

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ASTEPRO (azelastine hydrochloride) Nasal Spray 0.1%
ASTEPRO (azelastine hydrochloride) Nasal Spray 0.15%

Initial U.S. Approval: 1996

INDICATIONS AND USAGE

ASTEPRO Nasal Spray is an H₁ receptor antagonist indicated for the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older. (1.1)

DOSAGE AND ADMINISTRATION

For intranasal use only (2.3).

Seasonal allergic rhinitis:

- ASTEPRO Nasal Spray 0.1% and 0.15%: 1 or 2 sprays per nostril twice daily in adults and adolescents 12 years of age and older (2.1)
- ASTEPRO Nasal Spray 0.15%: 2 sprays per nostril once daily in adults and adolescents 12 years of age and older (2.1)

Perennial allergic rhinitis:

- ASTEPRO Nasal Spray 0.15%: 2 sprays per nostril twice daily in adults and adolescents 12 years of age and older (2.2)

- Prime ASTEPRO Nasal Spray before initial use and when it has not been used for 3 or more days. (2.3)

DOSAGE FORMS AND STRENGTHS

ASTEPRO Nasal Spray 0.1%: 137 mcg of azelastine hydrochloride in each 0.137 mL spray (3).
ASTEPRO Nasal Spray 0.15%: 205.5 mcg of azelastine hydrochloride in each 0.137 mL spray (3).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

The most common adverse reactions (≥2% incidence) are: bitter taste, nasal discomfort, epistaxis, headache, fatigue, somnolence and sneezing (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MEDA Pharmaceuticals Inc. at 1-800-526-3840 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

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

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

Revised mm/yy

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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 **1.1 Allergic Rhinitis**

4 ASTEPRO Nasal Spray 0.1% and 0.15% is indicated for the relief of the symptoms
5 of seasonal and perennial allergic rhinitis in patients 12 years of age and older.

6
7 **2 DOSAGE AND ADMINISTRATION**

8 **2.1 Seasonal Allergic Rhinitis**

9 The recommended dose of ASTEPRO Nasal Spray 0.1% and 0.15% is 1 or 2 sprays
10 per nostril twice daily for seasonal allergic rhinitis. ASTEPRO Nasal Spray 0.15% may
11 also be administered as 2 sprays per nostril once daily.

12 **2.2 Perennial Allergic Rhinitis**

13 The recommended dose of ASTEPRO Nasal Spray 0.15% for perennial allergic
14 rhinitis is 2 sprays per nostril twice daily.

15 **2.3 Important Administration Instructions**

16 Administer ASTEPRO Nasal Spray by the intranasal route only.

17
18 Priming: Prime ASTEPRO Nasal Spray before initial use by releasing 6 sprays or
19 until a fine mist appears. When ASTEPRO Nasal Spray has not been used for 3 or more
20 days, reprime with 2 sprays or until a fine mist appears. Avoid spraying ASTEPRO Nasal
21 Spray into the eyes.

22
23 **3 DOSAGE FORMS AND STRENGTHS**

24 ASTEPRO Nasal Spray is a nasal spray solution. Each spray of ASTEPRO Nasal
25 Spray 0.1% delivers a volume of 0.137 mL solution containing 137 mcg of azelastine
26 hydrochloride. Each spray of ASTEPRO Nasal Spray 0.15% delivers a volume of 0.137
27 mL solution containing 205.5 mcg of azelastine hydrochloride.

28
29 **4 CONTRAINDICATIONS**

30 None.

31
32 **5 WARNINGS AND PRECAUTIONS**

33 **5.1 Activities Requiring Mental Alertness**

34 In clinical trials, the occurrence of somnolence has been reported in some patients
35 taking ASTEPRO Nasal Spray [*see Adverse Reactions (6.1)*]. Patients should be
36 cautioned against engaging in hazardous occupations requiring complete mental alertness
37 and motor coordination such as operating machinery or driving a motor vehicle after
38 administration of ASTEPRO Nasal Spray. Concurrent use of ASTEPRO Nasal Spray
39 with alcohol or other central nervous system depressants should be avoided because
40 additional reductions in alertness and additional impairment of central nervous system
41 performance may occur [*see Drug Interactions (7.1)*].

42
43 **6 ADVERSE REACTIONS**

44 Use of ASTEPRO Nasal Spray has been associated with somnolence [*see Warnings
45 and Precautions (5.1)*].

46 **6.1 Clinical Trials Experience**

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

ASTEPRO Nasal Spray 0.1%

The safety data described below reflect exposure to ASTEPRO Nasal Spray 0.1% in 713 patients 12 years of age and older from 2 clinical trials of 2 weeks to 12 months duration. In a 2 week, double-blind, placebo-controlled, and active controlled (Astelin[®] Nasal Spray; azelastine hydrochloride) clinical trial, 285 patients (115 males and 170 females) 12 years of age and older with seasonal allergic rhinitis were treated with ASTEPRO Nasal Spray 0.1% one or two sprays per nostril daily. In the 12 month open-label, active controlled (Astelin Nasal Spray) clinical trial, 428 patients (207 males and 221 females) 12 years of age and older with perennial allergic rhinitis and/or nonallergic rhinitis were treated with ASTEPRO Nasal Spray 0.1% two sprays per nostril twice daily. The racial and ethnic distribution for the 2 clinical trials was 82% white, 8% black, 6% Hispanic, 3% Asian, and <1% other.

Adults and Adolescents 12 Years of Age and Older

In the two week clinical trial, 835 patients 12 years of age and older with seasonal allergic rhinitis were treated with one of six treatments: one spray per nostril of either ASTEPRO Nasal Spray 0.1%, Astelin Nasal Spray or placebo twice daily; or 2 sprays per nostril of ASTEPRO Nasal Spray 0.1%, Astelin Nasal Spray, or placebo twice daily. Overall, adverse reactions were more common in the ASTEPRO Nasal Spray 0.1% treatment groups (21-28%) than in the placebo groups (16-20%). Overall, less than 1% of patients discontinued due to adverse reactions and withdrawal due to adverse reactions was similar among the treatment groups.

Table 1 contains adverse reactions reported with frequencies greater than or equal to 2% and more frequently than placebo in patients treated with ASTEPRO Nasal Spray 0.1% in the controlled clinical trial described above.

Table 1. Adverse Reactions Reported in $\geq 2\%$ Incidence in a Placebo-Controlled Trial of 2 Weeks Duration with ASTEPRO Nasal Spray 0.1% in Adult and Adolescent Patients with Seasonal Allergic Rhinitis						
	1 spray twice daily			2 sprays twice daily		
	ASTEPRO Nasal Spray 0.1% (N=139)	Astelin Nasal Spray (N=137)	Vehicle Placebo (N=137)	ASTEPRO Nasal Spray 0.1% (N=146)	Astelin Nasal Spray (N=137)	Vehicle Placebo (N=138)
Bitter Taste	8 (6%)	13 (10%)	2 (2%)	10 (7%)	11 (8%)	3 (2%)
Epistaxis	3 (2%)	8 (6%)	3 (2%)	4 (3%)	3 (2%)	0 (0%)
Headache	2 (1%)	5 (4%)	1 (<1%)	4 (3%)	3 (2%)	1 (<1%)
Nasal Discomfort	0 (0%)	3 (2%)	1 (<1%)	2 (1%)	6 (4%)	0 (0%)
Fatigue	0 (0%)	1 (<1%)	1 (<1%)	3 (2%)	3 (2%)	1 (<1%)
Somnolence	2 (1%)	2 (2%)	0 (0%)	3 (2%)	2 (1%)	0 (0%)

Long-Term (12 Month) Safety Trial:

In the 12 month, open-label, active-controlled, long-term safety trial, 862 patients 12 years of age and older with perennial allergic and/or nonallergic rhinitis were treated with ASTEPRO Nasal Spray 0.1% two sprays per nostril twice daily or Astelin Nasal Spray two sprays per nostril twice daily. The most frequently reported adverse reactions were

83 headache, bitter taste, epistaxis, and nasopharyngitis and were generally similar between
84 treatment groups. Focused nasal examinations were performed and showed that the
85 incidence of nasal mucosal ulceration in each treatment group was approximately 1% at
86 baseline and approximately 1.5% throughout the 12 month treatment period. In each
87 treatment group, 5-7% of patients had mild epistaxis. No patients had reports of nasal
88 septal perforation or severe epistaxis. Twenty-two patients (5%) treated with ASTEPRO
89 Nasal Spray 0.1% and 17 patients (4%) treated with Astelin Nasal Spray discontinued from
90 the trial due to adverse events.

91

92 *ASTEPRO Nasal Spray 0.15%*

93 The safety data described below reflect exposure to ASTEPRO Nasal Spray 0.15%
94 in 1858 patients (12 years of age and older) with seasonal or perennial allergic rhinitis
95 from 8 clinical trials of 2 weeks to 12 months duration. In 7 double-blind, placebo-
96 controlled clinical trials of 2 to 4 weeks duration, 1544 patients (560 males and 984
97 females) with seasonal or perennial allergic rhinitis were treated with ASTEPRO Nasal
98 Spray 0.15% two sprays per nostril once or twice daily. In the 12 month open-label,
99 active-controlled clinical trial, 466 patients (156 males and 310 females) with perennial
100 allergic rhinitis were treated with ASTEPRO Nasal Spray 0.15% two sprays per nostril
101 twice daily. Of these 466 patients, 152 had participated in the 4-week placebo-controlled
102 perennial allergic rhinitis clinical trials. The racial distribution for the 8 clinical trials
103 was 80% white, 13% black, 2% Asian, and 5% other.

104

105 Adults and Adolescents 12 Years of Age and Older

106 In the 7 placebo controlled clinical trials of 2 to 4 week duration, 2343 patients with
107 seasonal allergic rhinitis and 540 patients with perennial allergic rhinitis were treated
108 with two sprays per nostril of either ASTEPRO Nasal Spray 0.15% or placebo once or
109 twice daily. Overall, adverse reactions were more common in the ASTEPRO Nasal Spray
110 0.15% treatment groups (16-31%) than in the placebo groups (11-24%). Overall, less
111 than 2% of patients discontinued due to adverse reactions and withdrawal due to adverse
112 reactions was similar among the treatment groups.

113 Table 2 contains adverse reactions reported with frequencies greater than or equal to
114 2% and more frequently than placebo in patients treated with ASTEPRO Nasal Spray
115 0.15% in the seasonal and perennial allergic rhinitis controlled clinical trials.

116

Table 2. Adverse Reactions with $\geq 2\%$ Incidence in Placebo-Controlled Trials of 2 to 4 Weeks' Duration with ASTEPRO Nasal Spray 0.15% in Adult and Adolescent Patients With Seasonal or Perennial Allergic Rhinitis				
	2 sprays twice daily		2 sprays once daily	
	ASTEPRO Nasal Spray 0.15% (N=523)	Vehicle Placebo (N=523)	ASTEPRO Nasal Spray 0.15% (N=1021)	Vehicle Placebo (N=816)
Bitter Taste	31 (6%)	5 (1%)	38 (4%)	2 (<1%)
Nasal Discomfort	18 (3%)	12 (2%)	37 (4%)	7 (1%)
Epistaxis	5 (1%)	7 (1%)	21 (2%)	14 (2%)
Sneezing	9 (2%)	1 (<1%)	14 (1%)	0 (0%)

117

118 In the above trials, somnolence was reported in <1% of patients treated with ASTEPRO
119 Nasal Spray 0.15% (11 of 1544) or vehicle placebo (1 of 1339).

120

121 Long-Term (12 Month) Safety Trial:

122 In the 12 month, open-label, active-controlled, long-term safety trial, 466 patients (12
123 years of age and older) with perennial allergic rhinitis were treated with ASTEPRO Nasal
124 Spray 0.15% two sprays per nostril twice daily and 237 patients were treated with
125 mometasone nasal spray two sprays per nostril once daily. The most frequently reported
126 adverse reactions (>5%) with ASTEPRO Nasal Spray 0.15% were bitter taste, headache,
127 sinusitis, and epistaxis. Focused nasal examinations were performed and no nasal
128 ulcerations or septal perforations were observed. In each treatment group, approximately
129 3% of patients had mild epistaxis. No patients had reports of severe epistaxis. Fifty-four
130 patients (12%) treated with ASTEPRO Nasal Spray 0.15% and 17 patients (7%) treated
131 with mometasone nasal spray discontinued from the trial due to adverse events.
132

133 **6.2 Postmarketing Experience**

134 The following adverse reactions have been identified during the post approval use
135 of the Astelin brand of azelastine hydrochloride 0.1% nasal spray (total daily dose 0.55
136 mg to 1.1 mg). Because these reactions are reported voluntarily from a population of
137 uncertain size, it is not always possible to reliably estimate their frequency or establish a
138 causal relationship to drug exposure. Adverse reactions reported include the following:
139 anaphylactoid reaction, application site irritation, atrial fibrillation, blurred vision, chest
140 pain, confusion, dizziness, dyspnea, facial edema, hypertension, involuntary muscle
141 contractions, nervousness, palpitations, paresthesia, parosmia, paroxysmal sneezing,
142 pruritus, rash, disturbance or loss of sense of smell and/or taste, tachycardia, tolerance,
143 urinary retention, and xerophthalmia.
144

145 **7 DRUG INTERACTIONS**

146 **7.1 Central Nervous System Depressants**

147 Concurrent use of ASTEPRO Nasal Spray with alcohol or other central nervous
148 system depressants should be avoided because reductions in alertness and impairment of
149 central nervous system performance may occur [*see Warnings and Precautions (5.1)*].

150 **7.2 Erythromycin and Ketoconazole**

151 Interaction studies investigating the cardiac effects, as measured by the corrected
152 QT interval (QTc), of concomitantly administered oral azelastine hydrochloride and
153 erythromycin or ketoconazole were conducted. Oral erythromycin (500 mg three times
154 daily for 7 days) had no effect on azelastine pharmacokinetics or QTc based on analyses
155 of serial electrocardiograms. Ketoconazole (200 mg twice daily for 7 days) interfered
156 with the measurement of azelastine plasma concentrations on the analytic HPLC;
157 however, no effects on QTc were observed [*see Clinical Pharmacology (12.2) and*
158 *(12.3)*].

159 **7.3 Cimetidine**

160 Cimetidine (400 mg twice daily) increased the mean C_{max} and AUC of orally
161 administered azelastine hydrochloride (4 mg twice daily) by approximately 65%
162 [*see Clinical Pharmacology (12.3)*].
163

164 **8 USE IN SPECIFIC POPULATIONS**

165 **8.1 Pregnancy**

166 Pregnancy Category C: There are no adequate and well-controlled clinical trials in
167 pregnant women. Azelastine hydrochloride has been shown to cause developmental
168 toxicity in mice, rats, and rabbits. ASTEPRO Nasal Spray should be used during
169 pregnancy only if the potential benefit justifies the potential risk to the fetus.

170 Teratogenic Effects: In mice, azelastine hydrochloride caused embryo-fetal death,
171 malformations (cleft palate; short or absent tail; fused, absent or branched ribs), delayed
172 ossification, and decreased fetal weight at an oral dose approximately 170 times the
173 maximum recommended human daily intranasal dose (MRHDID) in adults on a mg/m²
174 basis. This dose also caused maternal toxicity as evidenced by decreased body weight.
175 Neither fetal nor maternal effects occurred at a dose that was approximately 7 times the
176 MRHDID.

177 In rats, azelastine hydrochloride caused malformations (oligo- and brachydactylia),
178 delayed ossification and skeletal variations, in the absence of maternal toxicity, at an oral
179 dose approximately 150 times the MRHDID in adults on a mg/m² basis. At a dose
180 approximately 340 times the MRHDID, azelastine hydrochloride also caused embryo-
181 fetal death and decreased fetal weight; however, this dose caused severe maternal
182 toxicity. Neither fetal nor maternal effects occurred at a dose approximately 15 times the
183 MRHDID.

184 In rabbits, azelastine hydrochloride caused abortion, delayed ossification and
185 decreased fetal weight at oral doses approximately 300 times the MRHDID in adults on a
186 mg/m² basis; however, these doses also resulted in severe maternal toxicity. Neither fetal
187 nor maternal effects occurred at a dose approximately 3 times the MRHDID.

188 **8.3 Nursing Mothers**

189 It is not known whether azelastine hydrochloride is excreted in human milk.
190 Because many drugs are excreted in human milk, caution should be exercised when
191 ASTEPRO Nasal Spray is administered to a nursing woman.

192 **8.4 Pediatric Use**

193 Safety and effectiveness of ASTEPRO Nasal Spray in pediatric patients below the
194 age of 12 years have not been established.

195 **8.5 Geriatric Use**

196 Clinical trials of ASTEPRO Nasal Spray did not include sufficient numbers of
197 patients 65 years of age and older to determine whether they respond differently from
198 younger patients. Other reported clinical experience has not identified differences in
199 responses between the elderly and younger patients. In general, dose selection for an
200 elderly patient should be cautious, usually starting at the low end of the dosing range,
201 reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of
202 concomitant disease or other drug therapy.

203

204 **10 OVERDOSAGE**

205 There have been no reported overdosages with ASTEPRO Nasal Spray. Acute
206 overdose by adults with this dosage form is unlikely to result in clinically significant
207 adverse events, other than increased somnolence, since one 30-mL bottle of ASTEPRO
208 Nasal Spray 0.1% contains up to 30 mg of azelastine hydrochloride and one 30-mL bottle
209 ASTEPRO Nasal Spray 0.15% contains up to 45 mg of azelastine hydrochloride. Clinical
210 trials in adults with single doses of the oral formulation of azelastine hydrochloride (up to
211 16 mg) have not resulted in increased incidence of serious adverse events. General

212 supportive measures should be employed if overdose occurs. There is no known
213 antidote to ASTEPRO Nasal Spray. Oral ingestion of antihistamines has the potential to
214 cause serious adverse effects in children. Accordingly, ASTEPRO Nasal Spray should be
215 kept out of the reach of children. Oral doses of 120 mg/kg and greater (approximately
216 300 times the maximum recommended human daily intranasal dose [MRHDID] in adults
217 and children on a mg/m² basis) were lethal in mice. Responses seen prior to death were
218 tremor, convulsions, decreased muscle tone, and salivation. In dogs, single oral doses as
219 high as 10 mg/kg (approximately 160 times the MRHDID in adults and children on a
220 mg/m² basis) were well tolerated, but single oral doses of 20 mg/kg were lethal.

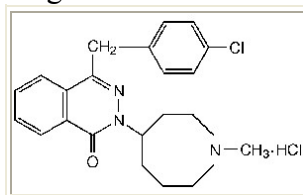
221

222 11 DESCRIPTION

223 ASTEPRO (azelastine hydrochloride) Nasal Spray 0.1%, 137 micrograms (mcg), is
224 an antihistamine formulated as a metered-spray solution for intranasal administration.
225 ASTEPRO (azelastine hydrochloride) Nasal Spray 0.15%, 205.5 micrograms (mcg), is
226 formulated as a metered-spray solution for intranasal administration.

227

228 Azelastine hydrochloride occurs as a white, almost odorless, crystalline powder
229 with a bitter taste. It has a molecular weight of 418.37. It is sparingly soluble in water,
230 methanol, and propylene glycol and slightly soluble in ethanol, octanol, and glycerine. It
231 has a melting point of about 225°C and the pH of a saturated solution is between 5.0 and
232 5.4. Its chemical name is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-
233 (hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride. Its molecular formula is
234 C₂₂H₂₄ClN₃O·HCl with the following chemical structure:



235

236 ASTEPRO Nasal Spray 0.1% contains 0.1% azelastine hydrochloride in an isotonic
237 aqueous solution containing sorbitol, sucralose, hypromellose, sodium citrate, edetate
238 disodium, benzalkonium chloride (125 mcg/mL), and purified water (pH 6.4).

239 After priming [*see Dosage and Administration (2.3)*], each metered spray delivers a
240 0.137 mL mean volume containing 137 mcg of azelastine hydrochloride (equivalent to
241 125 mcg of azelastine base). The 30-mL (net weight 30 gm of solution) bottle provides
242 200 metered sprays.

243 ASTEPRO Nasal Spray 0.15% contains 0.15% azelastine hydrochloride in an
244 isotonic aqueous solution containing sorbitol, sucralose, hypromellose, sodium citrate,
245 edetate disodium, benzalkonium chloride (125 mcg/mL), and purified water (pH 6.4).

246 After priming [*see Dosage and Administration (2.3)*], each metered spray delivers a
247 0.137 mL mean volume containing 205.5 mcg of azelastine hydrochloride (equivalent to
248 187.6 mcg of azelastine base). The 17 mL (net weight 17 gm of solution) bottle provides
249 106 metered sprays and the 30 mL (net weight 30 gm of solution) bottle provides 200
250 metered sprays.

251

252 12 CLINICAL PHARMACOLOGY

253 **12.1 Mechanism of Action**

254 Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H₁ -
255 receptor antagonist activity in isolated tissues, animal models, and humans. ASTEPRO
256 Nasal Spray is administered as a racemic mixture with no difference in pharmacologic
257 activity noted between the enantiomers in *in vitro* studies. The major metabolite,
258 desmethylazelastine, also possesses H₁ -receptor antagonist activity.

259 **12.2 Pharmacodynamics**

260 Cardiac Effects:

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

266 Interaction studies investigating the cardiac repolarization effects of concomitantly
267 administered oral azelastine hydrochloride and erythromycin or ketoconazole were
268 conducted. Oral erythromycin had no effect on azelastine pharmacokinetics or QTc based
269 on analysis of serial electrocardiograms. Ketoconazole interfered with the measurement
270 of azelastine plasma levels; however, no effects on QTc were observed [*see Drug*
271 *Interactions (7.2)*].

272 **12.3 Pharmacokinetics**

273 *Absorption:* After intranasal administration of 2 sprays per nostril (548 mcg total
274 dose) of ASTEPRO Nasal Spray 0.1%, the mean azelastine peak plasma concentration
275 (C_{max}) is 200 pg/mL, the mean extent of systemic exposure (AUC) is 5122 pg•hr/mL and
276 the median time to reach C_{max} (t_{max}) is 3 hours. After intranasal administration of 2 sprays
277 per nostril (822 mcg total dose) of ASTEPRO Nasal Spray 0.15%, the mean azelastine
278 peak plasma concentration (C_{max}) is 409 pg/mL, the mean extent of systemic exposure
279 (AUC) is 9312 pg•hr/mL and the median time to reach C_{max} (t_{max}) is 4 hours. The systemic
280 bioavailability of azelastine hydrochloride is approximately 40% after intranasal
281 administration.

282 *Distribution:* Based on intravenous and oral administration, the steady-state volume
283 of distribution of azelastine is 14.5 L/kg. *In vitro* studies with human plasma indicate that
284 the plasma protein binding of azelastine and its metabolite, desmethylazelastine, are
285 approximately 88% and 97%, respectively.

286 *Metabolism:* Azelastine is oxidatively metabolized to the principal active
287 metabolite, desmethylazelastine, by the cytochrome P450 enzyme system. The specific
288 P450 isoforms responsible for the biotransformation of azelastine have not been
289 identified. After a single-dose, intranasal administration of ASTEPRO Nasal Spray 0.1%
290 (548 mcg total dose), the mean desmethylazelastine C_{max} is 23 pg/mL, the AUC is 2131
291 pg•hr/mL and the median t_{max} is 24 hours. After a single-dose, intranasal administration
292 of ASTEPRO Nasal Spray 0.15% (822 mcg total dose), the mean desmethylazelastine
293 C_{max} is 38 pg/mL, the AUC is 3824 pg•hr/mL and the median t_{max} is 24 hours. After
294 intranasal dosing of azelastine to steady-state, plasma concentrations of
295 desmethylazelastine range from 20-50% of azelastine concentrations.

296 *Elimination:* Following intranasal administration of ASTEPRO Nasal Spray 0.1%,
297 the elimination half-life of azelastine is 22 hours while that of desmethylazelastine is 52
298 hours. Following intranasal administration of ASTEPRO Nasal Spray 0.15%, the

299 elimination half-life of azelastine is 25 hours while that of desmethylazelastine is 57
300 hours. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was
301 excreted in the feces with less than 10% as unchanged azelastine.

302 *Special Populations:*

303 *Hepatic Impairment:* Following oral administration, pharmacokinetic parameters
304 were not influenced by hepatic impairment.

305 *Renal Impairment:* Based on oral, single-dose studies, renal insufficiency
306 (creatinine clearance <50 mL/min) resulted in a 70-75% higher C_{max} and AUC compared
307 to healthy subjects. Time to maximum concentration was unchanged.

308 *Age:* Following oral administration, pharmacokinetic parameters were not
309 influenced by age.

310 *Gender:* Following oral administration, pharmacokinetic parameters were not
311 influenced by gender.

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

313 *Drug-Drug Interactions:*

314 *Erythromycin:* Co-administration of orally administered azelastine (4 mg twice
315 daily) with erythromycin (500 mg three times daily for 7 days) resulted in C_{max} of $5.36 \pm$
316 2.6 ng/mL and AUC of 49.7 ± 24 ng•h/mL for azelastine, whereas, administration of
317 azelastine alone resulted in C_{max} of 5.57 ± 2.7 ng/mL and AUC of 48.4 ± 24 ng•h/mL for
318 azelastine [*see Drug Interactions (7.2)*].

319 *Cimetidine and Ranitidine:* In a multiple-dose, steady-state drug interaction trial
320 in healthy subjects, cimetidine (400 mg twice daily) increased orally administered mean
321 azelastine (4 mg twice daily) concentrations by approximately 65%. Co-administration of
322 orally administered azelastine (4 mg twice daily) with ranitidine hydrochloride (150 mg
323 twice daily) resulted in C_{max} of 8.89 ± 3.28 ng/mL and AUC of 88.22 ± 40.43 ng•h/mL for
324 azelastine, whereas, administration of azelastine alone resulted in C_{max} of 7.83 ± 4.06
325 ng/mL and AUC of 80.09 ± 43.55 ng•h/mL for azelastine [*see Drug Interactions (7.3)*].

326 *Theophylline:* No significant pharmacokinetic interaction was observed with the
327 co-administration of an oral 4 mg dose of azelastine hydrochloride twice daily and
328 theophylline 300 mg or 400 mg twice daily.

329

330 **13 NONCLINICAL TOXICOLOGY**

331 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

332 In 2-year carcinogenicity studies in rats and mice, azelastine hydrochloride did not
333 show evidence of carcinogenicity at oral doses up to 30 mg/kg and 25 mg/kg,
334 respectively. These doses were approximately 150 and 60 times the maximum
335 recommended human daily intranasal dose [MRHDID] on a mg/m² basis.

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

339 Reproduction and fertility studies in rats showed no effects on male or female
340 fertility at oral doses up to 30 mg/kg (approximately 150 times the MRHDID in adults on
341 a mg/m² basis). At 68.6 mg/kg (approximately 340 times the MRHDID on a mg/m²
342 basis), the duration of estrous cycles was prolonged and copulatory activity and the
343 number of pregnancies were decreased. The numbers of corpora lutea and implantations
344 were decreased; however, pre-implantation loss was not increased.

345 **13.2 Animal Toxicology and/or Pharmacology**

346 *Reproductive Toxicology Studies*

347 Azelastine hydrochloride has been shown to cause developmental toxicity.
348 Treatment of mice with an oral dose of 68.6 mg/kg (approximately 170 times the
349 maximum recommended human daily intranasal dose [MRHDID] on a mg/m² basis)
350 caused embryo-fetal death, malformations (cleft palate; short or absent tail; fused, absent
351 or branched ribs), delayed ossification, and decreased fetal weight. This dose also caused
352 maternal toxicity as evidenced by decreased body weight. Neither fetal nor maternal
353 effects occurred at a dose of 3 mg/kg (approximately 7 times the MRHDID on a mg/m²
354 basis).

355 In rats, an oral dose of 30 mg/kg (approximately 150 times the MRHDID on a
356 mg/m² basis) caused malformations (oligo- and brachydactylia), delayed ossification and
357 skeletal variations, in the absence of maternal toxicity. At 68.6 mg/kg (approximately 340
358 times the MRHDID on a mg/m² basis) azelastine hydrochloride also caused embryo-fetal
359 death and decreased fetal weight; however, the 68.6 mg/kg dose caused severe maternal
360 toxicity. Neither fetal nor maternal effects occurred at a dose of 3 mg/kg (approximately
361 15 times the MRHDID on a mg/m² basis).

362 In rabbits, oral doses of 30 mg/kg and greater (approximately 300 times the
363 MRHDID on a mg/m² basis) caused abortion, delayed ossification and decreased fetal
364 weight; however, these doses also resulted in severe maternal toxicity. Neither fetal nor
365 maternal effects occurred at a dose of 0.3 mg/kg (approximately 3 times the MRHDID on
366 a mg/m² basis).

367

368 **14 CLINICAL STUDIES**

369 **14.1 Seasonal Allergic Rhinitis**

370 *ASTEPRO Nasal Spray 0.1%*

371 The efficacy and safety of ASTEPRO Nasal Spray 0.1% was evaluated in a 2 week,
372 randomized, multicenter, double-blind, placebo-controlled clinical trial including 834
373 adult and adolescent patients 12 years of age and older with symptoms of seasonal
374 allergic rhinitis. The population was 12 to 83 years of age (60% female, 40% male; 69%
375 white, 16% black, 12% Hispanic, 2% Asian, 1% other).

376 Patients were randomized to one of six treatment groups: 1 spray per nostril of
377 either ASTEPRO Nasal Spray 0.1%, Astelin (azelastine hydrochloride) Nasal Spray or
378 vehicle placebo twice daily; or 2 sprays per nostril of ASTEPRO Nasal Spray 0.1%,
379 Astelin (azelastine hydrochloride) Nasal Spray or vehicle placebo twice daily.

380 Assessment of efficacy was based on the 12-hour reflective total nasal symptom
381 score (rTNSS) assessed daily in the morning and evening, in addition to the instantaneous
382 total nasal symptom score (iTNSS) and other supportive secondary efficacy variables.
383 TNSS is calculated as the sum of the patients' scoring of the four individual nasal
384 symptoms (rhinorrhea, nasal congestion, sneezing, and nasal itching) on a 0 to 3
385 categorical severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). The rTNSS
386 required patients to record symptom severity over the previous 12 hours. For the primary
387 efficacy endpoint, the mean change from baseline rTNSS, morning (AM) and evening
388 (PM) rTNSS scores were summed for each day (maximum score of 24) and then
389 averaged over the 2 weeks. The iTNSS, recorded immediately prior to the next dose,

390 were assessed as an indication of whether the effect was maintained over the dosing
391 interval.

392 In this trial, ASTEPRO Nasal Spray 0.1% two sprays twice a day demonstrated a
393 greater decrease in rTNSS and iTNSS than placebo and the difference was statistically
394 significant. The trial results are presented in Table 3 (Trial 1).

395 The efficacy of ASTEPRO Nasal Spray 0.1% one spray per nostril twice daily for
396 seasonal allergic rhinitis is supported by two, 2-week, placebo controlled clinical trials
397 with Astelin (azelastine hydrochloride) Nasal Spray in 413 patients with seasonal allergic
398 rhinitis. In these trials, efficacy was assessed using the TNSS (described above). Astelin
399 Nasal Spray demonstrated a greater decrease from baseline in the summed AM and PM
400 rTNSS compared with placebo and the difference was statistically significant.

401

402 *ASTEPRO Nasal Spray 0.15%*

403 The efficacy and safety of ASTEPRO Nasal Spray 0.15% in seasonal allergic
404 rhinitis was evaluated in five randomized, multicenter, double-blind, placebo-controlled
405 clinical trials in 2499 adult and adolescent patients 12 years and older with symptoms of
406 seasonal allergic rhinitis (Trials 2, 3, 4, 5, and 6). The population of the trials was 12 to
407 83 years of age (64% female, 36% male; 81% white, 12% black, <2% Asian, 5% other;
408 23% Hispanic, 77% non-Hispanic). Assessment of efficacy was based on the rTNSS,
409 iTNSS as described above, and other supportive secondary efficacy variables. The
410 primary efficacy endpoint was the mean change from baseline in rTNSS over 2 weeks.

411 Two 2-week seasonal allergic rhinitis trials evaluated the efficacy of ASTEPRO
412 Nasal Spray 0.15% dosed at 2 sprays twice daily. The first trial (Trial 2) compared the
413 efficacy of ASTEPRO Nasal Spray 0.15% and Astelin (azelastine hydrochloride) Nasal
414 Spray to vehicle placebo. The other trial (Trial 3) compared the efficacy of ASTEPRO
415 Nasal Spray 0.15% and ASTEPRO Nasal Spray 0.1% to vehicle placebo. In these two
416 trials, ASTEPRO Nasal Spray 0.15% demonstrated greater decreases in rTNSS than
417 placebo and the differences were statistically significant (Table 3).

418 Three 2-week seasonal allergic rhinitis trials evaluated the efficacy of ASTEPRO
419 Nasal Spray 0.15% dosed at 2 sprays once daily compared to the vehicle placebo. Trial 4
420 demonstrated a greater decrease in rTNSS than placebo and the difference was
421 statistically significant (Table 3). Trial 5 and Trial 6 were conducted in patients with
422 Texas mountain cedar allergy. In Trial 5 and Trial 6, ASTEPRO Nasal Spray 0.15%
423 demonstrated a greater decrease in rTNSS than placebo and the differences were
424 statistically significant (Trials 5 and 6; Table 3). Instantaneous TNSS results for the once
425 daily dosing regimen of ASTEPRO Nasal Spray 0.15% are shown in Table 4. In Trials 5
426 and 6, ASTEPRO Nasal Spray 0.15% demonstrated a greater decrease in iTNSS than
427 placebo and the differences were statistically significant.

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429
430

Table 3. Mean Change from Baseline in Reflective TNSS over 2 Weeks* in Adults and Children ≥ 12 years with Seasonal Allergic Rhinitis							
	Treatment (sprays per nostril)	n	Baseline LS Mean	Change from Baseline	Difference From Placebo		
					LS Mean	95% CI	P value
Trial 1							
Two sprays twice daily	ASTEPRO Nasal Spray 0.1%	146	18.0	-5.0	-2.2	-3.2,-1.2	<0.001
	Astelin Nasal Spray	137	18.2	-4.2	-1.4	-2.4,-0.4	0.01
	Vehicle Placebo	138	18.2	-2.8			
One spray twice daily	ASTEPRO Nasal Spray 0.1%	139	18.2	-4.2	-0.7	-1.7, 0.3	0.18
	Astelin Nasal Spray	137	18.1	-4.0	-0.4	-1.5, 0.6	0.41
	Vehicle Placebo	137	18.0	-3.5			
Trial 2							
Two sprays twice daily	ASTEPRO Nasal Spray 0.15%	153	18.2	-4.3	-1.2	-2.1, -0.3	0.01
	Astelin Nasal Spray	153	17.9	-3.9	-0.9	-1.8, 0.1	0.07
	Vehicle Placebo	153	18.1	-3.0			
Trial 3							
Two sprays twice daily	ASTEPRO Nasal Spray 0.15%	177	17.7	-5.1	-3.0	-3.9, -2.1	<0.001
	ASTEPRO Nasal Spray 0.1%	169	18.2	-4.2	-2.1	-3.0, -1.2	<0.001
	Vehicle Placebo	177	17.7	-2.1			
Trial 4							
Two Sprays once daily	ASTEPRO Nasal Spray 0.15%	238	17.4	-3.4	-1.0	-1.7, -0.3	0.008
	Vehicle Placebo	242	17.4	-2.4			
Trial 5							
Two sprays once daily	ASTEPRO Nasal Spray 0.15%	266	18.5	-3.3	-1.4	-2.1, -0.8	<0.001
	Vehicle Placebo	266	18.0	-1.9			
Trial 6							
Two sprays once daily	ASTEPRO Nasal Spray 0.15%	251	18.5	-3.4	-1.4	-2.1, -0.7	<0.001
	Vehicle Placebo	254	18.8	-2.0			
*Sum of AM and PM rTNSS for each day (Maximum score=24) and averaged over the 14 day treatment period							

431

Table 4. Mean Change from Baseline AM Instantaneous TNSS over 2 Weeks* in Adults and Children ≥ 12 years with Seasonal Allergic Rhinitis							
	Treatment (sprays per nostril once daily)	n	Baseline LS Mean	Change from Baseline	Difference From Placebo		
					LS Mean	95% CI	P value
Trial 4							
Two sprays once daily	ASTEPRO Nasal Spray 0.15%	238	8.1	-1.3	-0.2	-0.6, 0.1	0.15
	Vehicle Placebo	242	8.3	-1.1			
Trial 5							
Two sprays once daily	ASTEPRO Nasal Spray 0.15%	266	8.7	-1.4	-0.7	-1.0, -0.4	<0.001
	Vehicle Placebo	266	8.3	-0.7			
Trial 6							
Two sprays once daily	ASTEPRO Nasal Spray 0.15%	251	8.9	-1.4	-0.6	-0.9, -0.3	<0.001
	Vehicle Placebo	254	8.9	-0.8			
*AM iTNSS for each day (Maximum score=12) and averaged over the 14 day treatment period							

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ASTEPRO Nasal Spray 0.15% at a dose of 1 spray twice daily was not studied. The ASTEPRO Nasal Spray 0.15% 1 spray twice daily dosing regimen is supported by previous findings of efficacy for Astelin (azelastine hydrochloride) Nasal Spray and a

436 favorable comparison of ASTEPRO Nasal Spray 0.15% to Astelin Nasal Spray and
437 ASTEPRO Nasal Spray 0.1% (Table 3).

438

439 **14.2 Perennial Allergic Rhinitis**

440 *ASTEPRO Nasal Spray 0.15%*

441 The efficacy and safety of ASTEPRO Nasal Spray 0.15% in perennial allergic
442 rhinitis was evaluated in one randomized, multicenter, double-blind, placebo-controlled
443 clinical trial in 578 adult and adolescent patients 12 years and older with symptoms of
444 perennial allergic rhinitis. The population of the trial was 12 to 84 years of age (68%
445 female, 32% male; 85% white, 11% black, 1% Asian, 3% other; 17% Hispanic, 83% non-
446 Hispanic).

447 Assessment of efficacy was based on the 12-hour reflective total nasal symptom score
448 (rTNSS) assessed daily in the morning and evening, the instantaneous total nasal
449 symptom score (iTNSS), and other supportive secondary efficacy variables. The primary
450 efficacy endpoint was the mean change from baseline rTNSS over 4 weeks. The one 4-
451 week perennial allergic rhinitis trial evaluated the efficacy of ASTEPRO Nasal Spray
452 0.15%, ASTEPRO Nasal Spray 0.1%, and vehicle placebo dosed at 2 sprays per nostril
453 twice daily. In this trial, ASTEPRO Nasal Spray 0.15% demonstrated a greater decrease
454 in rTNSS than placebo and the difference was statistically significant (Table 5).
455

Table 5. Mean Change from Baseline in Reflective TNSS over 4 Weeks* In Adults and Children ≥ 12 years with Perennial Allergic Rhinitis							
Treatment (sprays per nostril twice daily)		n	Baseline LS Mean	Change from Baseline	Difference From Placebo		
					LS Mean	95% CI	P value
Two sprays twice daily	ASTEPRO Nasal Spray 0.15%	192	15.8	-4.0	-0.9	-1.7, -0.1	0.03
	ASTEPRO Nasal Spray 0.1%	194	15.5	-3.8	-0.7	-1.5, 0.1	0.08
	Placebo Vehicle	192	14.7	-3.1			

*Sum of AM and PM rTNSS for each day (Maximum score=24) and averaged over the 28 day treatment period

456

457 **16 HOW SUPPLIED/STORAGE AND HANDLING**

458 ASTEPRO (azelastine hydrochloride) Nasal Spray 0.1% (NDC 0037-0242-30) is
459 supplied as a 30 mL package delivering 200 metered sprays in a high-density
460 polyethylene (HDPE) bottle fitted with a metered-dose spray pump unit. The spray pump
461 unit consists of a nasal spray pump fitted with a blue safety clip and a blue plastic dust
462 cover. The net content of the bottle is 30 mL (net weight 30 gm of solution). Each bottle
463 contains 30 mg (1 mg/mL) of azelastine hydrochloride. After priming [*see Dosage and*
464 *Administration (2.3)*], each spray delivers a fine mist containing a mean volume of 0.137
465 mL solution containing 137 mcg of azelastine hydrochloride. The correct amount of
466 medication in each spray cannot be assured before the initial priming and after 200 sprays
467 have been used, even though the bottle is not completely empty. The bottle should be
468 discarded after 200 sprays have been used.

469 ASTEPRO (azelastine hydrochloride) Nasal Spray 0.15% is supplied as a 17 mL
470 package (NDC 0037-0243-17) delivering 106 metered sprays or as a 30 mL package
471 (NDC 0037-0243-30) delivering 200 metered sprays in a high-density polyethylene
472 (HDPE) bottle fitted with a metered-dose spray pump unit. The spray pump unit consists
473 of a nasal spray pump fitted with a blue safety clip and a blue plastic dust cover. The net
474 contents of the bottles are 17 mL (net weight 17 gm of solution) or 30 mL (net weight 30

475 gm of solution). The 17 mL bottle contains 25.5 mg and the 30 mL bottle contains 45 mg
476 (1.5 mg/mL) of azelastine hydrochloride. After priming [*see Dosage and Administration*
477 (2.3)], each spray delivers a fine mist containing a mean volume of 0.137 mL solution
478 containing 205.5 mcg of azelastine hydrochloride. The correct amount of medication in
479 each spray cannot be assured before the initial priming and after 106 sprays for the 17 mL
480 bottle or 200 sprays for the 30 mL bottle have been used, even though the bottle is not
481 completely empty. The bottle should be discarded after 106 sprays for the 17 mL bottle or
482 200 sprays for the 30 mL bottle have been used.

483 ASTEPRO Nasal Spray 0.1% and 0.15% should not be used after the expiration
484 date “EXP” printed on the medicine label and carton.

485

486 **Storage:**

487 Store upright at controlled room temperature 20° - 25°C (68° - 77°F). Protect from
488 freezing.

489

490 **17 PATIENT COUNSELING INFORMATION**

491 [*See FDA-Approved Patient Labeling*]

492

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

496 **17.1 Activities Requiring Mental Alertness**

497 Somnolence has been reported in some patients taking ASTEPRO Nasal Spray.
498 Patients should be cautioned against engaging in hazardous occupations requiring
499 complete mental alertness and motor coordination such as driving or operating machinery
500 after administration of ASTEPRO Nasal Spray [*see Warnings and Precautions (5.1)*].

501 **17.2 Concurrent Use of Alcohol and other Central Nervous System Depressants**

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

506 **17.3 Common Adverse Reactions**

507 Patients should be informed that the treatment with ASTEPRO Nasal Spray may
508 lead to adverse reactions, which include bitter taste, nasal discomfort, epistaxis,
509 headache, fatigue, somnolence, and sneezing [*see Adverse Reactions (6.1)*].

510 **17.4 Priming**

511 Patients should be instructed to prime the pump before initial use and when
512 ASTEPRO Nasal Spray has not been used for 3 or more days [*see Dosage and*
513 *Administration (2.3)*].

514 **17.5 Keep Spray Out of Eyes**

515 Patients should be instructed to avoid spraying ASTEPRO Nasal Spray into their
516 eyes.

517 **17.6 Keep Out of Children’s Reach**

518 Patients should be instructed to keep ASTEPRO Nasal Spray out of the reach of
519 children. If a child accidentally ingests ASTEPRO Nasal Spray, seek medical help or call
520 a poison control center immediately.

521

522 **Manufactured by:**

523 MEDA Pharmaceuticals

524 MEDA Pharmaceuticals Inc.

525 Somerset, NJ 08873-4120

526

527 Astelin, ASTEPRO and MEDA Pharmaceuticals are registered trademarks of MEDA

528 Pharmaceuticals Inc.

529

530 **PATIENT INFORMATION**

531 ASTEPRO [*AS-ta-PRO*]

532 (azelastine hydrochloride)

533 Nasal Spray 0.1% and 0.15%

534

Important: For use in your nose only

535

536 Read this information carefully before you start using ASTEPRO Nasal Spray and each

537 time you get a refill. There may be new information. This leaflet does not take the place

538 of talking to your healthcare provider about your medical condition or your treatment.

539

540 **What is ASTEPRO Nasal Spray?**

541 • ASTEPRO Nasal Spray 0.1% and 0.15% is a prescription medicine used to relieve

542 symptoms of seasonal allergies in people age 12 and older.

543 • ASTEPRO Nasal Spray 0.15% is also used to relieve symptoms of year-round allergies

544 in people age 12 and older.

545 • ASTEPRO Nasal Spray contains an antihistamine that may help reduce the nasal

546 symptoms of rhinitis (inflammation of the lining of the nose): stuffy nose, runny nose,

547 itching and sneezing.

548

549 It is not known if ASTEPRO Nasal Spray works and is safe or effective in children

550 younger than age 12.

551

552 **What should I tell my healthcare provider before using ASTEPRO Nasal Spray?**

553 **Before using ASTEPRO Nasal Spray tell your healthcare provider about all your**

554 **medical conditions, including if you are:**

555 • allergic to any of the ingredients in ASTEPRO Nasal Spray. See the end of this leaflet

556 for a complete list of ingredients in ASTEPRO Nasal Spray.

557 • pregnant, think you may be pregnant, or planning to become pregnant. It is not known if

558 ASTEPRO Nasal Spray will harm your unborn baby.

559 • breastfeeding. It is not known if ASTEPRO Nasal Spray passes into your breast milk.

560

561 **Tell your healthcare provider about all the medicines you take**, including prescription

562 and non-prescription medicines, vitamins, and herbal products. ASTEPRO Nasal Spray

563 and other medicines may affect each other, causing side effects.

564

565 Know the medicines you take. Keep a list of your medicines and show it to your
566 healthcare provider when you get a new medicine.

567

568 **How should I use ASTEPRO Nasal Spray?**

569 • ASTEPRO Nasal Spray is to be sprayed in your nose only. **Do not spray it into your**
570 **eyes or mouth.**

571 • Use ASTEPRO Nasal Spray exactly as your healthcare provider tells you. **Do not** use
572 more than your healthcare provider tells you.

573 • Read the Patient Instructions for Use at the end of this leaflet for detailed instructions
574 about how to use ASTEPRO Nasal Spray.

575 • Before you use ASTEPRO Nasal Spray for the first time, you will need to prime the
576 bottle. See priming instructions at the end of this leaflet in the detailed Patient
577 Instructions for Use.

578 • Do not use ASTEPRO Nasal Spray unless you see a fine mist after you do the priming
579 sprays.

580 • Throw away your ASTEPRO Nasal Spray 0.1% bottle after using 200 sprays. Even
581 though the bottle may not be completely empty, you may not get the correct dose of
582 medicine.

583 • Throw away your ASTEPRO Nasal Spray 0.15% bottle after using 106 sprays (for the
584 17 mL bottle) or 200 sprays (for the 30 mL bottle). Even though the bottle may not be
585 completely empty, you may not get the correct dose of medicine.

586

587 • **If a child accidentally swallows ASTEPRO Nasal Spray, get medical help or call a**
588 **poison control center right away.**

589

590 **What should I avoid while using ASTEPRO Nasal Spray?**

591 **ASTEPRO Nasal Spray can cause sleepiness:**

592 • Do not drive a car, operate machinery or do dangerous activities after you use
593 ASTEPRO Nasal Spray.

594 • Avoid drinking alcohol or taking other medicines that may cause you to feel sleepy
595 while using ASTEPRO Nasal Spray.

596

597 **What are the possible side effects of ASTEPRO Nasal Spray?**

598 Side effects of ASTEPRO Nasal Spray include:

599 • unusual taste (bitter)

600 • nose pain or discomfort

601 • nosebleeds

602 • headache

603 • fatigue

604 • sleepiness

605 • sneezing

606

607 Tell your healthcare provider if you have any side effect that bothers you or that does not
608 go away. These are not all of the possible side effects of ASTEPRO Nasal Spray. For
609 more information, ask your healthcare provider or pharmacist.

610

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

613

614 **How should I store ASTEPRO Nasal Spray?**

- 615 • Keep ASTEPRO Nasal Spray upright at 68° to 77°F (20° to 25°C).
616 • Do not freeze ASTEPRO Nasal Spray.
617 • Do not use ASTEPRO Nasal Spray after the expiration date “EXP” on the medicine
618 label and box.

619

620 **Keep ASTEPRO Nasal Spray and all medicines out of reach of children.**

621

622 **General information about ASTEPRO Nasal Spray.**

623

624 Medicines are sometimes prescribed for conditions other than those mentioned in patient
625 information leaflets. Do not use ASTEPRO Nasal Spray for a condition for which it was
626 not prescribed. Do not give ASTEPRO Nasal Spray to other people, even if they have the
627 same symptoms that you have. It may harm them.

628

629 This patient information leaflet summarizes the most important information about
630 ASTEPRO Nasal Spray. If you would like more information, talk with your healthcare
631 provider. You can ask your pharmacist or healthcare provider for information about
632 ASTEPRO Nasal Spray that is written for health professionals.

633

634 For more information, go to www.ASTEPRO.com or call 1-800-598-4856.

635

636 **What are the ingredients in ASTEPRO Nasal Spray?**

637 Active ingredient: azelastine hydrochloride

638

639 Inactive ingredients: sorbitol, sucralose, hypromellose, sodium citrate, edetate disodium,
640 benzalkonium chloride, and purified water.

641

642 MEDA Pharmaceuticals
643 MEDA Pharmaceuticals Inc.
644 Somerset, NJ 08873-4120

645

646 **Patient Instructions for Use**

647

For use in your nose only

648

649 **It is important that you read and follow these Patient Instructions for Use carefully**
650 **to be sure you use ASTEPRO Nasal Spray the right way.**

651

652 **For the correct dose of medicine:**

- 653 • Use ASTEPRO Nasal Spray exactly as prescribed by your healthcare provider.
654 • Keep your head tilted downward when spraying into your nostril.
655 • Change nostrils each time you use the spray.

656 • **Breathe gently and do not tip your head back after using the spray.** This will keep
657 the medicine from running down into your throat. You may get a bitter taste in your
658 mouth.

659
660 Follow the instructions below to use your ASTEPRO Nasal Spray pump.
661 See Figure 1.

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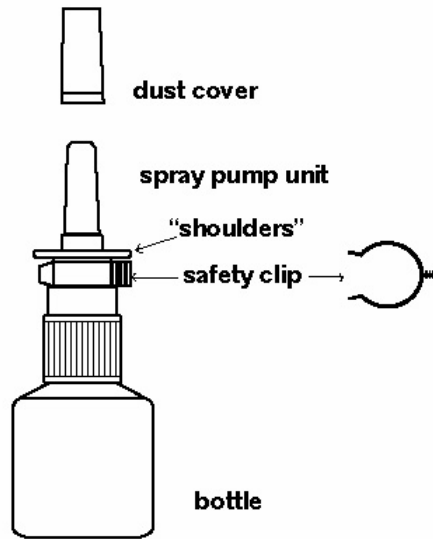


Figure 1

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704 **Before you use ASTEPRO Nasal Spray for the first time, you will need to prime the**
705 **bottle.**

706 **To prime:**

- 707 1. Remove the blue dust cover over the tip of the bottle and the blue safety clip just
708 under the “shoulders” of the bottle. See Figure 2.

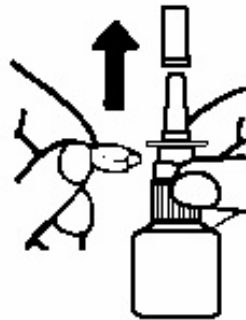


Figure 2

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- 712 2. Hold the bottle upright with two fingers on the shoulders of the spray pump unit and
713 put your thumb on the bottom of the bottle. Press upward with your thumb and
714 release for the pumping action. Repeat this until you see a fine mist. This should
715 happen in 6 sprays or less. See Figure 3.

716

718 Now your pump is primed and ready to use.

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- 743 3. To get a fine mist you must pump the spray fast and use firm pressure against the
744 bottom of the bottle. If you see a stream of liquid, the spray will not work right and
745 may cause nasal discomfort.

746

- 747 4. If you do not use ASTEPRO Nasal Spray for 3 or more days, you will need to prime
748 the pump with 2 sprays or until you see a fine mist. If you do not see a fine mist,
749 clean the tip of the spray nozzle. See the cleaning section below.

750

751 **To Use ASTEPRO Nasal Spray:**

- 752 1. Gently blow your nose to clear nostrils.
753 2. Keep your head tilted downward toward your toes.
754 3. Place the spray tip $\frac{1}{4}$ to $\frac{1}{2}$ inch into one nostril. Hold bottle upright and aim the spray
755 tip toward the back of the nose. See Figure 4.
756 4. Close your other nostril with a finger. Press the pump one time and sniff gently at the
757 same time, keeping your head tilted forward and down.

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- 782 5. Repeat in other nostril.

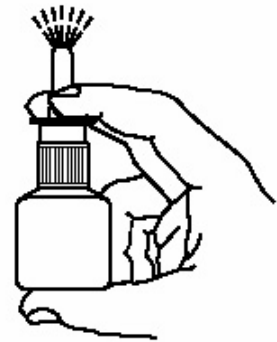


Figure 3



Figure 4

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6. If your healthcare provider tells you to use 2 sprays in each nostril, repeat Steps 2 through 5 above for the second spray in each nostril.

785

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7. Breathe in gently, and **do not tilt your head back** after using ASTEPRO Nasal Spray. This will help to keep the medicine from going into your throat.

787

788

8. When you finish using ASTEPRO Nasal Spray, wipe the spray tip with a clean tissue or cloth. Put the safety clip and dust cover back on the bottle.

789

790

791

To Clean the Spray Tip:

792

1. If the spray tip opening is clogged, do not use a pin or pointed object to unclog the tip. Unscrew the spray pump unit from the bottle by turning it counter-clockwise (to the left). See Figure 5.

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2. Soak only the spray pump unit in warm water. Squirt several times while holding it under water. Use the pumping action to clear the opening in the tip. See Figure 6.

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3. Let the spray pump unit air dry. Make sure it is dry before you put it back onto the bottle.

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4. Put the spray pump unit back into the open bottle and tighten it by turning clockwise (to the right).

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5. To keep the medicine from leaking out, use firm pressure when you put the pump back onto the bottle.

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6. After cleaning, follow the instructions for priming.

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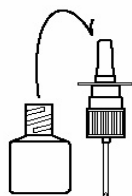


Figure 5

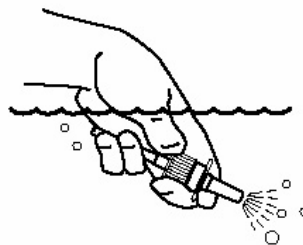


Figure 6

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