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 (1)	06/2021
Dosage and Administration, Recommended Dosage for Seasonal Allergic Rhinitis (2.1)	06/2021
Dosage and Administration, Recommended Dosage for Perennial Allergic Rhinitis (2.2)	06/2021

----------INDICATIONS AND USAGE----------

ASTEPRO is an H_1-receptor antagonist indicated for the relief of the symptoms of:

- Seasonal allergic rhinitis in adult and pediatric patients 2 years of age and older. (1.1)
- Perennial allergic rhinitis in pediatric patients 6 months to 11 years of age. (1.1)

----------DOSAGE AND ADMINISTRATION ----------

- For nasal use only (2.3)
- Seasonal allergic rhinitis:
  - *2 to 11 years:* ASTEPRO 0.1%: 1 spray per nostril twice daily (2.1)
  - *Adults and adolescents 12 years of age and older:*
    - ASTEPRO 0.1%: 1 or 2 sprays per nostril twice daily (2.1)
- Perennial allergic rhinitis:
  - *6 months to 11 years:* ASTEPRO 0.1%: 1 spray per nostril twice daily (2.2)
- Prime ASTEPRO before initial use and when it has not been used for 3 or more days. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Nasal spray:

- ASTEPRO 0.1% (137 mcg of azelastine hydrochloride) in each spray (3).

----------CONTRAINDICATIONS ----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

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

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥2% incidence) are: pyrexia, dysgeusia, nasal discomfort, epistaxis, headache, sneezing, fatigue, somnolence, upper respiratory infection, cough, rhinalgia, vomiting, otitis media, contact dermatitis, and oropharyngeal pain (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*.

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

Revised: 06/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ASTEPRO is indicated for the relief of the symptoms of seasonal allergic rhinitis in adult and pediatric patients 2 years of age and older and perennial allergic rhinitis in pediatric patients 6 months to 11 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Seasonal Allergic Rhinitis

Pediatric Patients 2 to 11 years of age: 1 spray of ASTEPRO (137 mcg of azelastine hydrochloride) in each nostril twice daily.

Adults and adolescents 12 years of age and older: 1 or 2 sprays of ASTEPRO (137 mcg of azelastine hydrochloride per spray) in each nostril twice daily.

2.2 Recommended Dosage for Perennial Allergic Rhinitis

Pediatric Patients 6 months to 11 years of age: 1 spray of ASTEPRO (137 mcg of azelastine hydrochloride) in each nostril twice daily.

2.3 Important Administration Instructions

- Administer ASTEPRO by the nasal route only.
- Avoid spraying ASTEPRO into the eyes.

Priming or re-priming: Prime ASTEPRO before initial use by releasing 6 sprays or until a fine mist appears. When ASTEPRO has not been used for 3 or more days, re-prime with 2 sprays or until a fine mist appears.

3 DOSAGE FORMS AND STRENGTHS

Nasal spray:

- ASTEPRO 0.1% (137 mcg of azelastine hydrochloride) per spray

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Somnolence

In clinical trials, the occurrence of somnolence has been reported in some patients taking ASTEPRO *[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. Concurrent use of ASTEPRO 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

The following clinically significant adverse reaction is described elsewhere in the labeling:

- 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.

The safety data described below reflect exposure to ASTEPRO 0.1% in 975 patients 6 months of age and older from 4 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 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 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 0.1% one spray per nostril twice daily. In a 4-week clinical trial, 96 patients (51 males and 45 females) ages 6 months to 5 years of age with seasonal and/or perennial allergic rhinitis were treated with ASTEPRO 0.1% one spray per nostril twice daily. The racial and ethnic distribution for the 4 clinical trials was 80% white, 11% black, 8% 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 0.1%, Astelin Nasal Spray or placebo twice daily; or 2 sprays per nostril of ASTEPRO 0.1%, Astelin Nasal Spray, or placebo twice daily. Overall, adverse reactions were more common in the ASTEPRO 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 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 0.1% in Adult and Adolescent Patients with Seasonal Allergic Rhinitis

	1 spray twice daily			2 sprays twice daily		
	ASTEPRO 0.1% (N=139)	**Astelin Nasal Spray (N=137)**	**Vehicle Placebo (N=137)**	**ASTEPRO 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 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 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 0.1%, ASTEPRO 0.15% or placebo, one spray per nostril twice daily. Overall, adverse events were similar in the ASTEPRO 0.15% group (24%), ASTEPRO 0.1% group (26%) and the placebo group (24%). Overall, less than 1% of the combined ASTEPRO 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 0.1% or ASTEPRO 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 0.1% or ASTEPRO 0.15% in Children 6 to 11 Years of Age with Perennial Allergic Rhinitis

	1 spray twice daily		
	ASTEPRO 0.1% (N=166)	**ASTEPRO 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%)

Children 6 Months to 5 Years

In a 4-week clinical trial, 191 patients ages 6 months to 5 years with either seasonal and/or perennial allergic rhinitis were treated with either ASTEPRO 0.1% or ASTEPRO 0.15% one spray per nostril twice daily. The most frequently (≥2%) reported adverse reactions were pyrexia, cough, epistaxis, sneezing, dysgeusia, rhinalgia, upper respiratory infection, vomiting, otitis media, contact dermatitis, and oropharyngeal pain. Overall, adverse events were slightly higher in the ASTEPRO 0.15% group (28%) compared to ASTEPRO 0.1% group (21%). Focused nasal examinations were performed and showed no incidence of nasal mucosal ulceration at any time point during the study. No patients had reports of nasal septal perforation. Overall, less than 3% of the combined ASTEPRO groups discontinued due to adverse events.

6.2 Postmarketing Experience

During the post approval use of ASTEPRO, 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, atrial fibrillation, blurred vision, chest pain, confusion, disturbance or loss of sense of smell and/or taste, dizziness, dyspnea, facial swelling, hypertension, involuntary muscle contractions, nasal burning, nausea, nervousness, palpitations, paresthesia, parosmia, pruritus, rash, sneezing, insomnia, sweet taste, tachycardia, 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, facial edema, paroxysmal sneezing, tolerance, urinary retention, and xerophthalmia.

7 DRUG INTERACTIONS

7.1 Central Nervous System Depressants

Concurrent use of ASTEPRO 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

Risk Summary

Limited data from postmarketing experience over decades of use with ASTEPRO in pregnant women have not identified any drug associated risks of miscarriage, birth defects, or other adverse maternal or fetal outcomes. In animal reproduction studies, there was no evidence of fetal harm at oral doses approximately 4 times the clinical daily dose. Oral administration of azelastine hydrochloride to pregnant mice, rats, and rabbits, during the period of organogenesis, produced developmental toxicity that included structural abnormalities, decreased embryo-fetal survival, and decreased fetal body weights at doses 180 times and higher than the maximum recommended human daily intranasal dose (MRHDID) of 1.644 mg. However, the relevance of these findings in animals to pregnant women was considered questionable based upon the high animal to human dose multiple.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study in mice dosed during the period of organogenesis, azelastine hydrochloride caused embryo-fetal death, structural abnormalities (cleft palate; short or absent tail; fused, absent or branched ribs), delayed ossification, and decreased fetal weight at approximately 200 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 maternal body weight. Neither fetal nor maternal effects occurred in mice at approximately 9 times the MRHDID in adults (on a mg/m^2 basis at a maternal oral dose of 3 mg/kg/day).

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 7 to 17, azelastine hydrochloride caused structural abnormalities (oligo-and brachydactylia), delayed ossification, and skeletal variations, in the absence of maternal toxicity, at approximately 180 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 410 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 10 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 2 mg/kg/day).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6 to 18, azelastine hydrochloride caused abortion, delayed

ossification and decreased fetal weight and severe maternal toxicity at approximately 360 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 4 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 0.3 mg/kg/day).

In a prenatal and postnatal development study in pregnant rats dosed from late in the gestation period and through the lactation period from gestation day 17 through lactation day 21, azelastine hydrochloride produced no adverse developmental effects on pups at maternal doses up to approximately 180 times the MRHDID (on mg/m^2 basis at a maternal dose of 30 mg/kg/day).

8.2 Lactation

Risk Summary

There are no data on the presence of azelastine hydrochloride in human milk, the effects on the breastfed infant, or the effects on milk production following use of azelastine hydrochloride. Because many drugs are excreted in human milk, caution should be exercised when ASTEPRO is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ASTEPRO and any potential adverse effects on the breastfed infant from ASTEPRO or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of ASTEPRO have been established for seasonal allergic rhinitis in pediatric patients 2 to 17 years of age and perennial allergic rhinitis in pediatric patients 6 months of age to 11 years of age *[see Clinical Studies (14)]*.

Use of ASTEPRO for seasonal allergic rhinitis in patients 2 to 17 years of age is supported by evidence from the following studies:

- An adequate and well-controlled study of ASTEPRO in a 2-week randomized, multi-center, double-blind, placebo-controlled clinical trial of 834 adult and adolescent patients 12 years of age and older with seasonal allergic rhinitis
- A randomized, double-blind, placebo-controlled trial in 486 pediatric patients 6 to 11 years of age with perennial allergic rhinitis with or without concomitant seasonal allergic rhinitis
- A 4-week, randomized, open-label safety trial in 191 pediatric patients 6 months to 5 years of age; data from this study supported use for this indication in patients 2 to 5 years of age

Use of ASTEPRO for perennial allergic rhinitis in pediatric patients 6 months to 11 years of age is supported by evidence from a randomized, double-blind, placebo-controlled trial in 486 pediatric patients 6 to 11 years of age with perennial allergic rhinitis with or without concomitant seasonal allergic rhinitis.

The safety and effectiveness of ASTEPRO in pediatric patients below 6 months of age have not been established.

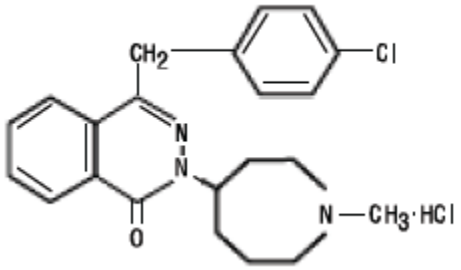
8.5 Geriatric Use

Clinical trials of ASTEPRO 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.

11 DESCRIPTION

ASTEPRO (azelastine hydrochloride) 0.1% nasal spray is an antihistamine (H_1 receptor antagonist) formulated as a metered-spray solution for nasal 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 $C_{22}H_{24}ClN_3O$•HCl with the following chemical structure:



ASTEPRO 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.

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 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 nasal administration of 2 sprays per nostril (548 mcg total dose) of ASTEPRO 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. The systemic bioavailability of azelastine hydrochloride is approximately 40% after nasal 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.

Elimination

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

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, nasal administration of ASTEPRO 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 nasal dosing of azelastine to steady-state, plasma concentrations of desmethylazelastine range from 20-50% of azelastine concentrations.

Specific Populations

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

Patients with 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.

Male and Female Patients: Following oral administration, pharmacokinetic parameters were not influenced by gender.

Race: The effect of race has not been evaluated.

Drug Interaction Studies

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

Two-year carcinogenicity studies in Crl:CD(SD)BR rats and NMRI mice were conducted to assess the carcinogenic potential of azelastine hydrochloride. No evidence of tumorigenicity was observed in rats at doses up to 30 mg/kg day (approximately 180 and 160 times the MRHDID for adults and children, respectively, on a mg/m^2 basis). No evidence for tumorigenicity was observed in mice at doses up to 25 mg/kg (approximately 75 and 65 times the MRHDID for adults and children, respectively, 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.

There were no effects on male or female fertility and reproductive performance in male and female rats at oral doses up to 30 mg/kg (approximately 180 times the MRHDID in adults on a

mg/m^2 basis). At 68.6 mg/kg (approximately 410 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

Adult and Adolescents 12 Years and Older

The efficacy and safety of ASTEPRO 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 0.1%, Astelin (azelastine hydrochloride) Nasal Spray or vehicle placebo twice daily; or 2 sprays per nostril of ASTEPRO 0.1%, Astelin 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 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 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 demonstrated a greater decrease from baseline in the summed AM and PM rTNSS compared with placebo and the difference was statistically significant.

Pediatric Patients 6 Months to 5 Years of Age

The efficacy of ASTEPRO 0.1% and ASTEPRO 0.15% in pediatric patients 6 months to 5 years of age with allergic rhinitis was explored in a 4-week, randomized, open-label safety trial in 191 patients. While the primary objective was to determine the safety of ASTEPRO in this age group, the study included an exploratory efficacy assessment of daily overall allergy symptom scores. Efficacy in children 6 months to 5 years of age was supported by a numerical decrease in

the overall allergy symptom score in both treatment groups. There was no statistically significant difference between the two treatment groups.

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 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 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			
*Sum of AM and PM rTNSS for each day (Maximum score=24) and averaged over the 14 day treatment period							

The efficacy and safety of ASTEPRO 0.1% 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

Pediatric Patients 6 to 11 Years of Age

The efficacy and safety of ASTEPRO 0.1% and ASTEPRO 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 statistically significant 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 0.15%	159	16.6	-3.5	-1.0	-1.7, -0.3	0.005

	ASTEPRO 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							

The efficacy of ASTEPRO 0.1% in children 6 months to 5 years of age with allergic rhinitis was explored in a clinical study (described above in Section 14.1).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied: ASTEPRO (azelastine hydrochloride) 0.1% nasal spray is supplied as a 30-mL package (NDC 0037-0242-30) 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). 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 should not be used after the expiration date "EXP" printed on the medicine label and carton.

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

17 PATIENT COUNSELING INFORMATION

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

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

Concurrent Use of Alcohol and other Central Nervous System Depressants
Avoid concurrent use of ASTEPRO with alcohol or other central nervous system depressants because additional reductions in alertness and additional impairment of central nervous system performance may occur *[see Warnings and Precautions (5.1)]*.

Common Adverse Reactions
Inform patients that the treatment with ASTEPRO may lead to adverse reactions, most common of which include pyrexia, dysgeusia, nasal discomfort, epistaxis, headache, sneezing, fatigue, somnolence, upper respiratory infection, cough, rhinalgia, vomiting, otitis media, contact dermatitis, and oropharyngeal pain *[see Adverse Reactions (6.1)]*.

Priming

Instruct patients to prime the pump before initial use and when ASTEPRO has not been used for 3 or more days *[see Dosage and Administration (2.3)]*.

Keep Spray Out of Eyes
Instruct patients to avoid spraying ASTEPRO into their eyes.

Keep Out of Children's Reach
Instruct patients to keep ASTEPRO out of the reach of children. If a child accidentally ingests ASTEPRO, seek medical help or call a poison control center immediately.

Manufactured for:
Meda Pharmaceuticals Inc.
Somerset, New Jersey 08873-4120

ASTEPRO is a registered trademark of Meda Pharmaceuticals Inc., a Viatris Company.
U.S. Patents 8,071,073; 8,518,919

PATIENT INFORMATION
ASTEPRO [*AS-ta-PRO*]
(azelastine hydrochloride)
nasal spray 0.1%

Important: For use in your nose only.

What is ASTEPRO Nasal Spray?

- ASTEPRO is a prescription medicine used to treat symptoms of seasonal allergic rhinitis in people 2 years of age and older and year-round allergic rhinitis in people 6 months to 11 years of age.
- ASTEPRO may help to reduce your nasal symptoms including stuffy nose, runny nose, itching and sneezing.

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

What should I tell my healthcare provider before using ASTEPRO?

Before using ASTEPRO, tell your healthcare provider about all of your medical conditions, including if you are:

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

How should I use ASTEPRO?

- Read the **Instructions for Use** at the end of this leaflet for information about the right way to use ASTEPRO.
- An adult should help a young child use ASTEPRO.
- Spray ASTEPRO in **your nose only**. **Do not spray it into your eyes or mouth.**
- Use ASTEPRO exactly as your healthcare provider tells you to use it.
- **Do not** use more than your healthcare provider tells you.
- Throw away your ASTEPRO 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.

If you use too much or a child accidentally swallows ASTEPRO, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while using ASTEPRO?

ASTEPRO can cause sleepiness:

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

What are the possible side effects of ASTEPRO?

The most common side effects of ASTEPRO include:

- fever
- unusual taste
- nose pain or discomfort
- nosebleeds
- headache
- sneezing
- fatigue
- upper respiratory tract infections
- cough
- vomiting
- middle ear infection
- skin rash
- sore throat

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. 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?

- Store ASTEPRO at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not freeze ASTEPRO.
- Do not use ASTEPRO after the expiration date “EXP” on the medicine label and carton.

Keep ASTEPRO and all medicines out of reach of children.

General information about the safe and effective use of ASTEPRO.

Medicines are sometimes prescribed for conditions other than those listed in a Patient Information leaflet. Do not use ASTEPRO for a condition for which it was not prescribed. Do not give ASTEPRO 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. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about ASTEPRO that is written for health professionals.

What are the ingredients in ASTEPRO?
Active ingredient: azelastine hydrochloride
Inactive ingredients: sorbitol, sucralose, hypromellose, sodium citrate, edetate disodium, benzalkonium chloride, and purified water.

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

Instructions for Use

ASTEPRO [*AS-ta-PRO*]
(azelastine hydrochloride)
nasal spray 0.1%

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

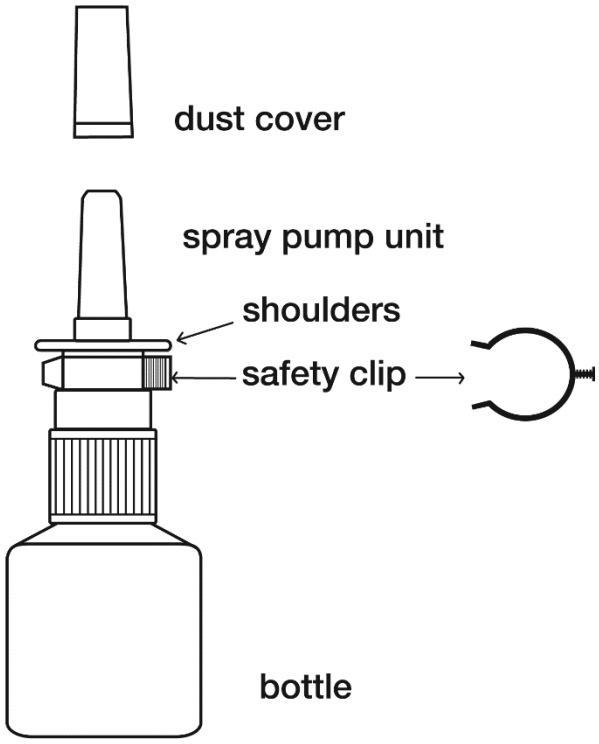


Figure A

Before you use ASTEPRO for the first time, you will need to prime the bottle.
For use in young children: An adult should help a young child use ASTEPRO. (See Using your ASTEPRO Steps 1 through 8).

Priming your ASTEPRO

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**).

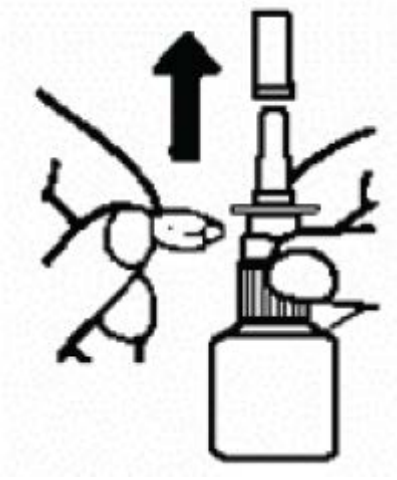


Figure B

- 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 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** section below.
- If you do not use ASTEPRO 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
For use in young children: An adult should help a young child use ASTEPRO. (See Steps 1 through 8).

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. This will help to keep the medicine from going into your throat.

Step 8. When you finish using your ASTEPRO, 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

- 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**).

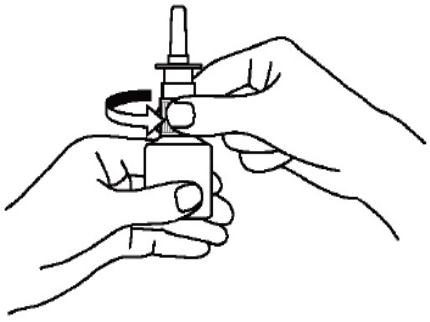


Figure F

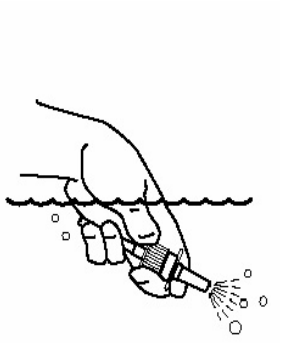


Figure G

- 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 have been approved by the U.S. Food and Drug Administration.

MEDA

Manufactured for:
MEDA Pharmaceuticals Inc.
Somerset, New Jersey 08873-4120

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