

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-203

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ASTEPRO™ (azelastine hydrochloride) Nasal Spray
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 allergic rhinitis in patients 12 years of age and older. (1.1)

DOSAGE AND ADMINISTRATION

For intranasal use only. Usual starting dosages:

- Seasonal allergic rhinitis:
Adults and adolescents 12 years of age and older: 1 or 2 sprays per nostril twice daily (2.1)
- Priming Information: Prime ASTEPRO Nasal Spray before initial use and when ASTEPRO Nasal Spray has not been used for 3 or more days. (2.2)

DOSAGE FORMS AND STRENGTHS

Nasal Spray: 137 mcg of azelastine hydrochloride in each 0.137 mL spray (3)
Supplied in 30 mL bottle providing 200 metered sprays (16)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- 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 depressants with ASTEPRO Nasal Spray (5.1)

ADVERSE REACTIONS

The most common adverse reactions (≥2% incidence) include bitter taste, epistaxis, headache, fatigue and somnolence (6.1)

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

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

revised 10/08

FULL PRESCRIBING INFORMATION: CONTENTS*

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

3 **FULL PRESCRIBING INFORMATION**

4 **1 INDICATIONS AND USAGE**

5 **1.1 Seasonal Allergic Rhinitis**

6 ASTEPRO Nasal Spray is indicated for the relief of the symptoms of seasonal
7 allergic rhinitis in patients 12 years of age and older.

8
9 **2 DOSAGE AND ADMINISTRATION**

10 Administer ASTEPRO Nasal Spray by the intranasal route only.

11 **2.1 Adults and Adolescents 12 Years of Age and Older**

12 The recommended dose of ASTEPRO Nasal Spray is 1 or 2 sprays per nostril twice
13 daily.

14 **2.2 Administration Information**

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

19
20 **3 DOSAGE FORMS AND STRENGTHS**

21 ASTEPRO Nasal Spray is a nasal spray solution. Each spray delivers a volume of
22 0.137 mL solution containing 137 mcg of azelastine hydrochloride.

23
24 **4 CONTRAINDICATIONS**

25 None.

26
27 **5 WARNINGS AND PRECAUTIONS**

28 **5.1 Activities Requiring Mental Alertness**

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

37
38 **6 ADVERSE REACTIONS**

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

41 **6.1 Clinical Studies Experience**

42 The safety data described below reflect exposure to ASTEPRO Nasal Spray in 564
43 patients 12 years of age and older from 2 clinical trials of 2 weeks to 6 months duration.
44 In a 2 week, double-blind, placebo-controlled, and active controlled (Astelin[®] Nasal
45 Spray) clinical trial, 285 patients 12 years of age and older with seasonal allergic rhinitis
46 were treated with ASTEPRO Nasal Spray one or two sprays per nostril daily. In the 6
47 month open-label, active controlled (Astelin Nasal Spray) clinical trial, 279 patients 12
48 years of age and older with perennial allergic rhinitis and/or nonallergic rhinitis were

49 treated with ASTEPRO Nasal Spray two sprays per nostril twice daily. Of the 564
 50 patients, 256 were male and 308 were female. The racial and ethnic distribution of the
 51 564 patients was 86% white, 11% black, 6% Hispanic, < 2% Asian, and 1% other.

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

55
 56 Adults and Adolescents 12 years of Age and Older

57 In the two week clinical trial, 835 patients 12 years of age and older with seasonal
 58 allergic rhinitis were treated with one of six treatments: one spray per nostril of either
 59 ASTEPRO Nasal Spray, Astelin Nasal Spray or placebo twice daily; or 2 sprays per
 60 nostril of ASTEPRO Nasal Spray, Astelin Nasal Spray, or placebo twice daily. Overall,
 61 adverse reactions were more common on the ASTEPRO Nasal Spray treatment group
 62 (21-28%) than in the placebo group (16-20%). Overall, less than 1% of patients
 63 discontinued due to adverse reactions and withdrawal due to adverse reactions was
 64 similar among the treatment groups.

65 Table 1 contains adverse reactions reported with frequencies greater than 2% and
 66 more frequently than placebo in patients treated with ASTEPRO Nasal Spray in the
 67 controlled clinical trial described above.
 68

69

Table 1. Adverse Reactions Reported in >2% Patients in a 2 Week Controlled Trial in Adult and Adolescent Patients with Seasonal Allergic Rhinitis						
	1 spray twice daily			2 sprays twice daily		
	ASTEPRO Nasal Spray (N=139)	Astelin Nasal Spray (N=137)	Vehicle Placebo (N=137)	ASTEPRO Nasal Spray (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%)

70

71 Long-Term (6 Month) Safety Trial:

72 In the 6 month, open-label, active-controlled, long-term safety trial, 555 patients 12
 73 years of age and older with perennial allergic and/or nonallergic rhinitis were treated with
 74 ASTEPRO Nasal Spray two sprays per nostril twice daily or Astelin Nasal Spray two
 75 sprays per nostril twice daily. The most frequently reported adverse reactions were
 76 headache, bitter taste, epistaxis, and nasopharyngitis and were generally similar between
 77 treatment groups. Focused nasal examinations were performed and showed that the
 78 incidence of nasal mucosal ulceration in each treatment group was approximately 1.5% at
 79 baseline and approximately 4% throughout the 6 month treatment period. In each treatment
 80 group, 3% - 5% of patients had mild epistaxis. No patients had reports of nasal septal
 81 perforation or severe epistaxis.

82 **6.2 Postmarketing Experience**

83 The following adverse reactions have been identified during the post approval use
 84 of Astelin Nasal Spray. Because these reactions are reported voluntarily from a
 85 population of uncertain size, it is not always possible to reliably estimate their frequency
 86 or establish a causal relationship to drug exposure. Adverse reactions reported include the

87 following: anaphylactoid reaction, application site irritation, atrial fibrillation, blurred
88 vision, chest pain, confusion, dizziness, dyspnea, facial edema, hypertension, involuntary
89 muscle contractions, nervousness, palpitations, paresthesia, parosmia, paroxysmal
90 sneezing, pruritus, rash, disturbance or loss of sense of smell and/or taste, tachycardia,
91 tolerance, urinary retention, and xerophthalmia.

92

93 **7 DRUG INTERACTIONS**

94 **7.1 Central Nervous System Depressants**

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

98 **7.2 Erythromycin and Ketoconazole**

99 Interaction studies investigating the cardiac effects, as measured by the corrected
100 QT interval (QTc), of concomitantly administered oral azelastine hydrochloride and
101 erythromycin or ketoconazole were conducted. Oral erythromycin (500 mg three times
102 daily for 7 days) had no effect on azelastine pharmacokinetics or QTc based on analyses
103 of serial electrocardiograms. Ketoconazole (200 mg twice daily for 7 days) interfered
104 with the measurement of azelastine plasma concentrations; however, no effects on QTc
105 were observed [*see Pharmacodynamics (12.2) Pharmacokinetics (12.3)*].

106 **7.3 Cimetidine**

107 Cimetidine (400 mg twice daily) increased the mean C_{max} and AUC of orally
108 administered azelastine hydrochloride (4 mg twice daily) by approximately 65%
109 [*see Pharmacokinetics (12.3)*].
110

111 **8 USE IN SPECIFIC POPULATIONS**

112 **8.1 Pregnancy**

113 Pregnancy Category C: There are no adequate and well-controlled clinical studies in
114 pregnant women. ASTEPRO Nasal Spray should be used during pregnancy only if the
115 potential benefit justifies the potential risk to the fetus.

116 Teratogenic Effects: Azelastine hydrochloride has been shown to cause
117 developmental toxicity in mice, rats, and rabbits. In mice, azelastine hydrochloride
118 caused embryo-fetal death, malformations (cleft palate; short or absent tail; fused, absent
119 or branched ribs), delayed ossification, and decreased fetal weight at an oral dose
120 approximately 280 times the maximum recommended daily intranasal dose (MRDID) in
121 adults on a mg/m² basis. This dose also caused maternal toxicity as evidenced by
122 decreased body weight. Neither fetal nor maternal effects occurred at a dose that was
123 approximately 10 times the MRDID.

124 In rats, azelastine hydrochloride caused malformations (oligo- and brachydactylia),
125 delayed ossification and skeletal variations, in the absence of maternal toxicity, at an oral
126 dose approximately 240 times the MRDID in adults on a mg/m² basis. At a dose
127 approximately 560 times the MRDID, azelastine hydrochloride also caused embryo-fetal
128 death and decreased fetal weight; however, this dose caused severe maternal toxicity.
129 Neither fetal nor maternal effects occurred at a dose approximately 25 times the MRDID.

130 In rabbits, azelastine hydrochloride caused abortion, delayed ossification and
131 decreased fetal weight at oral doses approximately 500 times or greater the MRDID in

132 adults on a mg/m^2 basis; however, these doses also resulted in severe maternal toxicity.
133 Neither fetal nor maternal effects occurred at a dose approximately 5 times the MRDID.

134 **8.3 Nursing Mothers**

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

138 **8.4 Pediatric Use**

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

141 **8.5 Geriatric Use**

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

149 **8.6 Asthmatic Patients**

150 Oral azelastine has been safely administered to over 1400 asthmatic subjects,
151 supporting the safety of administering azelastine hydrochloride nasal spray to allergic
152 rhinitis patients with asthma.

153

154 **10 OVERDOSAGE**

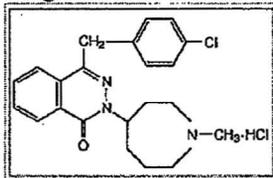
155 There have been no reported overdosages with ASTEPRO Nasal Spray. Acute
156 overdosage by adults with this dosage form is unlikely to result in clinically significant
157 adverse events, other than increased somnolence, since one bottle of ASTEPRO Nasal
158 Spray contains 30 mg of azelastine hydrochloride. Clinical studies in adults with single
159 doses of the oral formulation of azelastine hydrochloride (up to 16 mg) have not resulted
160 in increased incidence of serious adverse events. General supportive measures should be
161 employed if overdosage occurs. There is no known antidote to ASTEPRO Nasal Spray.
162 Oral ingestion of antihistamines has the potential to cause serious adverse effects in
163 children. Accordingly, ASTEPRO Nasal Spray should be kept out of the reach of
164 children. Oral doses of 120 mg/kg and greater (approximately 460 times the maximum
165 recommended daily intranasal dose (MRDID) in adults and children on a mg/m^2 basis)
166 were lethal in mice. Responses seen prior to death were tremor, convulsions, decreased
167 muscle tone, and salivation. In dogs, single oral doses as high as 10 mg/kg
168 (approximately 260 times the MRDID in adults and children on a mg/m^2 basis) were well
169 tolerated, but single oral doses of 20 mg/kg were lethal.

170

171 **11 DESCRIPTION**

172 ASTEPRO (azelastine hydrochloride) Nasal Spray, 137 micrograms (mcg), is an
173 antihistamine formulated as a metered-spray solution for intranasal administration.
174 Azelastine hydrochloride occurs as a white, almost odorless, crystalline powder with a
175 bitter taste. It has a molecular weight of 418.37. It is sparingly soluble in water, methanol,
176 and propylene glycol and slightly soluble in ethanol, octanol, and glycerine. It has a
177 melting point of about 225°C and the pH of a saturated solution is between 5.0 and 5.4.

178 Its chemical name is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-
179 (hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride. Its molecular formula is
180 C₂₂H₂₄ClN₃O·HCl with the following chemical structure:



181 ASTEPRO Nasal Spray contains 0.1% azelastine hydrochloride in an isotonic
182 aqueous solution containing sorbitol, sucralose, hypromellose, sodium citrate, edetate
183 disodium, benzalkonium chloride (125 mcg/mL), and purified water (pH 6.4).
184 After priming [*see Dosage and Administration (2.2)*], each metered spray delivers a
185 0.137 mL mean volume containing 137 mcg of azelastine hydrochloride (equivalent to
186 125 mcg of azelastine base). The 30-mL (net weight 30 gm of solution) bottle provides
187 200 metered sprays.

189 12 CLINICAL PHARMACOLOGY

190 12.1 Mechanism of Action

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

196 12.2 Pharmacodynamics

197 Cardiac Effects:

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

203 Interaction studies investigating the cardiac repolarization effects of concomitantly
204 administered oral azelastine hydrochloride and erythromycin or ketoconazole were
205 conducted. Oral erythromycin had no effect on azelastine pharmacokinetics or QTc based
206 on analysis of serial electrocardiograms. Ketoconazole interfered with the measurement
207 of azelastine plasma levels; however, no effects on QTc were observed [*see Drug*
208 *Interactions (7)*].

209 12.3 Pharmacokinetics

210 *Absorption:* After intranasal administration of 2 sprays per nostril (548 mcg total
211 dose) of ASTEPRO, the mean azelastine peak plasma concentration (C_{max}) is 200 pg/mL,
212 the mean extent of systemic exposure (AUC) is 5122 pg·hr/ml and the median time to
213 reach C_{max} (t_{max}) is 3 hours. Azelastine hydrochloride administered intranasally at doses
214 above two sprays per nostril twice daily for 29 days resulted in greater than proportional
215 increases in C_{max} and AUC for azelastine. The systemic bioavailability of azelastine
216 hydrochloride is approximately 40% after intranasal administration.

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

219 the plasma protein binding of azelastine and its metabolite, desmethylazelastine, are
220 approximately 88% and 97%, respectively.

221 *Metabolism:* Azelastine is oxidatively metabolized to the principal active
222 metabolite, desmethylazelastine, by the cytochrome P450 enzyme system. The specific
223 P450 isoforms responsible for the biotransformation of azelastine have not been
224 identified. After a single-dose, intranasal administration of ASTEPRO Nasal Spray, the
225 mean desmethylazelastine C_{max} is 23 pg/mL, the AUC is 2131 pg•hr/mL and the median
226 t_{max} is 24 hours. After intranasal dosing of azelastine to steady-state, plasma
227 concentrations of desmethylazelastine range from 20-50% of azelastine concentrations.

228 *Elimination:* Following intranasal administration of ASTEPRO Nasal Spray, the
229 elimination half-life of azelastine is 22 hours while that of desmethylazelastine is 52
230 hours. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was
231 excreted in the feces with less than 10% as unchanged azelastine.

232 *Special Populations:*

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

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

238 *Age:* Following oral administration, pharmacokinetic parameters were not
239 influenced by age.

240 *Gender:* Following oral administration, pharmacokinetic parameters were not
241 influenced by gender.

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

243 *Drug-Drug Interactions:*

244 *Erythromycin:* Clinical interaction studies with a moderate CYP3A4 inhibitor
245 erythromycin failed to demonstrate a pharmacokinetic interaction.

246 *Cimetidine and Ranitidine:* In a multiple-dose, steady-state drug interaction study
247 in healthy subjects, cimetidine (400 mg twice daily), a nonspecific P450 inhibitor, raised
248 orally administered mean azelastine (4 mg twice daily) concentrations by approximately
249 65%. Ranitidine hydrochloride (150 mg twice daily) had no effects on azelastine
250 pharmacokinetics.

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

254

255 13 NONCLINICAL TOXICOLOGY

256 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

257 In 2-year carcinogenicity studies in rats and mice azelastine hydrochloride did not
258 show evidence of carcinogenicity at oral doses up to 30 mg/kg and 25 mg/kg,
259 respectively (approximately 240 and 100 times the maximum recommended daily
260 intranasal dose (MRDID) in adults and children on a mg/m^2 basis).

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

264 Reproduction and fertility studies in rats showed no effects on male or female
265 fertility at oral doses up to 30 mg/kg (approximately 240 times the MRDID in adults on a
266 mg/m² basis). At 68.6 mg/kg (approximately 560 times the MRDID in adults on a mg/m²
267 basis), the duration of estrous cycles was prolonged and copulatory activity and the
268 number of pregnancies were decreased. The numbers of corpora lutea and implantations
269 were decreased; however, pre-implantation loss was not increased.

270 **13.2 Animal Toxicology and/or Pharmacology**

271 **Reproductive Toxicology Studies**

272 Azelastine hydrochloride has been shown to cause developmental toxicity.
273 Treatment of mice with an oral dose of 68.6 mg/kg (approximately 280 times the
274 maximum recommended daily intranasal dose [MRDID] in adults on a mg/m² basis)
275 caused embryo-fetal death, malformations (cleft palate; short or absent tail; fused, absent
276 or branched ribs), delayed ossification, and decreased fetal weight. This dose also caused
277 maternal toxicity as evidenced by decreased body weight. Neither fetal nor maternal
278 effects occurred at a dose of 3 mg/kg (approximately 10 times the MRDID in adults on a
279 mg/m² basis).

280 In rats, an oral dose of 30 mg/kg (approximately 240 times the MRDID in adults on
281 a mg/m² basis) caused malformations (oligo- and brachydactylia), delayed ossification and
282 skeletal variations, in the absence of maternal toxicity. At 68.6 mg/kg (approximately 560
283 times the MRDID in adults on a mg/m² basis) azelastine hydrochloride also caused
284 embryo-fetal death and decreased fetal weight; however, the 68.6 mg/kg dose caused
285 severe maternal toxicity. Neither fetal nor maternal effects occurred at a dose of 3 mg/kg
286 (approximately 25 times the MRDID in adults on a mg/m² basis).

287 In rabbits, oral doses of 30 mg/kg and greater (approximately 500 times the
288 MRDID in adults on a mg/m² basis) caused abortion, delayed ossification and decreased
289 fetal weight; however, these doses also resulted in severe maternal toxicity. Neither fetal
290 nor maternal effects occurred at a dose of 0.3 mg/kg (approximately 5 times the MRDID
291 in adults on a mg/m² basis).

292

293 **14 CLINICAL STUDIES**

294 **14.1 Seasonal Allergic Rhinitis**

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

300 Patients were randomized to one of six treatment groups: 1 spray per nostril of
301 either ASTEPRO Nasal Spray, Astelin Nasal Spray or placebo twice daily; or 2 sprays
302 per nostril of ASTEPRO Nasal Spray, Astelin Nasal Spray or placebo twice daily.

303 Assessment of efficacy was based on the 12-hour reflective total nasal symptom
304 score (rTNSS) assessed daily in the morning and evening. TNSS is calculated as the sum
305 of the patients' scoring of the four individual nasal symptoms (rhinorrhea, nasal
306 congestion, sneezing, and nasal itching) on a 0 to 3 categorical severity scale (0 = absent,
307 1 = mild, 2 = moderate, 3 = severe). The rTNSS required patients to record symptom
308 severity over the previous 12 hours. For the primary efficacy endpoint, morning (AM)