and emotional) evaluated on a 7-point scale where 0=no impairment and 6=maximum  
553 impairment), which was administered to patients 18 years of age and older. An overall RQLQ  
554 score is calculated from the mean of all items in the instrument. A change from baseline of at  
555 least 0.5 points is considered a clinically meaningful improvement. In each of these trials,  
556 Dymista Nasal Spray demonstrated a statistically significant greater decrease from baseline in  
557 the overall RQLQ than placebo, which ranged from -0.55 (95% CI -0.72, -0.39) to -0.80 (95% CI

558 -1.05, -0.55). In these trials, the treatment differences between Dymista Nasal Spray and the  
559 monotherapies were less than the minimum important difference of 0.5 points.

## 560 **16 HOW SUPPLIED/STORAGE AND HANDLING**

561 Dymista Nasal Spray (NDC 0037-0245-23) is supplied as an amber glass bottle fitted with a  
562 metered-dose spray pump unit. The spray pump unit consists of a nasal spray pump with a white  
563 nasal adapter and clear plastic dust cap. Each bottle contains a net fill weight of 23 g and will  
564 deliver 120 metered sprays after priming [*see Dosage and Administration (2.2)*]. Dymista Nasal  
565 Spray should be shaken gently before each use and primed with 6 sprays before the initial use or  
566 with 1 spray after a non-use period of 14 days. Each spray delivers a suspension volume of  
567 0.137 mL as a fine mist, containing 137 mcg of azelastine hydrochloride and 50 mcg of  
568 fluticasone propionate (137 mcg/50 mcg). The correct amount of medication in each spray  
569 cannot be assured before the initial priming and after 120 sprays have been used, even though the  
570 bottle is not completely empty. The bottle should be discarded after 120 medicated sprays have  
571 been used.

572 Dymista Nasal Spray should not be used after the expiration date “EXP” printed on the bottle  
573 label and carton.

### 574 **Storage:**

575 Store upright with the dust cap in place at controlled room temperature 20° - 25°C (68° -  
576 77°F). [See USP Controlled Temperature] Protect from light. Do not store in the freezer or  
577 refrigerator.

## 578 **17 PATIENT COUNSELING INFORMATION**

579 *See FDA-approved patient labeling (Patient Information and Instructions for Use)*

580 Patients should be instructed to use Dymista Nasal Spray only as prescribed. For the proper use  
581 of the nasal spray and to attain maximum improvement, the patient should read and follow  
582 carefully the accompanying FDA-Approved Patient Labeling.

### 583 **17.1 Somnolence**

584 Somnolence has been reported in some patients (6 of 853 patients) taking Dymista Nasal Spray.  
585 Patients should be cautioned against engaging in hazardous occupations requiring complete  
586 mental alertness and motor coordination such as driving or operating machinery after  
587 administration of Dymista Nasal Spray [*see Warnings and Precautions (5.1)*].

### 588 **17.2 Concurrent Use of Alcohol and other Central Nervous System 589 Depressants**

590 Concurrent use of Dymista Nasal Spray with alcohol or other central nervous system depressants  
591 should be avoided because additional reductions in alertness and additional impairment of central  
592 nervous system performance may occur [*see Warnings and Precautions (5.1)*].

593 **17.3 Local Nasal Effects**

594 Nasal corticosteroids are associated with nasal septal perforation and impaired wound healing.  
595 Patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should not use  
596 Dymista Nasal Spray until healing has occurred [*see Warnings and Precautions (5.2)*].

597 **17.4 Cataracts and Glaucoma**

598 Patients should be informed that glaucoma and cataracts are associated with nasal and inhaled  
599 corticosteroid use. Patients should inform his/her health care provider if a change in vision is  
600 noted while using Dymista Nasal Spray [*see Warnings and Precautions (5.5)*].

601 **17.5 Immunosuppression**

602 Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid  
603 exposure to chickenpox or measles and, if exposed, to consult their physician without delay.  
604 Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial,  
605 viral or parasitic infections, or ocular herpes simplex [*see Warnings and Precautions (5.4)*].

606 **17.6 Priming**

607 Patients should be instructed to shake the bottle gently before each use and prime the pump  
608 before initial use and when Dymista Nasal Spray has not been used for 14 or more days [*see*  
609 *Dosage and Administration (2.2)*].

610 **17.7 Keep Spray Out of Eyes**

611 Patients should be instructed to avoid spraying Dymista Nasal Spray into their eyes.

612 **17.8 Keep Out of Children's Reach**

613 Patients should be instructed to keep Dymista Nasal Spray out of the reach of children. If a child  
614 accidentally ingests Dymista Nasal Spray, seek medical help or call a poison control center  
615 immediately.

616 **17.9 Potential Drug Interactions**

617 Patients should be advised that coadministration of Dymista Nasal Spray and ritonavir is not  
618 recommended and to be cautious if Dymista Nasal Spray is coadministered with ketoconazole  
619 [*see Drug Interactions (7.2)*].

620

621 **U.S. Patent Pending**

622 **Manufactured by:**

623 Cipla Ltd. Goa, India

624 M.L. No. 546

625

626 **Distributed by:**



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629 Dymista is a trademark of Meda Pharmaceuticals Inc.

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631 Made in India.

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## PATIENT INFORMATION

Dymista Nasal Spray (*Dy-Mist-A*)

(azelastine hydrochloride and fluticasone propionate)  
Nasal Spray

### **Important: For use in your nose only**

Read this Patient Information before you start using Dymista Nasal Spray and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

### **What is Dymista Nasal Spray?**

Dymista Nasal Spray is a prescription medicine used to treat symptoms of seasonal allergic rhinitis in people 12 years of age and older, who need treatment with both azelastine hydrochloride and fluticasone propionate. It helps reduce the symptoms of seasonal allergic rhinitis (inflammation of the lining of the nose), such as stuffy nose, itching, and sneezing.

It is not known if Dymista Nasal Spray is safe or effective in children under 12 years of age.

### **What should I tell my healthcare provider before using Dymista Nasal Spray?**

**Before using Dymista Nasal Spray tell your healthcare provider if you:**

- have had recent nasal sores, nasal surgery, or nasal injury
- have eye or vision problems, such as cataracts or glaucoma (increased pressure in your eye)
- have tuberculosis or any untreated fungal, bacterial, viral infections or eye infections caused by herpes
- have been near someone who has chickenpox or measles
- are not feeling well or have any other symptoms that you do not understand
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if Dymista Nasal Spray will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.

- 668
- are breastfeeding or plan to breastfeed. It is not known if Dymista
- 669 Nasal Spray passes into your breast milk. Talk to your doctor about
- 670 the best way to feed your baby while using Dymista Nasal Spray.

671

672 **Tell your healthcare provider about all the medicines you take,**

673 including prescription and non-prescription medicines, vitamins, and herbal

674 supplements.

675 Dymista Nasal Spray may affect the way other medicines work, and other

676 medicines may affect how Dymista Nasal Spray works.

677 **Especially tell your healthcare provider if you take:**

- 678 • ritanovir (Norvir) or medicines that contain ritanovir (commonly
- 679 used to treat HIV infection or AIDS)
- 680 • ketoconazole, fluconazole, or itraconazole (for fungal infections)

681 Ask your healthcare provider or pharmacist for a list of these medications, if

682 you are not sure.

683 Know the medicines you take. Keep a list of your medicines and show it to

684 your healthcare provider and pharmacist when you get a new medicine.

685 **How should I use Dymista Nasal Spray?**

- 686 • **See the Patient Instructions for Use at the end of this leaflet**
- 687 **for information about the right way to use Dymista Nasal**
- 688 **Spray.**

- 689 • Dymista Nasal Spray is for use in your nose only. **Do not spray it**
- 690 **into your eyes or mouth. If you spray Dymista Nasal Spray**
- 691 **into your eyes, flush your eye(s) with large amounts of**
- 692 **water for 10 minutes and then call your doctor.**

- 693 • Use Dymista Nasal Spray exactly as your healthcare provider tells
- 694 you to use it. Your healthcare provider will tell you how much
- 695 Dymista Nasal Spray to use and when to use it.

- 696 • If a child accidentally swallows Dymista Nasal Spray or you use too
- 697 much Dymista Nasal Spray, call your doctor or go to the nearest
- 698 hospital emergency room right away.

699 **What should I avoid while using Dymista Nasal Spray?**

- 700 • Dymista Nasal Spray can cause sleepiness or drowsiness. Do not
- 701 drive, operate machinery, or do anything that needs you to be alert
- 702 until you know how Dymista Nasal Spray affects you.

- 703           • Do not drink alcohol or take any other medicines that may cause  
704           you to feel sleepy while using Dymista Nasal Spray. It can increase  
705           your chances of having serious side effects.

706 **What are the possible side effects of Dymista Nasal Spray?**

707 **Dymista Nasal Spray may cause serious side effects including:**

- 708           • **Sleepiness or drowsiness.**
- 709           • **Nasal Problems.** Symptoms of nasal problems may include:
- 710                 o crusting in the nose
- 711                 o nosebleeds
- 712                 o runny nose
- 713                 o hole in the cartilage between your nose (nasal septal
- 714                     perforation). A whistling sound when you breathe may be a
- 715                     symptom of nasal septal perforation.
- 716           • **Slow wound healing.** You should not use Dymista Nasal Spray
- 717           until your nose has healed if you have a sore in your nose, if you
- 718           have had surgery on your nose, or if your nose has been injured.
- 719           • **Thrush (candida), a fungal infection in your nose and throat.**
- 720           Tell your doctor if you have any redness or white colored patches in
- 721           your nose or mouth.
- 722           • **Eye problems, such as glaucoma or cataracts.** Some people
- 723           may have eye problems, including glaucoma and cataracts. You
- 724           should have regular eye exams when using Dymista Nasal Spray.
- 725           • **Immune system problems that may increase your risk of**
- 726           **infections.** Dymista Nasal Spray may cause problems with the
- 727           way your immune system protects your body against infection and
- 728           increase your risk of infection. Avoid contact with people who have
- 729           contagious diseases such as chickenpox or measles while you use
- 730           Dymista Nasal Spray. Symptoms of infection may include:
- 731                 o fever
- 732                 o aches or pains
- 733                 o chills
- 734                 o feeling tired
- 735           • **Adrenal Insufficiency.** Adrenal insufficiency is a condition in
- 736           which the adrenal glands do not make enough steroid hormones.
- 737           Symptoms of adrenal insufficiency may include:
- 738                 o tiredness

- 739                   o weakness  
740                   o nausea  
741                   o vomiting  
742                   o low blood pressure
- 743                   • **Slowed or delayed growth in children.** A child's growth should  
744                   be checked regularly while using Dymista Nasal Spray.

745 **Call your healthcare provider or get medical help right away if you**  
746 **have symptoms of any of the serious side effects listed above.**

747

748 The most common side effects of Dymista Nasal Spray include:

- 749                   • changes in taste  
750                   • nosebleeds  
751                   • headache

752

753 Tell your healthcare provider if you have any side effect that bothers you or  
754 that does not go away. These are not all of the possible side effects of  
755 Dymista Nasal Spray. For more information, ask your healthcare provider or  
756 pharmacist.

757

758 Call your doctor for medical advice about side effects. You may report side  
759 effects to FDA at 1-800-FDA-1088.

760

### 761 **How should I store Dymista Nasal Spray?**

- 762                   • Store Dymista Nasal Spray upright at controlled room temperature  
763                   68° to 77°F (20° to 25°C).
- 764                   • Do not freeze or refrigerate Dymista Nasal Spray.
- 765                   • Protect Dymista Nasal Spray from light.
- 766                   • Safely throw away medicine that is out of date or no longer needed.
- 767                   • Throw away your Dymista Nasal Spray bottle after using 120 sprays  
768                   after initial priming. Even though the bottle may not be completely  
769                   empty, you may not get the correct dose of medicine if you  
770                   continue to use it.

771

772 **Keep Dymista Nasal Spray and all medicines out of reach of children.**

773

### 774 **General information about Dymista Nasal Spray**

775



776 Medicines are sometimes prescribed for purposes other than those listed in a  
777 Patient Information leaflet. Do not use Dymista Nasal Spray for a condition  
778 for which it was not prescribed. Do not give Dymista Nasal Spray to other  
779 people, even if they have the same symptoms that you have. It may harm  
780 them.

781  
782 This Patient Information leaflet summarizes the most important information  
783 about Dymista Nasal Spray. If you would like more information, talk with  
784 your healthcare provider. You can ask your pharmacist or healthcare  
785 provider for information about Dymista Nasal Spray that is written for health  
786 professionals.

787  
788 For more information, go to [www.DYMISTA.com](http://www.DYMISTA.com) or call Meda  
789 Pharmaceuticals Inc. at 1-888-939-6478.

790  
791 **What are the ingredients in Dymista Nasal Spray?**

792 **Active ingredients:** azelastine hydrochloride and fluticasone propionate  
793

794 **Inactive ingredients:** glycerin, microcrystalline cellulose and  
795 carboxymethylcellulose sodium, phenylethyl alcohol, edetate disodium,  
796 benzalkonium chloride, polysorbate 80, and purified water.

797

798 **Instructions for Use**

799

800 **For use in your nose only. Do not spray in your eyes.**

801

802 Read the Instructions for Use before you start to use Dymista Nasal Spray  
803 and each time you get a refill. There may be new information. This leaflet  
804 does not take the place of talking with your healthcare provider about your  
805 medical condition or treatment. Before you use Dymista Nasal Spray, make  
806 sure your healthcare provider shows you the right way to use it.

807

808 **Shake the bottle gently before each use.**

809

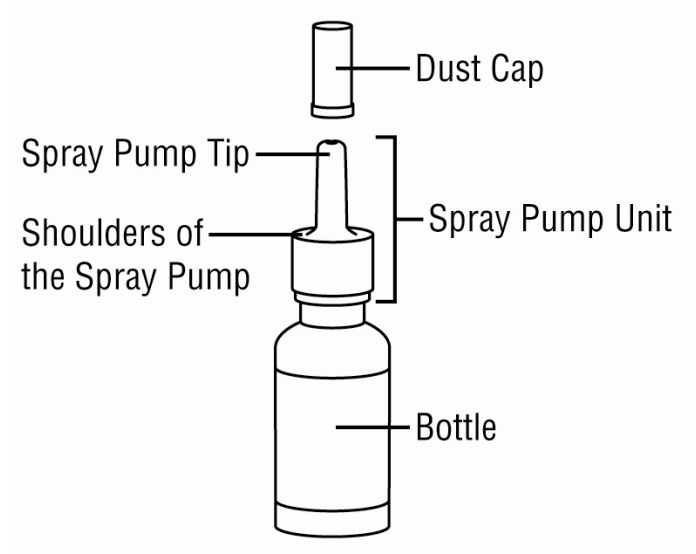
810 **Your Dymista Nasal Spray pump. (See Figure A)**

811

812

813  
814

**Figure A**



815  
816

817 **Instructions for Using Your Dymista Nasal Spray Pump.**  
818 **Before you use Dymista Nasal Spray for the first time, you will need**  
819 **to prime the bottle.**

820

821 Before you prime the bottle, shake it gently.

822

823 **Step 1.**

824 Remove the clear plastic dust cap from the spray pump tip of the bottle.

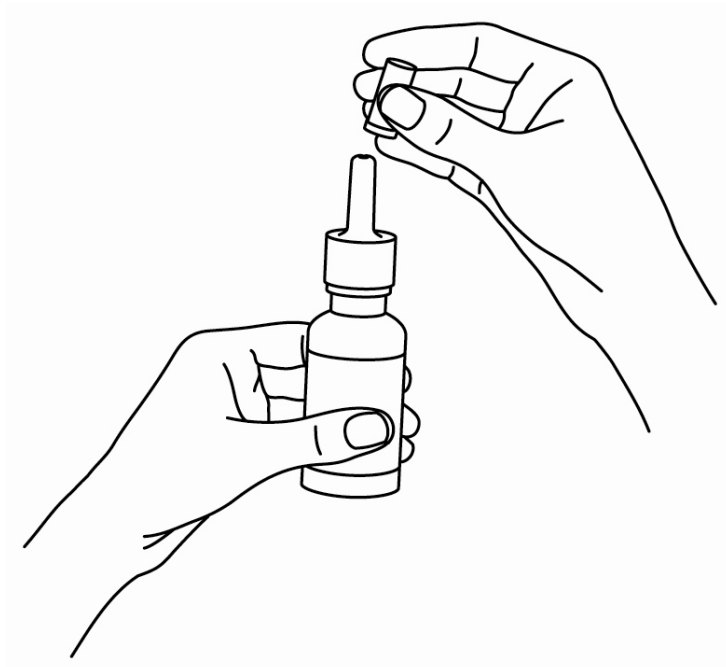
825 **(See Figure B)**

826

827

828  
829

Figure B



830  
831  
832

**Step 2.**

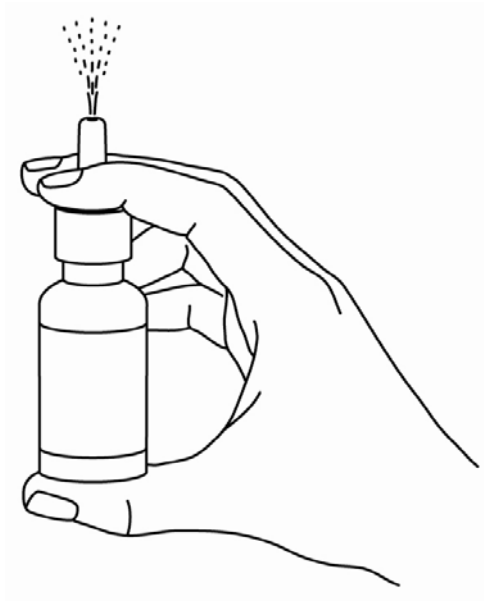
834 Hold the bottle upright with two fingers on the shoulders of the spray pump  
835 unit and put your thumb on the bottom of the bottle. Press upward with your  
836 thumb and release for the pumping action.

- 837 • Repeat the pumping action until you see a fine mist. You should  
838 see a fine mist of the medicine after 6 pumps or less. **(See Figure**  
839 **C)**
- 840 • To get a fine mist of medicine, you must repeat the pumping action  
841 fast and use firm pressure against the bottom of the bottle.
- 842 • If you see a stream of liquid, the spray will not work right and may  
843 cause nasal discomfort.
- 844 • If you do not use Dymista Nasal Spray for 14 or more days, you will  
845 need to prime the pump with 1 spray or until you see a fine mist. If  
846 you do not see a fine mist, clean the tip of the spray nozzle. See  
847 the cleaning section below.
- 848 • **Once you see the fine mist of medicine, your Dymista Nasal**  
849 **Spray pump is ready for use.**

850  
851

852  
853

**Figure C**



854  
855  
856

857 **To Use Dymista Nasal Spray:**

858 **Step 3.**

859 Gently blow your nose to clear nostrils. **(See Figure D)**

860  
861

862  
863

**Figure D**



864  
865  
866  
867  
868  
869  
870

**Step 4.**

Shake the bottle gently. Close 1 nostril with a finger. Tilt your head forward slightly. Keep the bottle upright and carefully place the spray pump tip  $\frac{1}{4}$  to  $\frac{1}{2}$  inch into your other nostril. **(See Figure E)**

871  
872

Figure E



873  
874  
875

876 **Step 5.**

877 For each spray firmly press the pump 1 time. Keep your head tilted down  
878 and at the same time, gently breathe in through your nostril. **(See Figure**  
879 **F) Do not** spray directly onto the nasal septum (the wall between your 2  
880 nostrils).

- 881 • Repeat Step 5 in your other nostril.
- 882 • **Do not tilt your head back.** This will help to keep the medicine  
883 from going into your throat.
- 884 • If the medicine goes into your throat you may get a bitter taste in  
885 your mouth. This is normal.

886  
887  
888  
889  
890  
891

892

Figure F



893

894

895 **Step 6.**

896 When you finish using Dymista Nasal Spray, wipe the spray tip with a clean  
897 tissue or cloth. Put the dust cap back on the spray pump tip of the bottle.

898 **(See Figure G)**

899

900

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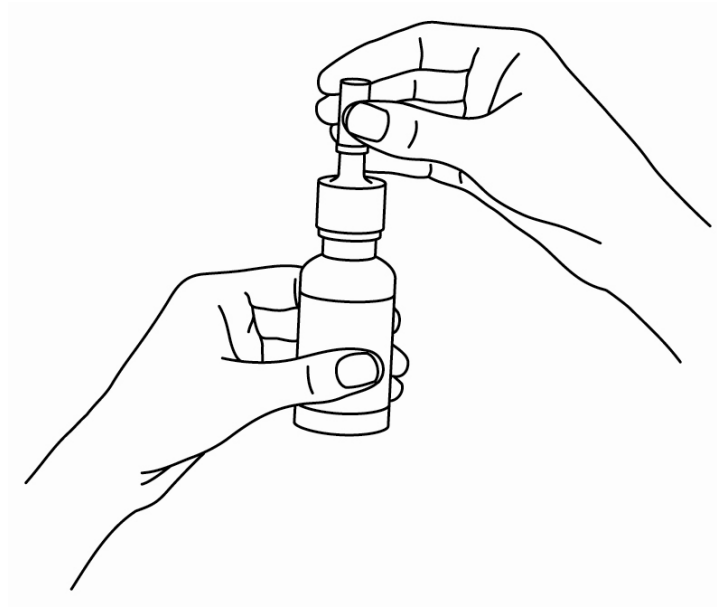
908

909

910

911  
912

**Figure G**



913  
914  
915

916 Each bottle of Dymista Nasal Spray contains enough medicine for you to  
917 spray medicine from the bottle 120 times. **After initial priming, do not**  
918 **use your bottle of Dymista Nasal Spray after 120 sprays.** You may not  
919 receive the right amount of medicine. Keep track of the number of sprays  
920 you use from your bottle of Dymista Nasal Spray and throw away the bottle  
921 even if it has medicine left in it. **Do not count any sprays used for**  
922 **initially priming the bottle.**

923

924 **To Clean the Spray Pump Tip:**

925 Your Dymista Nasal Spray should be cleaned at least 1 time each week. To  
926 do this:

927 **Step 7.**

928 Remove the dust cap and then gently pull upward on the spray pump unit to  
929 remove it from the bottle. **(See Figure H)**

930  
931



932

Figure H



933

934

935 **Step 8.**

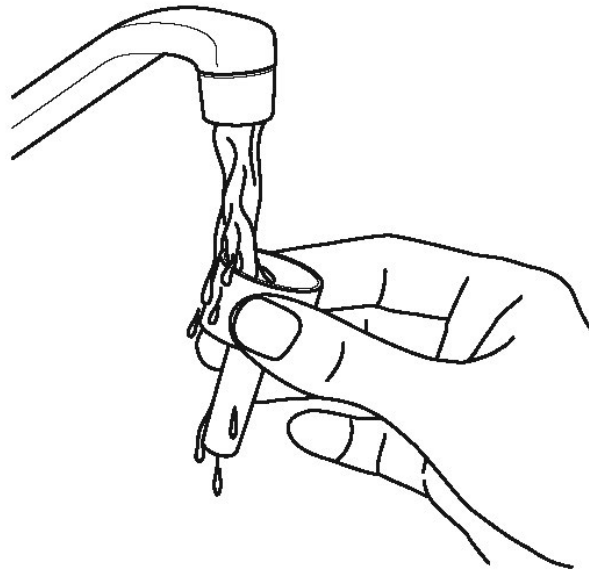
936 Wash the spray pump unit and dust cap in warm tap water. **(See Figure I)**

937

938

939

Figure I



940

941

942 **Step 9.**

943 Allow to dry completely. When dry, place the spray pump unit and dust cap  
944 back on the bottle. **(See Figure J)**

945

946

Figure J



948

949 **Step 10.**

950 If the spray pump unit becomes blocked, it can be removed as instructed  
951 above in Step 7 and placed in warm water to soak.

952 **Do not try to unblock the spray pump unit by inserting a pin or other**  
953 **sharp object. This will damage the spray pump unit and cause you**  
954 **not to get the right dose of medicine.**

955

956 **Step 11.**

957 After the spray pump unit is unblocked, rinse the applicator and cap with  
958 cold water, and allow them to dry as in Step 10 above. When dry, place the  
959 spray pump unit back on the bottle and put the dust cap on the spray pump  
960 tip.

961

962 **Step 12.**

963 Reprime the bottle as in Steps 1 and 2 above. Replace the dust cap and  
964 your Dymista Nasal Spray is ready for use.

965

966 This Patient Package Insert and Instructions for Use has been approved by  
967 the U.S. Food and Drug Administration.

968

969 Distributed by:

970



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