ASTEPRO- azelastine hydrochloride spray, metered
Meda Pharmaceuticals Inc.

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

RECENT MAJOR CHANGES

- Indications and Usage, Allergic Rhinitis (1.1) 8/2013
- Dosage and Administration, Seasonal Allergic Rhinitis (2.1) 8/2013
- Dosage and Administration, Perennial Allergic Rhinitis (2.2) 8/2013

INDICATIONS AND USAGE

ASTEPRO Nasal Spray is an H_1-receptor antagonist indicated for the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 6 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 spray per nostril twice daily in children 6 to 11 years of age (2.1)
• 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 0.1% and 0.15%: 1 spray per nostril twice daily in children 6 to 11 years of age (2.2)
• 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 (4)

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, sneezing, fatigue, somnolence, and upper respiratory infection (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: 8/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Allergic Rhinitis

ASTEPRO Nasal Spray 0.1% and 0.15% is indicated for the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 6 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Seasonal Allergic Rhinitis

In children 6 to 11 years of age, the recommended dose of ASTEPRO Nasal Spray 0.1% and 0.15% is 1 spray per nostril twice daily.

In adults and adolescents 12 years of age and older, the recommended dose of ASTEPRO Nasal Spray 0.1% and 0.15% is 1 or 2 sprays per nostril twice daily. ASTEPRO Nasal Spray 0.15% may also be administered as 2 sprays per nostril once daily.

2.2 Perennial Allergic Rhinitis

In children 6 to 11 years of age, the recommended dose of ASTEPRO Nasal Spray 0.1% and 0.15% is 1 spray per nostril twice daily.

In adults and adolescents 12 years of age and older, the recommended dose of ASTEPRO Nasal Spray 0.15% is 2 sprays per nostril twice daily.

2.3 Important Administration Instructions

Administer ASTEPRO Nasal Spray by the intranasal route only.

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Activities Requiring Mental Alertness

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

6 ADVERSE REACTIONS

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

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 879 patients 6 years of age and older from 3 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. In a 4-week, double-blind, placebo-controlled clinical trial, 166 patients (101 males and 65 females) ages 6 to 11 years of age with perennial allergic rhinitis, with or without concomitant seasonal allergic rhinitis, were treated with ASTEPRO Nasal Spray 0.1% one spray per nostril twice daily. The racial and ethnic distribution for the 3 clinical trials was 81% white, 9% black, 5% Hispanic, 3% Asian, and 2% 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 ≥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 headache, bitter taste, epistaxis, and nasopharyngitis and were generally similar between treatment groups. Focused nasal examinations were performed and showed that the incidence of nasal mucosal ulceration in each treatment group was approximately 1% at baseline and approximately 1.5% throughout the 12 month treatment period. In each treatment group, 5-7% of patients had mild epistaxis. No patients had reports of nasal septal perforation or severe epistaxis. Twenty-two patients (5%) treated with ASTEPRO Nasal Spray 0.1% and 17 patients (4%) treated with Astelin Nasal Spray discontinued from the trial due to adverse events.

Children 6 to 11 years of age

In a 4 week clinical trial, 489 patients ages 6 to 11 years with perennial allergic rhinitis, with or without concomitant seasonal allergic rhinitis, were treated with either ASTEPRO Nasal Spray 0.1%, ASTEPRO Nasal Spray 0.15% or placebo one spray per nostril twice daily. Overall, adverse events were similar in the ASTEPRO Nasal Spray 0.15% group (24%), ASTEPRO Nasal Spray 0.1% group (26%) and the placebo group (24%). Overall, less than 1% of the combined ASTEPRO Nasal Spray groups discontinued due to adverse events.
Table 2 contains adverse reactions reported with frequencies greater than or equal to 2% and more frequently than placebo in children 6 to 11 years of age treated with ASTEPRO Nasal Spray 0.1% or 0.15% in the controlled trial described above.

Table 2. Adverse Reactions Reported in ≥2% Incidence in a Placebo-Controlled Trial of 4 Weeks' Duration with ASTEPRO Nasal Spray 0.1% or ASTEPRO Nasal Spray 0.15% in Children 6 to 11 Years of Age with Perennial Allergic Rhinitis

	1 spray twice daily		
	ASTEPRO Nasal Spray 0.1% (N=166)	**ASTEPRO Nasal Spray 0.15% (N=161)**	**Vehicle Placebo (N=162)**

Epistaxis	8 (5%)	7 (4%)	5 (3%)
Nasal Discomfort	1 (<1%)	7 (4%)	0 (0%)
Dysgeusia	4 (2%)	6 (4%)	1 (<1%)
Upper respiratory infection	4 (2%)	4 (3%)	3 (2%)
Sneezing	3 (2%)	4 (3%)	2 (1%)

ASTEPRO Nasal Spray 0.15%

The safety data described below reflect exposure to ASTEPRO Nasal Spray 0.15% in 2019 patients (6 years of age and older) with seasonal or perennial allergic rhinitis from 9 clinical trials of 2 weeks to 12 months duration. In 8 double-blind, placebo-controlled clinical trials of 2 to 4 weeks duration, 1703 patients (646 males and 1059 females) with seasonal or perennial allergic rhinitis were treated with ASTEPRO Nasal Spray 0.15% one or two sprays per nostril once or twice daily. In the 12 month open-label, active-controlled clinical trial, 466 patients (156 males and 310 females) with perennial allergic rhinitis were treated with ASTEPRO Nasal Spray 0.15% two sprays per nostril twice daily. Of these 466 patients, 152 had participated in the 4-week placebo-controlled perennial allergic rhinitis clinical trials. In a 4-week, double-blind, placebo-controlled clinical trial, 161 patients (87 males and 74 females) ages 6 to 11 years of age with perennial allergic rhinitis, with or without concomitant seasonal allergic rhinitis, were treated with ASTEPRO Nasal Spray 0.15% one spray per nostril twice daily. The racial distribution for the 9 clinical trials was 80% white, 13% black, 2% Asian, and 5% other.

Adults and Adolescents 12 Years of Age and Older

In the 7 placebo controlled clinical trials of 2 to 4 week duration, 2343 patients with seasonal allergic rhinitis and 540 patients with perennial allergic rhinitis were treated with two sprays per nostril of either ASTEPRO Nasal Spray 0.15% or placebo once or twice daily. Overall, adverse reactions were more common in the ASTEPRO Nasal Spray 0.15% treatment groups (16-31%) than in the placebo groups (11-24%). Overall, less than 2% of patients discontinued due to adverse reactions and withdrawal due to adverse reactions was similar among the treatment groups.
Table 3 contains adverse reactions reported with frequencies greater than or equal to 2% and more frequently than placebo in patients treated with ASTEPRO Nasal Spray 0.15% in the seasonal and perennial allergic rhinitis controlled clinical trials.

Table 3. Adverse Reactions with ≥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%)

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

Long-Term (12 Month) Safety Trial:

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

Children 6 to 11 years of age

See summary under *ASTEPRO Nasal Spray 0.1%*

6.2 Postmarketing Experience

During the post approval use of ASTEPRO Nasal Spray 0.1% and 0.15%, the following adverse reactions have been identified. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions reported include: abdominal pain, nasal burning, nausea, sweet taste, and throat irritation.

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

7 DRUG INTERACTIONS

7.1 Central Nervous System Depressants

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

7.2 Erythromycin and Ketoconazole

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

7.3 Cimetidine

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Teratogenic Effects: In mice, azelastine hydrochloride caused embryo-fetal death, malformations (cleft palate; short or absent tail; fused, absent or branched ribs), delayed ossification, and decreased fetal weight at approximately 170 times the maximum recommended human daily intranasal dose (MRHDID) in adults (on a mg/m^2 basis at a maternal oral dose of 68.6 mg/kg/day which also caused maternal toxicity as evidenced by decreased body weight). Neither fetal nor maternal effects occurred in mice at approximately 7 times the MRHDID in adults (on a mg/m^2 basis at a maternal oral dose of 3 mg/kg/day).

In rats, azelastine hydrochloride caused malformations (oligo- and brachydactylia), delayed ossification and skeletal variations, in the absence of maternal toxicity, at approximately 150 times the MRHDID in adults (on a mg/m^2 basis at a maternal oral dose of 30 mg/kg/day). Azelastine hydrochloride caused embryo-fetal death and decreased fetal weight and severe maternal toxicity at approximately 340 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 68.6 mg/kg/day). Neither fetal nor maternal effects occurred at approximately 15 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 2

mg/kg/day).

In rabbits, azelastine hydrochloride caused abortion, delayed ossification and decreased fetal weight and severe maternal toxicity at approximately 300 times the MRHDID in adults (on a mg/m^2 basis at a maternal oral dose of 30 mg/kg/day). Neither fetal nor maternal effects occurred at approximately 3 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 0.3 mg/kg/day).

8.3 Nursing Mothers

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

8.4 Pediatric Use

The safety and effectiveness of ASTEPRO Nasal Spray in pediatric patients 6 to 17 years of age have been established [*see Clinical Studies (14)*]. The safety and effectiveness of ASTEPRO Nasal Spray in pediatric patients below 6 years of age have not been established.

8.5 Geriatric Use

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

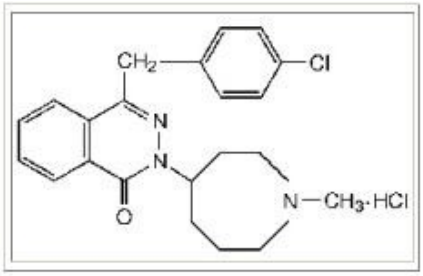
10 OVERDOSAGE

There have been no reported overdosages with ASTEPRO Nasal Spray. Acute overdosage by adults with this dosage form is unlikely to result in clinically significant adverse events, other than increased somnolence, since one 30-mL bottle of ASTEPRO Nasal Spray 0.1% contains up to 30 mg of azelastine hydrochloride and one 30-mL bottle of ASTEPRO Nasal Spray 0.15% contains up to 45 mg of azelastine hydrochloride. Clinical trials in adults with single doses of the oral formulation of azelastine hydrochloride (up to 16 mg) have not resulted in increased incidence of serious adverse events. General supportive measures should be employed if overdosage occurs. There is no known antidote to ASTEPRO Nasal Spray. Oral ingestion of antihistamines has the potential to cause serious adverse effects in children. Accordingly, ASTEPRO Nasal Spray should be kept out of the reach of children.

11 DESCRIPTION

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

Azelastine hydrochloride occurs as a white, almost odorless, crystalline powder with a bitter taste. It has a molecular weight of 418.37. It is sparingly soluble in water, methanol, and propylene glycol and slightly soluble in ethanol, octanol, and glycerine. It has a melting point of about 225°C and the pH of a saturated solution is between 5.0 and 5.4. Its chemical name is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride. Its molecular formula is $C_{22}H_{24}ClN_3O \cdot HCl$ with the following chemical structure:



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

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H_1 -receptor antagonist activity in isolated tissues, animal models, and humans. ASTEPRO Nasal Spray is administered as a racemic mixture with no difference in pharmacologic activity noted between the enantiomers in *in vitro* studies. The major metabolite, desmethylazelastine, also possesses H_1 -receptor antagonist activity.

12.2 Pharmacodynamics

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

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

12.3 Pharmacokinetics

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

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

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

Elimination: Following intranasal administration of ASTEPRO Nasal Spray 0.1%, the elimination half-life of azelastine is 22 hours while that of desmethylazelastine is 52 hours. Following intranasal administration of ASTEPRO Nasal Spray 0.15%, the elimination half-life of azelastine is 25 hours while that of desmethylazelastine is 57 hours. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was excreted in the feces with less than 10% as unchanged azelastine.

Special Populations:

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

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

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

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

Race: The effect of race has not been evaluated.

Drug-Drug Interactions:

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses up to 30 mg/kg (approximately 150 times the MRHDID in adults on a mg/m^2 basis). At 68.6 mg/kg (approximately 340 times the MRHDID on a mg/m^2 basis), the duration of estrous cycles was prolonged and copulatory activity and the number of pregnancies were decreased. The numbers of corpora lutea and implantations were decreased; however, pre-implantation loss was not increased.

14 CLINICAL STUDIES

14.1 Seasonal Allergic Rhinitis

ASTEPRO Nasal Spray 0.1%

The efficacy and safety of ASTEPRO Nasal Spray 0.1% was evaluated in a 2-week, randomized, multicenter, double-blind, placebo-controlled clinical trial including 834 adult and adolescent patients 12 years of age and older with symptoms of seasonal allergic rhinitis. The population was 12 to 83

years of age (60% female, 40% male; 69% white, 16% black, 12% Hispanic, 2% Asian, 1% other).

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

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

In this trial, ASTEPRO Nasal Spray 0.1% two sprays twice a day demonstrated a greater decrease in rTNSS and iTNSS than placebo and the difference was statistically significant. The trial results are presented in Table 4 (Trial 1).

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

ASTEPRO Nasal Spray 0.15%

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

Two 2-week seasonal allergic rhinitis trials evaluated the efficacy of ASTEPRO Nasal Spray 0.15% dosed at 2 sprays twice daily. The first trial (Trial 2) compared the efficacy of ASTEPRO Nasal Spray 0.15% and Astelin (azelastine hydrochloride) Nasal Spray to vehicle placebo. The other trial (Trial 3) compared the efficacy of ASTEPRO Nasal Spray 0.15% and ASTEPRO Nasal Spray 0.1% to vehicle placebo. In these two trials, ASTEPRO Nasal Spray 0.15% demonstrated greater decreases in rTNSS than placebo and the differences were statistically significant (Table 4).

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

Table 4. 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

Table 5. 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

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 favorable comparison of ASTEPRO Nasal Spray 0.15% to Astelin Nasal Spray and ASTEPRO Nasal Spray 0.1% (Table 4).

The efficacy and safety of ASTEPRO Nasal Spray 0.1% and 0.15% in children 6 to 11 years of age with seasonal allergic rhinitis was evaluated in a clinical study that enrolled pediatric patients with perennial allergic rhinitis, with or without concomitant seasonal allergic rhinitis (described below in Section 14.2).

14.2 Perennial Allergic Rhinitis

ASTEPRO Nasal Spray 0.1% and 0.15%

The efficacy and safety of ASTEPRO Nasal Spray 0.15% in perennial allergic rhinitis was evaluated in one randomized, multicenter, double-blind, placebo-controlled clinical trial in 578 adult and adolescent

patients 12 years and older with symptoms of perennial allergic rhinitis. The population of the trial was 12 to 84 years of age (68% female, 32% male; 85% white, 11% black, 1% Asian, 3% other; 17% Hispanic, 83% non-Hispanic).

Assessment of efficacy was based on the 12-hour reflective total nasal symptom score (rTNSS) assessed daily in the morning and evening, the instantaneous total nasal symptom score (iTNSS), and other supportive secondary efficacy variables. The primary efficacy endpoint was the mean change from baseline rTNSS over 4 weeks. The one 4-week perennial allergic rhinitis trial evaluated the efficacy of ASTEPRO Nasal Spray 0.15%, ASTEPRO Nasal Spray 0.1%, and vehicle placebo dosed at 2 sprays per nostril twice daily. In this trial, ASTEPRO Nasal Spray 0.15% demonstrated a greater decrease in rTNSS than placebo and the difference was statistically significant (Table 6).

Table 6. 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
	Vehicle Placebo	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

The efficacy and safety of ASTEPRO Nasal Spray 0.1% and 0.15% in pediatric patients 6 to 11 years of age with perennial allergic rhinitis, with or without concomitant seasonal allergic rhinitis, was evaluated in a randomized, double-blind, placebo-controlled clinical trial in 486 patients. All patients received one spray per nostril twice daily. The study population was 58% males and 42% females; 78% white, 13% black, 3% Asian, and 6% other.

Assessment of efficacy was based on the 12-hour reflective total nasal symptom score (rTNSS) assessed daily in the morning and evening. The primary efficacy endpoint was the mean change from baseline rTNSS over 4 weeks (Table 7). Both active treatments demonstrated statistically significant decreases in rTNSS compared to placebo. There was no difference between the two active-treatment groups. There was also no difference in treatment effect between patients with perennial allergic rhinitis only compared to those with perennial allergic rhinitis and concomitant seasonal allergic rhinitis.

Table 7. Mean Change from Baseline in Reflective TNSS over 4 Weeks* In Children 6 to 11 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
One spray twice daily	ASTEPRO Nasal Spray 0.15%	159	16.6	-3.5	-1.0	-1.7, -0.3	0.005
	ASTEPRO Nasal Spray 0.1%	166	16.4	-3.4	-0.9	-1.6, -0.2	0.015
	Vehicle Placebo	161	16.1	-2.5			

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

ASTEPRO (azelastine hydrochloride) Nasal Spray 0.15% is supplied as a 30-mL package (NDC 0037-0243-30) delivering 200 metered sprays in a high-density polyethylene (HDPE) bottle fitted with a metered-dose spray pump unit. The spray pump unit consists of a nasal spray pump fitted with a blue safety clip and a blue plastic dust cover. The net content of the bottle is 30 mL (net weight 30 gm of solution). The 30-mL bottle contains 45 mg (1.5 mg/mL) of azelastine hydrochloride. After priming [*see Dosage and Administration (2.3)*], each spray delivers a fine mist containing a mean volume of 0.137 mL solution containing 205.5 mcg of azelastine hydrochloride. The correct amount of medication in each spray cannot be assured before the initial priming and after 200 sprays for the 30-mL bottle have been used, even though the bottle is not completely empty. The bottle should be discarded after 200 sprays have been used.

ASTEPRO Nasal Spray should not be used after the expiration date "EXP" printed on the medicine label and carton.

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

17 PATIENT COUNSELING INFORMATION

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

17.1 Activities Requiring Mental Alertness

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

17.2 Concurrent Use of Alcohol and other Central Nervous System Depressants

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

17.3 Common Adverse Reactions

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

17.4 Priming

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

17.5 Keep Spray Out of Eyes

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

17.6 Keep Out of Children's Reach

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

Manufactured by:
MEDA Pharmaceuticals
Meda Pharmaceuticals Inc.
Somerset, NJ 08873-4120

U.S. Patents 8,071,073; D447,419; 8,518,919

PATIENT INFORMATION
ASTEPRO [*AS-ta-PRO*]

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

Important: For use in your nose only.

What is ASTEPRO Nasal Spray?

- ASTEPRO Nasal Spray is a prescription medicine used to treat symptoms of seasonal and year-round allergic rhinitis in people age 6 and older.
- ASTEPRO Nasal Spray may help to reduce your nasal symptoms including stuffy nose, runny nose, itching and sneezing.

It is not known if ASTEPRO Nasal Spray is safe and effective in children under 6 years of age.

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

Before using ASTEPRO Nasal Spray, tell your healthcare provider if you are:

- allergic to any of the ingredients in ASTEPRO Nasal Spray. See the end of this leaflet for a complete list of ingredients in ASTEPRO Nasal Spray.
- pregnant, or plan to become pregnant. It is not known if ASTEPRO Nasal Spray will harm your unborn baby.
- breastfeeding, or plan to breastfeed. It is not known if ASTEPRO Nasal Spray passes into your breast milk. You and your healthcare provider should decide if you will use ASTEPRO Nasal Spray if you plan to breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ASTEPRO Nasal Spray and other medicines may affect each other, causing side effects.

How should I use ASTEPRO Nasal Spray?

- Read the **Instructions for Use** at the end of this leaflet for information about the right way to use ASTEPRO Nasal Spray.
- Spray ASTEPRO Nasal Spray in your nose only. **Do not spray it into your eyes or mouth.**
- Use ASTEPRO Nasal Spray exactly as your healthcare provider tells you to use it.
- **Do not** use more than your healthcare provider tells you.
- Throw away your ASTEPRO Nasal Spray 0.1% bottle after using 200 sprays. Even though the bottle may not be completely empty, you may not get the correct dose of medicine.
- Throw away your ASTEPRO Nasal Spray 0.15% bottle after using 200 sprays. Even though the bottle may not be completely empty, you may not get the correct dose of medicine.
- If you use too much or a child accidentally swallows ASTEPRO Nasal Spray, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while using ASTEPRO Nasal Spray?

ASTEPRO Nasal Spray can cause sleepiness:

- **Do not** drive, operate machinery, or do other dangerous activities until you know how ASTEPRO Nasal Spray affects you.
- **Do not** drink alcohol or take other medicines that may cause you to feel sleepy while using ASTEPRO Nasal Spray. It may make your sleepiness worse.

What are the possible side effects of ASTEPRO Nasal Spray?

The most common side effects of ASTEPRO Nasal Spray include:

- unusual bitter taste
- nose pain or discomfort
- nosebleeds
- headache
- sneezing
- fatigue
- sleepiness
- upper respiratory tract infections

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of ASTEPRO Nasal Spray. For more information, ask your healthcare provider or pharmacist.

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

How should I store ASTEPRO Nasal Spray?

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

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

General information about the safe and effective use of ASTEPRO Nasal Spray.

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

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

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

What are the ingredients in ASTEPRO Nasal Spray?
Active ingredient: azelastine hydrochloride

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

Instructions for Use
ASTEPRO [*AS-ta-PRO*]
(azelastine hydrochloride)
Nasal Spray 0.1%
Nasal Spray 0.15%

Important: For use in your nose only.

For the correct dose of medicine:

- Keep your head tilted downward when spraying into your nostril.
- Change nostrils each time you use the spray.
- **Breathe gently and do not tip your head back after using the spray.** This will keep the medicine from running down into your throat. You may get a bitter taste in your mouth.

Figure A identifies the parts of your ASTEPRO Nasal Spray pump.

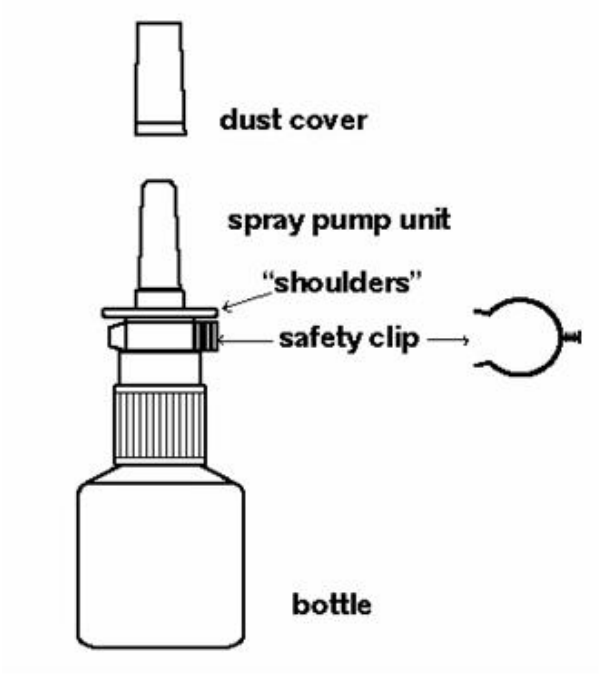


Figure A

Before you use ASTEPRO Nasal Spray for the first time, you will need to prime the bottle.
Priming your ASTEPRO Nasal Spray

Remove the blue dust cover over the tip of the bottle and the blue safety clip just under the "shoulders" of the bottle. (**See Figure B**).

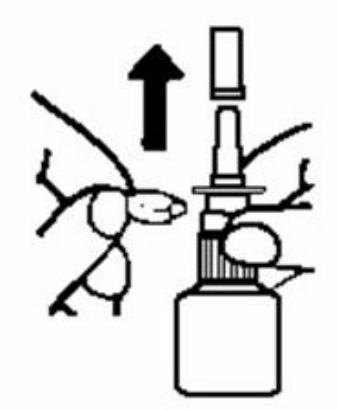


Figure B

Hold the bottle upright with 2 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 this until you see a fine mist (**See Figure C**).
- To get a fine mist you must pump the spray fast and use firm pressure against the bottom of the bottle. If you see a stream of liquid, the pump is not working correctly and you may have nasal discomfort.
- This should happen in 6 sprays or less.

Now your pump is primed and ready to use.

Figure C

- **Do not** use ASTEPRO Nasal Spray unless you see a fine mist after you do the priming sprays. If you do not see a fine mist, clean the tip of the spray nozzle. See the "**Cleaning the Spray Tip of your ASTEPRO Nasal Spray**" section below.
- If you do not use ASTEPRO Nasal Spray for 3 or more days, you will need to prime the pump with 2 sprays or until you see a fine mist.

Using your ASTEPRO Nasal Spray

Step 1. Blow your nose to clear your nostrils.

Step 2. Keep your head tilted downward toward your toes.

Step 3. Place the spray tip about ¼ inch to ½ inch into 1 nostril. Hold bottle upright and aim the spray tip toward the back of your nose (**See Figure D**).

Figure D

Step 4. Close your other nostril with a finger. Press the pump 1 time and sniff gently at the same time, keeping your head tilted forward and down (**See Figure E**).

Figure E

Step 5. Repeat **Step 3** and **Step 4** in your other nostril.

Step 6. If your healthcare provider tells you to use 2 sprays in each nostril, repeat **Steps 2 through 4** above for the second spray in each nostril.

Step 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.

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

Cleaning the Spray Tip of your ASTEPRO Nasal Spray

- 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 to the left (counter-clockwise) (**See Figure F**).
- Soak only the spray pump unit in warm water. Squirt the spray unit several times while holding it under water. Use the pumping action to clear the opening in the tip (**See Figure G**).

Figure F

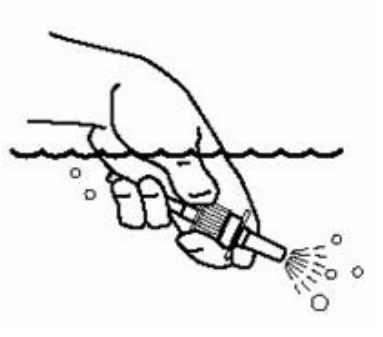


Figure G

- Let the spray pump unit air dry. Make sure it is dry before you put it back onto the bottle.
- Put the spray pump unit back into the open bottle and tighten it by turning clockwise (to the right).
- To keep the medicine from leaking out, use firm pressure when you put the pump back onto the bottle.
- After cleaning, follow the instructions for priming.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
MEDA Pharmaceuticals
Meda Pharmaceuticals Inc.
Somerset, NJ 08873-4120

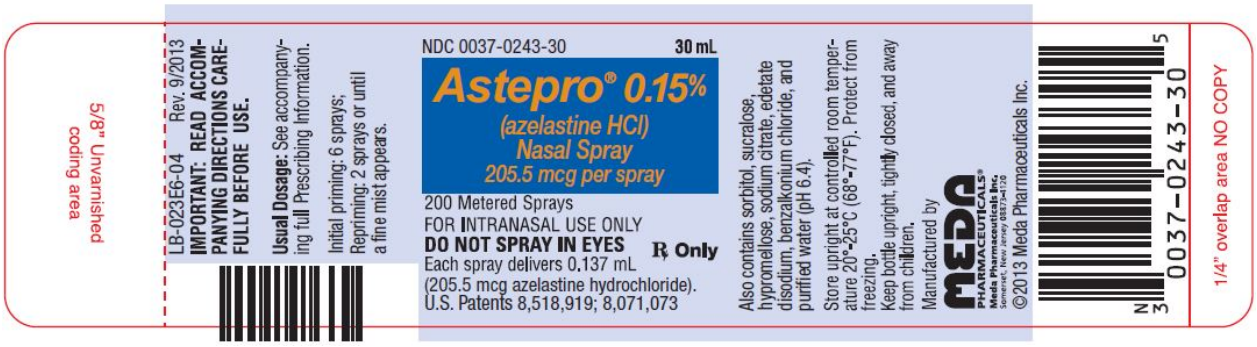
U.S. Patents 8,518,919, 8,071,073 and D447,419
IN-023D6-07 Revised: 8/2013

Package Label - Principal Display Panel – 30 mL Bottle, Astepro Nasal Spray 0.15%

NDC 0037-0243-30
30 mL
Astepro® 0.15%
(azelastine HCl)
Nasal Spray
205.5 mcg per spray
200 Metered Sprays
FOR INTRANASAL USE ONLY
DO NOT SPRAY IN EYES Rx Only
Each spray delivers 0.137 mL
(205.5 mcg azelastine hydrochloride).
U.S. Patents 8,518,919; 8,071,073
LB-023E6-04 Rev. 9/2013
IMPORTANT: READ ACCOMPANYING DIRECTIONS CAREFULLY BEFORE USE.
Usual Dosage: See accompanying full Prescribing Information.
Initial priming: 6 sprays;
Repriming: 2 sprays or until a fine mist appears.

Also contains sorbitol, sucralose, hypromellose, sodium citrate, edetate disodium, benzalkonium chloride, and purified water (pH 6.4).

Store upright at controlled room temperature 20°-25°C (68°-77°F).
Protect from freezing.
Keep bottle upright, tightly closed, and away from children.
Manufactured by
MEDA
Pharmaceuticals®
Meda Pharmaceuticals Inc.
Somerset, New Jersey 08873-4120



ASTEPRO

azelastine hydrochloride spray, metered

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0037-0243
Route of Administration	NASAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AZELASTINE HYDROCHLORIDE (AZELASTINE)	AZELASTINE HYDROCHLORIDE	205.5 ug

Inactive Ingredients

Ingredient Name	Strength
SORBITOL	
SUCRALOSE	
HYPROMELLOSES	
SODIUM CITRATE	
EDETATE DISODIUM	
BENZALKONIUM CHLORIDE	125 ug
WATER	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0037-0243-04	1 in 1 BOX		
1		22 in 1 BOTTLE, SPRAY		
2	NDC:0037-0243-30	1 in 1 BOX		
2		200 in 1 BOTTLE, SPRAY		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022371	10/12/2009	

Labeler - Meda Pharmaceuticals Inc. (051229602)

Revised: 4/2014 Meda Pharmaceuticals Inc.