

Dear Pharmacist:

Meda Pharmaceuticals would like to take this opportunity to inform you that ASTEPRO[®] (azelastine HCl) Nasal Spray 0.15%, 205.5 mcg, is the only ASTEPRO formulation available.

ASTEPRO 0.15% has no AB-rated generic equivalent, so do not substitute with another azelastine HCl formulation; please dispense ASTEPRO 0.15% as prescribed.

Greater concentration of azelastine HCl, with a great concentration of benefits:

- First and only once-daily nasal antihistamine for seasonal allergic rhinitis
- 50% greater concentration per spray of azelastine HCl than ASTELIN (205.5 mcg vs 137 mcg per spray)
- First and only nasal antihistamine indicated for both seasonal and perennial allergic rhinitis
- When prescribed once daily for seasonal allergic rhinitis, provides nearly 2 months of therapy from a single bottle

In addition, eligible, insured patients will pay no more than a \$15 copay on all prescriptions with the ASTEPRO 0.15% Instant Savings Card.

Indication for ASTEPRO 0.15%

- ASTEPRO[®] (azelastine HCl) Nasal Spray 0.15% is indicated for the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older

Important Safety Information

- Avoid engaging in hazardous occupations requiring complete mental alertness when taking ASTEPRO Nasal Spray 0.15%
- Avoid concurrent use of alcohol or other central nervous system depressants with ASTEPRO Nasal Spray 0.15%
- In clinical studies, the most commonly reported adverse reactions, when dosed at 2 sprays per nostril once or twice daily, respectively, included bitter taste (4%, 6%), nasal discomfort (4%, 3%), epistaxis (2%, 1%), and sneezing (1%, 2%)

Indication for ASTELIN

- ASTELIN[®] (azelastine HCl) Nasal Spray is indicated for the treatment of the nasal symptoms of seasonal allergic rhinitis (patients 5 years of age and older) and nonallergic vasomotor rhinitis (patients 12 years of age and older)

Important Safety Information

- Avoid engaging in hazardous occupations requiring complete mental alertness when taking ASTELIN Nasal Spray
- Avoid concurrent use of alcohol or other central nervous system depressants with ASTELIN Nasal Spray
- The most commonly reported adverse events in seasonal allergic rhinitis and nonallergic vasomotor rhinitis patients 12 years of age and older were bitter taste, headache, somnolence, nasal burning, and rhinitis
- The adverse event profile in seasonal allergic rhinitis patients 5 to 11 years of age was similar to that in the adult population and also included rhinitis/cold symptoms, cough, conjunctivitis, and asthma

Please see the enclosed informational piece that describes the benefits that ASTEPRO 0.15% offers your patients. Thank you for your continued support of ASTEPRO 0.15%. For more information about ASTEPRO 0.15%, please call 1-800-526-3840.

Please see accompanying full Prescribing Information.

Sincerely,

Jeff Hofmeister
Director, Trade Relations

Enclosure:
ASTEPRO 0.15% Pharmacist Ordering Information

*For eligible, insured patients only. Coupon covers the balance of the copay over \$15 (if any) for the first unit dispensed and for refills. Maximum value of \$100 per dispensed unit. Offer expires 12/31/2010. Please see program terms and conditions on the back of the Instant Savings Card brochure or visit ASTEPRO.com.

ASTEPRO 0.15% IS AVAILABLE—DO NOT SUBSTITUTE



ASTEPRO 0.15%
NDC No. 0037-0243-30

ASTEPRO 0.15% has no AB-rated generic equivalent

- Do not substitute with another azelastine HCl formulation

ASTEPRO 0.15% is different from other antihistamines

- First and only once-daily nasal antihistamine for seasonal allergic rhinitis
- 50% greater concentration per spray of azelastine HCl than ASTELIN (205.5 mcg vs 137 mcg per spray)
- Relieves both seasonal and perennial allergic rhinitis in patients 12 years of age and older

Important: Please dispense ASTEPRO 0.15% as prescribed

Please see Important Safety Information on reverse side.

Astepto® 0.15%
(azelastine HCl) Nasal Spray,
205.5 mcg



ASTEPRO 0.15% IS AVAILABLE— DO NOT SUBSTITUTE



Greater concentration of azelastine HCl, with a great concentration of benefits

First and only once-daily nasal antihistamine for seasonal allergic rhinitis	✓
50% greater concentration per spray of azelastine HCl than ASTELIN (205.5 mcg vs 137 mcg per spray)	✓
Relieves both seasonal and perennial allergic rhinitis in patients 12 years of age and older	✓
Minimizes the copay with the Instant Savings Card*	✓
When prescribed once daily for seasonal allergic rhinitis, provides nearly 2 months of therapy from a single bottle	✓

Eligible, insured patients will pay no more than a \$15 copay on all prescriptions with the ASTEPRO 0.15% Instant Savings Card



Indication for ASTEPRO 0.15%

- ASTEPRO® (azelastine HCl) Nasal Spray 0.15% is indicated for the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older

Important Safety Information

- Avoid engaging in hazardous occupations requiring complete mental alertness when taking ASTEPRO Nasal Spray 0.15%
- Avoid concurrent use of alcohol or other central nervous system depressants with ASTEPRO Nasal Spray 0.15%
- In clinical studies, the most commonly reported adverse reactions, when dosed at 2 sprays per nostril once or twice daily, respectively, included bitter taste (4%, 6%), nasal discomfort (4%, 3%), epistaxis (2%, 1%), and sneezing (1%, 2%)

Please see accompanying full Prescribing Information.

*For eligible, insured patients only. Coupon covers the balance of the copay over \$15 (if any) for the first unit dispensed and for refills. Maximum value of \$100 per dispensed unit. Offer expires 12/31/2010. Please see program terms and conditions on the back of the Instant Savings Card brochure or visit ASTEPRO.com.

Indication for ASTELIN

- ASTELIN® (azelastine HCl) Nasal Spray is indicated for the treatment of the nasal symptoms of seasonal allergic rhinitis (patients 5 years of age and older) and nonallergic vasomotor rhinitis (patients 12 years of age and older)

Important Safety Information

- Avoid engaging in hazardous occupations requiring complete mental alertness when taking ASTELIN Nasal Spray
- Avoid concurrent use of alcohol or other central nervous system depressants with ASTELIN Nasal Spray
- The most commonly reported adverse events in seasonal allergic rhinitis and nonallergic vasomotor rhinitis patients 12 years of age and older were bitter taste, headache, somnolence, nasal burning, and rhinitis
- The adverse event profile in seasonal allergic rhinitis patients 5 to 11 years of age was similar to that in the adult population and also included rhinitis/cold symptoms, cough, conjunctivitis, and asthma



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AES1019

February 2010

Astepro® 0.15%
(azelastine HCl) Nasal Spray,
205.5 mcg



ASTEPRO® 0.1%
(azelastine hydrochloride) Nasal Spray

ASTEPRO® 0.15%
(azelastine hydrochloride) Nasal Spray

IN-023D6-04

Rev. 9/09

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ASTEPRO (azelastine hydrochloride) Nasal Spray 0.1%

ASTEPRO (azelastine hydrochloride) Nasal Spray 0.15%

Initial U.S. Approval: 1996

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

For intranasal use only (2.3).

Seasonal allergic rhinitis:

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

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

Perennial allergic rhinitis:

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

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

DOSAGE FORMS AND STRENGTHS

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

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

• Somnolence may occur. Avoid engaging in hazardous occupations requiring complete mental alertness such as driving or operating machinery when taking ASTEPRO Nasal Spray (5.1)

• Avoid concurrent use of alcohol or other central nervous system (CNS) depressants with ASTEPRO Nasal Spray because further decreased alertness and impairment of CNS performance may occur (5.1)

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

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

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

Revised 9/09

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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 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Seasonal Allergic Rhinitis

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

2.2 Perennial Allergic Rhinitis

The recommended dose of ASTEPRO Nasal Spray 0.15% for perennial allergic rhinitis 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 713 patients 12 years of age and older from 2 clinical trials of 2 weeks to 12 months duration. In a 2-week, double-blind, placebo-controlled, and active-controlled (Astelin® Nasal Spray; azelastine hydrochloride) clinical trial, 285 patients (115 males and 170 females) 12 years of age and older with seasonal allergic rhinitis were treated with ASTEPRO Nasal Spray 0.1% one or two sprays per nostril daily. In the 12 month open-label, active-controlled (Astelin Nasal Spray) clinical trial, 428 patients (207 males and 221 females) 12 years of age and older with perennial allergic rhinitis and/or nonallergic rhinitis were treated with ASTEPRO Nasal Spray 0.1% two sprays per nostril twice daily. The racial and ethnic distribution for the 2 clinical trials was 82% white, 8% black, 6% Hispanic, 3% Asian, and <1% other.

Adults and Adolescents 12 Years of Age and Older

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

groups (16-20%). Overall, less than 1% of patients discontinued due to adverse reactions and withdrawal due to adverse reactions was similar among the treatment groups.

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

	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.

ASTEPRO Nasal Spray 0.15%

The safety data described below reflect exposure to ASTEPRO Nasal Spray 0.15% in 1858 patients (12 years of age and older) with seasonal or perennial allergic rhinitis from 8 clinical trials of 2 weeks to 12 months duration. In 7 double-blind, placebo-controlled clinical trials of 2 to 4 weeks duration, 1544 patients (560 males and 984 females) with seasonal or perennial allergic rhinitis were treated with ASTEPRO Nasal Spray 0.15% 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. The racial distribution for the 8 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 2 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.

	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.

6.2 Postmarketing Experience

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 an oral dose approximately 170 times the maximum recommended human daily intranasal dose (MRHDID) in adults on a mg/m² basis. This dose also caused maternal toxicity as evidenced by decreased body weight. Neither fetal nor maternal effects occurred at a dose that was approximately 7 times the MRHDID.

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

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

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

Safety and effectiveness of ASTEPRO Nasal Spray in pediatric patients below the age of 12 years 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.

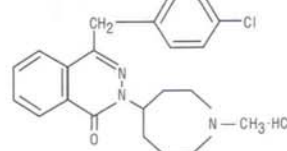
10 OVERDOSAGE

There have been no reported overdoses with ASTEPRO Nasal Spray. Acute overdose 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 overdose 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. Oral doses of 120 mg/kg and greater (approximately 300 times the maximum recommended human daily intranasal dose [MRHDID] in adults and children on a mg/m² basis) were lethal in mice. Responses seen prior to death were tremor, convulsions, decreased muscle tone, and salivation. In dogs, single oral doses as high as 10 mg/kg (approximately 160 times the MRHDID in adults and children on a mg/m² basis) were well tolerated, but single oral doses of 20 mg/kg were lethal.

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-(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)]-, mono-hydrochloride. Its molecular formula is C₂₂H₂₄ClN₃O·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 phthalazine derivative, exhibits histamine H₁-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 H₁-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/m² 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/m² basis). At 68.6 mg/kg (approximately 340 times the MRHDID on a mg/m² 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.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

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

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

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

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 3 (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 3).

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 3). 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 3). Instantaneous TNSS results for the once daily dosing regimen of ASTEPRO Nasal Spray 0.15% are shown in Table 4. In Trials 5 and 6, ASTEPRO Nasal Spray 0.15% demonstrated a greater decrease in iTNSS than placebo and the differences were statistically significant.