

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202236Orig1s000

LABELING

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 H₁-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.

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 [†] (N=851)	Fluticasone Propionate Nasal Spray [†] (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 [†] 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/m² 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/m² 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/m² basis at a maternal dose of 30
233 mg/kg). At a dose approximately 1200 times the MRHDID (on a mg/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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

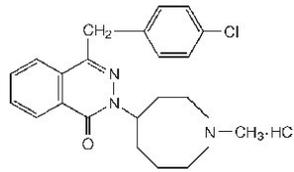
313 **Fluticasone propionate:** Chronic fluticasone propionate overdosage may result in
314 signs/symptoms of hypercorticism [*see Warnings and Precautions (5.2)*]. Intranasal
315 administration of 2 mg (10 times the recommended dose) of fluticasone propionate twice daily
316 for 7 days to healthy human 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 (H₁ 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 C₂₂H₂₄ClN₃O•HCl with the following chemical structure:

334

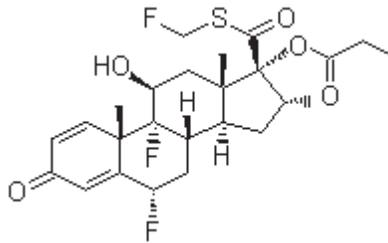


335

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 C₂₅H₃₁F₃O₅S. 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 H₁-receptor antagonist and synthetic corticosteroid).

361 **Azelastine hydrochloride:** Azelastine hydrochloride, a phthalazinone derivative, exhibits
362 histamine H₁-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 H₁-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[®]) 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 β -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_{max} 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 ± 2.6 ng/mL and
449 AUC of 49.7 ± 24 ng•h/mL for azelastine, whereas, administration of azelastine alone resulted in
450 C_{\max} of 5.57 ± 2.7 ng/mL and AUC of 48.4 ± 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 ± 3.28 ng/mL and AUC of 88.22 ± 40.43 ng•h/mL
459 for azelastine hydrochloride, whereas, administration of azelastine hydrochloride alone resulted
460 in C_{\max} of 7.83 ± 4.06 ng/mL and AUC of 80.09 ± 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- τ) averaged 8.43 pg•hr/mL (range,
471 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C_{\max} and AUC(0- τ) 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/m² 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/m² basis). At
495 68.6 mg/kg (approximately 1200 times the MRHDID on a mg/m² 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/m² 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/m² 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/m² 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

Table 2. Mean Change from Baseline in Reflective Total Nasal Symptom Scores over 2 Weeks* in Adults and Children \geq 12 years with Seasonal Allergic Rhinitis						
		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	--	--	--
Azelaatine HCl Nasal Spray [†]	208	18.3	-4.3	-1.4	(-2.2, -0.5)	0.002
Fluticasone Propionate Nasal Spray [†]	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						
[†] 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

Table 3. Mean Change from Baseline in Instantaneous Total Nasal Symptom Scores over 2 Weeks* in Adults and Children \geq 12 years with Seasonal Allergic Rhinitis						
		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
Azelaatine HCl Nasal Spray [†]	208	16.8	-3.9	-1.3	(-2.0, -0.6)	<0.001
Fluticasone Propionate Nasal Spray [†]	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						
[†] 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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628

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 ○ crusting in the nose
- 711 ○ nosebleeds
- 712 ○ runny nose
- 713 ○ 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 ○ fever
- 732 ○ aches or pains
- 733 ○ chills
- 734 ○ 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 ○ 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 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

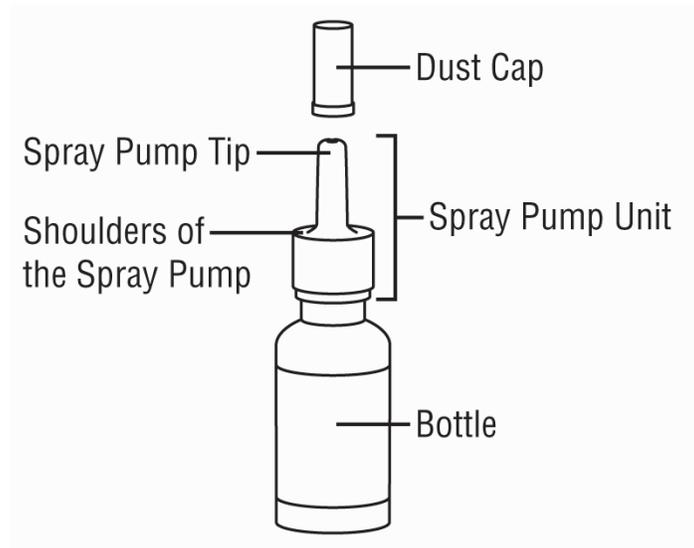
810 **Your Dymista Nasal Spray pump. (See Figure A)**

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



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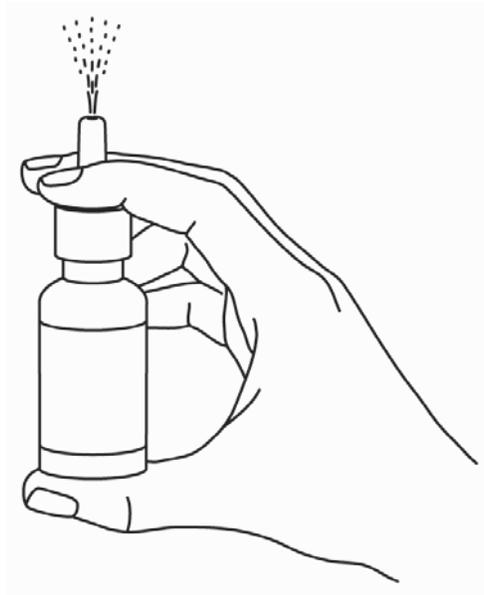
Step 2.

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

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

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
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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
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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)**

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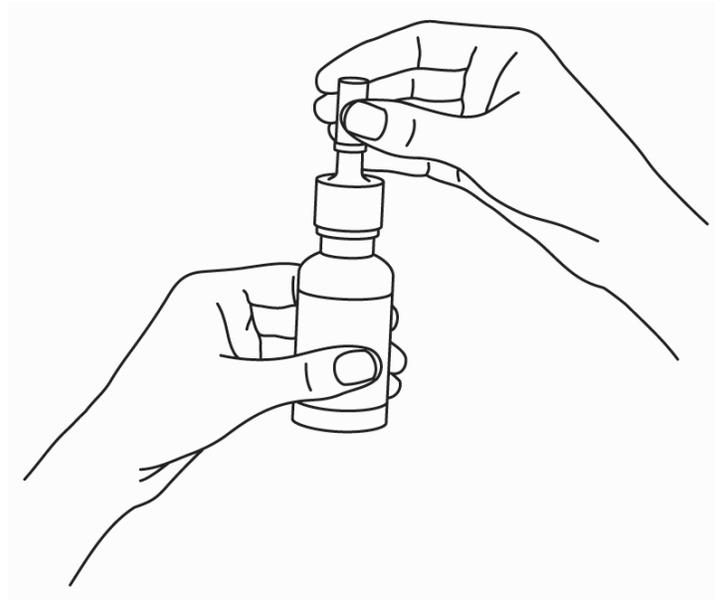
908

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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)**

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931

932

Figure H



933

934

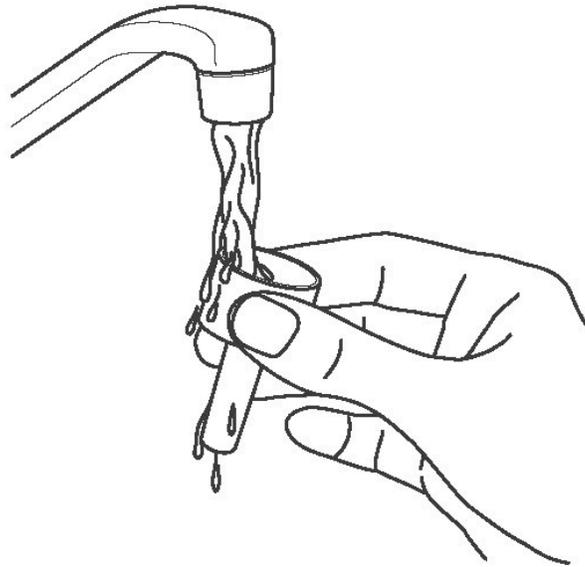
935 **Step 8.**

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

937

938

Figure I



940

941

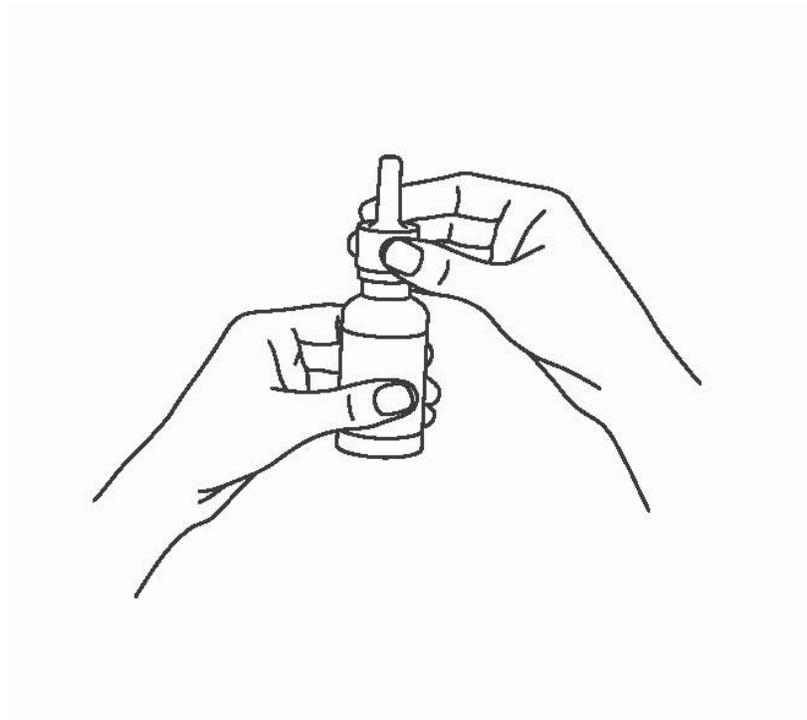
942 **Step 9.**

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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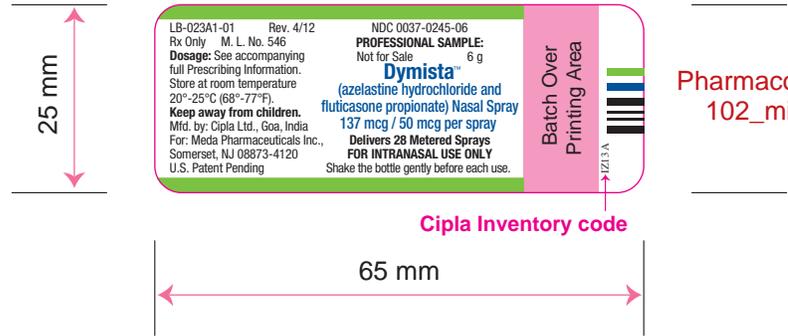
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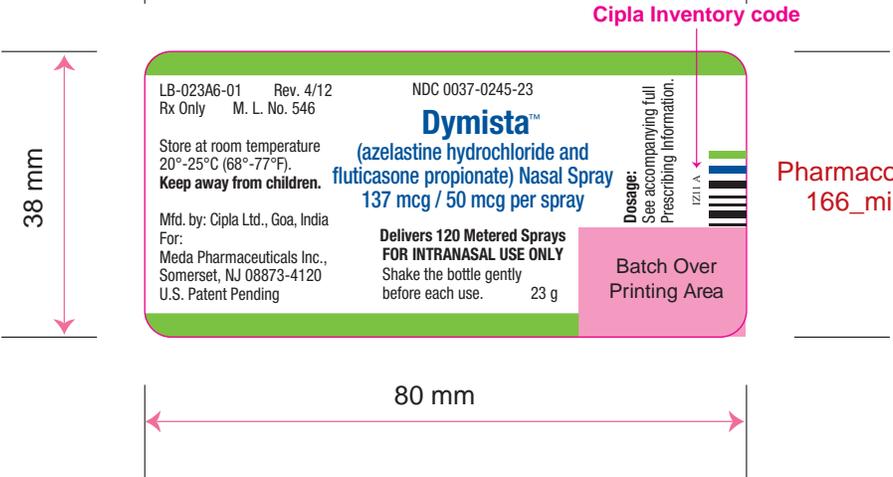
U.S. Patent Pending

IN-XXXXX-XX Rev. 4/2012

Sample Label 6 g



Trade Label 23 g



LB-023A6-01 Rev. 4/12 NDC 0037-0245-23
Rx Only M. L. No. 546

Store at room temperature
20°-25°C (68°-77°F).
Keep away from children.

Mfd. by: Cipla Ltd., Goa, India
For:
Meda Pharmaceuticals Inc.,
Somerset, NJ 08873-4120
U.S. Patent Pending

Dymista™
(azelastine hydrochloride and
fluticasone propionate) Nasal Spray
137 mcg / 50 mcg per spray

**Delivers 120 Metered Sprays
FOR INTRANASAL USE ONLY**
Shake the bottle gently
before each use. 23 g

Dosage:
See accompanying full
Prescribing Information.



Batch Over
Printing Area

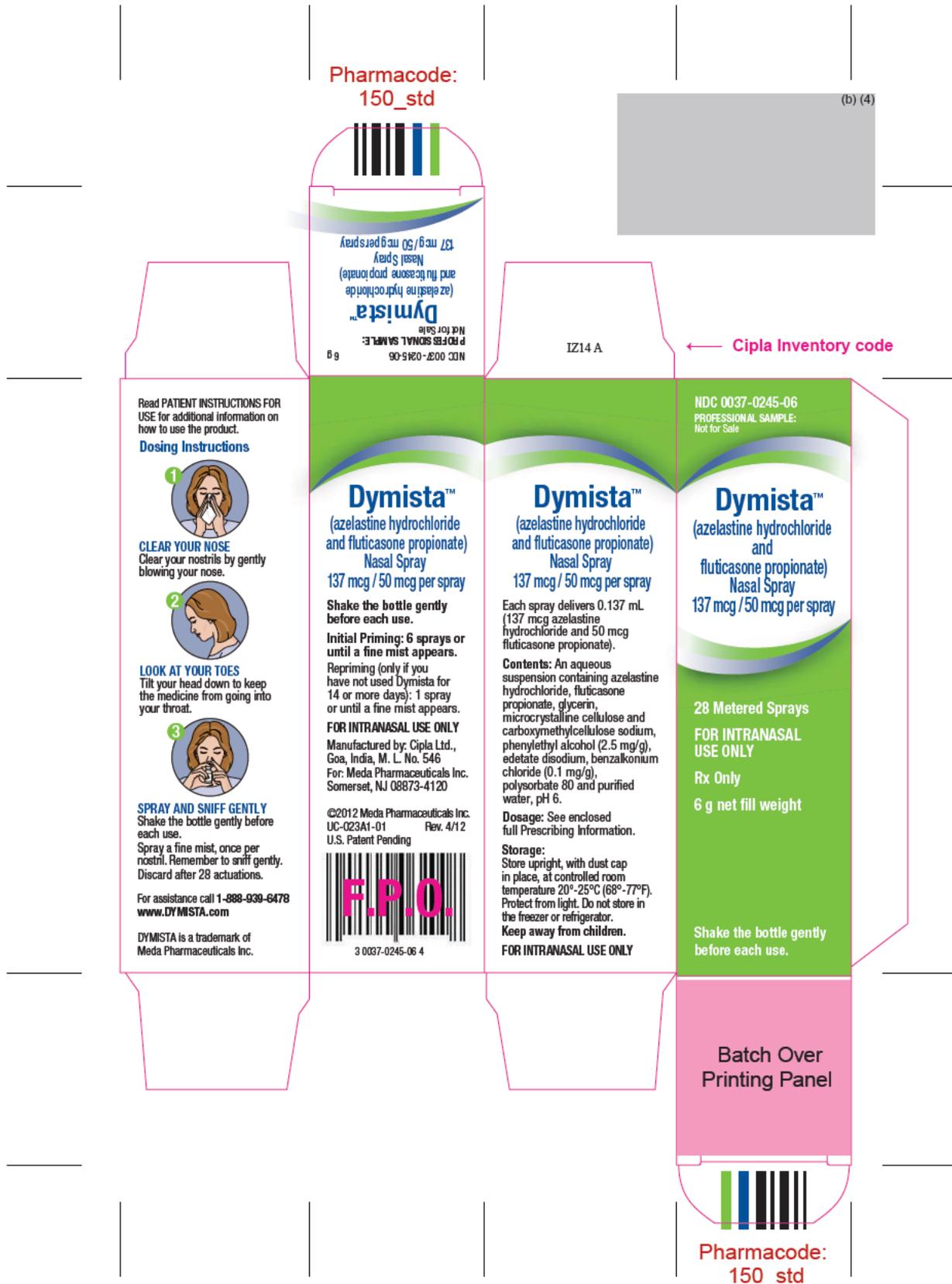
Pharmacode:
166_mini

38 mm

80 mm

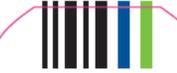
Cipla Inventory code

Sample Carton 6 g



Pharmacode:
150_std

(b) (4)



NDC 0037-0245-06
 PROFESSIONAL SAMPLE:
 Not for Sale
 6 g
Dymista™
 (azelastine hydrochloride
 and fluticasone propionate)
 Nasal Spray
 137 mcg / 50 mcg per spray

IZ14 A

← Cipla Inventory code

Read **PATIENT INSTRUCTIONS FOR USE** for additional information on how to use the product.

Dosing Instructions



1 CLEAR YOUR NOSE
Clear your nostrils by gently blowing your nose.



2 LOOK AT YOUR TOES
Tilt your head down to keep the medicine from going into your throat.



3 SPRAY AND SNIFF GENTLY
Shake the bottle gently before each use.

Spray a fine mist, once per nostril. Remember to sniff gently. Discard after 28 actuations.

For assistance call 1-888-939-6478
www.DYMISTA.com

DYMISTA is a trademark of Meda Pharmaceuticals Inc.

Dymista™
(azelastine hydrochloride and fluticasone propionate)
Nasal Spray
137 mcg / 50 mcg per spray

Shake the bottle gently before each use.
Initial Priming: 6 sprays or until a fine mist appears.
Repriming (only if you have not used Dymista for 14 or more days): 1 spray or until a fine mist appears.

FOR INTRANASAL USE ONLY
Manufactured by: Cipla Ltd.,
Goa, India, M. L. No. 546
For: Meda Pharmaceuticals Inc.
Somerset, NJ 08873-4120

©2012 Meda Pharmaceuticals Inc.
UC-023A1-01 Rev. 4/12
U.S. Patent Pending



3 0037-0245-06 4

Dymista™
(azelastine hydrochloride and fluticasone propionate)
Nasal Spray
137 mcg / 50 mcg per spray

Each spray delivers 0.137 mL (137 mcg azelastine hydrochloride and 50 mcg fluticasone propionate).

Contents: An aqueous suspension containing azelastine hydrochloride, fluticasone propionate, glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, phenylethyl alcohol (2.5 mg/g), edetate disodium, benzalkonium chloride (0.1 mg/g), polysorbate 80 and purified water, pH 6.

Dosage: See enclosed full Prescribing Information.

Storage: Store upright, with dust cap in place, at controlled room temperature 20°-25°C (68°-77°F). Protect from light. Do not store in the freezer or refrigerator.

Keep away from children.
FOR INTRANASAL USE ONLY

NDC 0037-0245-06
PROFESSIONAL SAMPLE:
Not for Sale

Dymista™
(azelastine hydrochloride and fluticasone propionate)
Nasal Spray
137 mcg / 50 mcg per spray

28 Metered Sprays

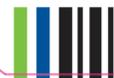
FOR INTRANASAL USE ONLY

Rx Only

6 g net fill weight

Shake the bottle gently before each use.

Batch Over
Printing Panel



Pharmacode:
150_std

Pharmacode:
342_std

(b) (4)

23 g
NDC 0037-0245-23
Dymista™
(azelastine hydrochloride
and fluticasone propionate)
Nasal Spray
137 mcg / 50 mcg per spray

IZ12 A

← Cipla Inventory code

Read PATIENT INSTRUCTIONS FOR USE
for additional information on how
to use the product.

Dosing Instructions



1 CLEAR YOUR NOSE
Clear your nostrils by gently blowing
your nose.



2 LOOK AT YOUR TOES
Tilt your head down to keep the
medicine from going into your throat.



3 SPRAY AND SNIFF GENTLY
Shake the bottle gently before
each use.
Spray a fine mist, once per nostril.
Remember to sniff gently.
Discard after 120 actuations.

For assistance call 1-888-939-6478
www.DYMISTA.com

DYMISTA is a trademark of
Meda Pharmaceuticals Inc.

Dymista™
(azelastine hydrochloride
and fluticasone propionate)
Nasal Spray
137 mcg / 50 mcg per spray

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

**Initial Priming: 6 sprays or
until a fine mist appears.**

Repriming (only if you have not
used Dymista for 14 or more
days): 1 spray or until a fine
mist appears.

FOR INTRANASAL USE ONLY

Manufactured by: Cipla Ltd.,
Goa, India, M. L. No. 546
For: Meda Pharmaceuticals Inc.
Somerset, New Jersey 08873-4120
©2012 Meda Pharmaceuticals Inc.
UC-023A6-01 Rev. 4/12
U.S. Patent Pending



3 0037-0245-23 1

Dymista™
(azelastine hydrochloride
and fluticasone propionate)
Nasal Spray
137 mcg / 50 mcg per spray

Each spray delivers 0.137 mL
(137 mcg azelastine hydrochloride
and 50 mcg fluticasone propionate).

Contents: An aqueous suspension
containing azelastine hydrochloride,
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microcrystalline cellulose and
carboxymethylcellulose sodium,
phenylethyl alcohol (2.5 mg/g),
edetate disodium, benzalkonium
chloride (0.1 mg/g), polysorbate 80
and purified water, pH 6.

Dosage: See enclosed full
Prescribing Information.

Storage:
Store upright, with dust cap
in place, at controlled room
temperature 20°-25°C (68°-77°F).
Protect from light. Do not store
in the freezer or refrigerator.
Keep away from children.

FOR INTRANASAL USE ONLY

NDC 0037-0245-23

Dymista™
(azelastine hydrochloride
and
fluticasone propionate)
Nasal Spray
137 mcg / 50 mcg per spray

120 Metered Sprays
**FOR INTRANASAL
USE ONLY**

Rx Only
23 g net fill weight

Shake the bottle gently
before each use.

Batch Over
Printing Panel



Pharmacode:
342_std

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/s/

BADRUL A CHOWDHURY
05/01/2012