

AZELASTINE HYDROCHLORIDE- azelastine spray, metered

Amneal Pharmaceuticals LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AZELASTINE HYDROCHLORIDE NASAL SPRAY safely and effectively. See full prescribing information for AZELASTINE HYDROCHLORIDE NASAL SPRAY.

AZELASTINE HYDROCHLORIDE nasal spray, for intranasal use
Initial U.S. Approval: 1996

INDICATIONS AND USAGE

Azelastine HCl nasal spray, 0.1% is an H₁-receptor antagonist indicated for the treatment of the symptoms of seasonal allergic rhinitis in adults and pediatric patients 5 years and older and for the treatment of the symptoms of vasomotor rhinitis in adults and adolescent patients 12 years and older. (1)

DOSAGE AND ADMINISTRATION

- For intranasal use only. (2.3)
- Seasonal allergic rhinitis:
 - Pediatric patients 5 to 11 years of age: 1 spray per nostril twice daily. (2.1)
 - Adults and adolescents 12 years of age and older: 1 or 2 sprays per nostril twice daily. (2.1)
- Vasomotor rhinitis: 2 sprays per nostril twice daily in adults and adolescents 12 years of age and older. (2.2)
- Prime azelastine HCl nasal spray, 0.1% before initial use and when it has not been used for 3 or more days. (2.3)

DOSAGE FORMS AND STRENGTHS

Azelastine HCl nasal spray, 0.1%: 137 mcg of azelastine HCl, USP in each 0.137 mL 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 azelastine HCl nasal spray, 0.1%. (5.1)
- Alcohol and other central nervous system (CNS) depressants: Avoid concurrent use with azelastine HCl nasal spray, 0.1% because further decreased alertness and impairment of CNS performance may occur. (5.1)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 2\%$ incidence) are: bitter taste, headache, somnolence, dysesthesia, rhinitis, nasal burning, pharyngitis, epistaxis, sinusitis, paroxysmal sneezing, nausea, dry mouth, fatigue, dizziness, and weight increase. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

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FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Seasonal Allergic Rhinitis

2.2 Vasomotor Rhinitis

2.3 Important Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Somnolence in Activities Requiring Mental Alertness

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Central Nervous System Depressants

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Seasonal Allergic Rhinitis

14.2 Vasomotor Rhinitis

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Azelastine hydrochloride (HCl) nasal spray, 0.1% is indicated for the treatment of the symptoms of seasonal allergic rhinitis in adults and pediatric patients 5 years and older, and for the treatment of the symptoms of vasomotor rhinitis in adults and adolescent patients 12 years and older.

2 DOSAGE AND ADMINISTRATION

2.1 Seasonal Allergic Rhinitis

The recommended dosage of azelastine HCl nasal spray, 0.1% in adults and adolescent patients 12 years and older with seasonal allergic rhinitis is one or two sprays per nostril twice daily. The recommended dosage of azelastine HCl nasal spray, 0.1% in pediatric patients 5 years to 11 years of age is one spray per nostril twice daily.

2.2 Vasomotor Rhinitis

The recommended dosage of azelastine HCl nasal spray, 0.1% in adults and adolescent patients 12 years and older with vasomotor rhinitis is two sprays per nostril twice daily.

2.3 Important Administration Instructions

Administer azelastine HCl nasal spray, 0.1% by the intranasal route only.

Priming: Prime azelastine HCl nasal spray, 0.1% before initial use by releasing 4 sprays or until a fine mist appears. When azelastine HCl nasal spray, 0.1% has not been used for 3 or more days, reprime with 2 sprays or until a fine mist appears. Avoid spraying azelastine HCl nasal spray, 0.1% into the eyes.

3 DOSAGE FORMS AND STRENGTHS

Azelastine HCl nasal spray, 0.1% is a nasal spray solution. Each spray of azelastine HCl nasal spray, 0.1% delivers a volume of 0.137 mL solution containing 137 mcg of azelastine HCl, USP.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Somnolence in Activities Requiring Mental Alertness

In clinical trials, the occurrence of somnolence has been reported in some patients taking azelastine HCl nasal spray, 0.1% [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 azelastine HCl nasal spray, 0.1%. Concurrent use of azelastine HCl nasal spray, 0.1% 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 azelastine HCl nasal spray, 0.1% 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.

Seasonal Allergic Rhinitis

Azelastine HCl nasal spray, 0.1% Two Sprays Per Nostril Twice Daily

Adverse experience information for azelastine HCl nasal spray, 0.1% is derived from six placebo- and active-controlled, 2-day to 8-week clinical trials which included 391 patients, 12 years of age and older, with seasonal allergic rhinitis who received azelastine HCl nasal spray, 0.1% at a dose of 2 sprays per nostril twice daily. In placebo-controlled efficacy trials, the incidence of discontinuation due to adverse reactions in patients receiving azelastine HCl nasal spray, 0.1% and vehicle placebo was 2.2% and 2.8%, respectively.

Table 1 contains adverse reactions that were reported with frequencies $\geq 2\%$ in the azelastine HCl nasal spray, 0.1% 2 sprays per nostril twice daily treatment group and more frequently than placebo.

Table 1: Adverse Reactions Reported in $\geq 2\%$ Incidence in Placebo-Controlled Trials in Patients with Seasonal Allergic Rhinitis [n (%)]

	Azelastine HCl Nasal Spray, 0.1% N = 391	Vehicle Placebo N = 353
Bitter Taste	77 (19.7%)	2 (0.6%)
Headache	58 (14.8%)	45 (12.7%)
Somnolence	45 (11.5%)	19 (5.4%)
Nasal Burning	16 (4.1%)	6 (1.7%)
Pharyngitis	15 (3.8%)	10 (2.8%)
Paroxysmal Sneezing	12 (3.1%)	4 (1.1%)
Dry Mouth	11 (2.8%)	6 (1.7%)
Nausea	11 (2.8%)	4 (1.1%)
Rhinitis	9 (2.3%)	5 (1.4%)
Fatigue	9 (2.3%)	5 (1.4%)
Dizziness	8 (2.0%)	5 (1.4%)
Epistaxis	8 (2.0%)	5 (1.4%)
Weight Increase	8 (2.0%)	0 (0.0%)

Azelastine HCl Nasal Spray, 0.1% One Spray Per Nostril Twice Daily

Adverse experience information for azelastine HCl nasal spray, 0.1% at a dose of one spray per nostril twice daily is derived from two placebo-controlled 2-week clinical studies which included 276 patients 12 years of age and older with seasonal allergic rhinitis. The incidence of discontinuation due to adverse reactions in patients receiving azelastine HCl nasal spray, 0.1% and vehicle placebo was 0.0% and 0.8%, respectively. Bitter taste was reported in 8.3% of patients compared to none in the placebo group. Somnolence was reported in 0.4% of patients compared to none in the placebo group.

A total of 176 patients 5 to 11 years of age were exposed to azelastine HCl nasal spray, 0.1% at a dose of 1 spray each nostril twice daily in 3 placebo-controlled studies. In these studies, adverse reactions that occurred more frequently in patients treated with azelastine HCl nasal spray, 0.1% than with placebo, and that were not represented in the adult adverse reactions table above include rhinitis/cold symptoms (17.0% vs. 9.5%), cough (11.4% vs. 8.3%), conjunctivitis (5.1% vs. 1.8%), and asthma (4.5% vs. 4.1%).

Adverse Reactions <2% in azelastine HCl nasal spray, 0.1% One or Two Sprays Per Nostril Twice Daily

The following reactions were observed infrequently (<2% and exceeding placebo incidence) in patients who received azelastine HCl nasal spray, 0.1% dosed at 1 or 2 sprays per nostril twice daily in U.S. clinical trials.

Cardiovascular: flushing, hypertension, tachycardia.

Dermatological: contact dermatitis, eczema, hair and follicle infection, furunculosis, skin laceration.

Digestive: constipation, gastroenteritis, glossitis, ulcerative stomatitis, vomiting, increased SGPT, aphthous stomatitis, diarrhea, toothache.

Metabolic and Nutritional: increased appetite.

Musculoskeletal: myalgia, temporomandibular dislocation, rheumatoid arthritis.

Neurological: hyperkinesia, hypoesthesia, vertigo.

Psychological: anxiety, depersonalization, depression, nervousness, sleep disorder, thinking abnormal.

Respiratory: bronchospasm, coughing, throat burning, laryngitis, bronchitis, dry throat, nocturnal dyspnea, nasopharyngitis, nasal congestion, pharyngolaryngeal pain, sinusitis, nasal dryness, paranasal sinus hypersecretion, post nasal drip.

Special Senses: conjunctivitis, eye abnormality, eye pain, watery eyes, taste loss.

Urogenital: albuminuria, amenorrhea, breast pain, hematuria, increased urinary frequency.

Whole Body: allergic reaction, back pain, herpes simplex, viral infection, malaise, pain in extremities, abdominal pain, pyrexia.

Vasomotor Rhinitis

Adverse experience information for azelastine HCl nasal spray, 0.1% is derived from two placebo-controlled clinical studies which included 216 patients 12 years and older with vasomotor rhinitis who received azelastine HCl nasal spray, 0.1% at a dose of 2 sprays per nostril twice daily for up to 28 days. The incidence of discontinuation due to adverse reactions in patients receiving azelastine HCl nasal spray, 0.1% and vehicle placebo was 2.8% and 2.9%, respectively.

The following adverse reactions were reported with frequencies $\geq 2\%$ in the azelastine HCl nasal spray, 0.1% treatment group and more frequently than placebo.

Table 2: Adverse Reactions Reported in $\geq 2\%$ Incidence in Placebo-Controlled Trials in Patients with Vasomotor Rhinitis [n (%)]

	Azelastine HCl Nasal Spray, 0.1% N = 216	Vehicle Placebo N = 210
Bitter Taste	42 (19.4%)	5 (2.4%)
Headache	17 (7.9%)	16 (7.6%)
Dysesthesia	17 (7.9%)	7 (3.3%)

Rhinitis	12 (5.6%)	5 (2.4%)
Epistaxis	7 (3.2%)	5 (2.4%)
Sinusitis	7 (3.2%)	4 (1.9%)
Somnolence	7 (3.2%)	2 (1.0%)

Reactions observed infrequently (<2% and exceeding placebo incidence) in patients who received azelastine HCl nasal spray, 0.1% (2 sprays/nostril twice daily) in U.S. clinical trials in vasomotor rhinitis were similar to those observed in U.S. clinical trials in seasonal allergic rhinitis.

In controlled trials involving nasal and oral azelastine HCl formulations, there were infrequent occurrences of hepatic transaminase elevations.

6.2 Postmarketing Experience

During the post approval use of azelastine HCl nasal spray, 0.1%, 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: anaphylaxis, application site irritation, atrial fibrillation, chest pain, confusion, dyspnea, facial edema, involuntary muscle contractions, nasal sores, palpitations, paresthesia, parosmia, pruritus, rash, disturbance or loss of sense of smell and/or taste, tolerance, urinary retention, vision abnormal and xerophthalmia.

7 DRUG INTERACTIONS

7.1 Central Nervous System Depressants

Concurrent use of azelastine HCl nasal spray, 0.1% 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)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data from post-marketing experience over decades of use with azelastine HCl nasal spray, 0.1% 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 5 times the clinical daily dose. Oral administration of azelastine HCl 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 270 times and higher than the maximum recommended human daily intranasal dose (MRHDID) of 1.096 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% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in mice dosed during the period of organogenesis, azelastine HCl 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 300 times the maximum recommended human daily intranasal dose (MRHDID) in adults (on a mg/m² 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 15 times the MRHDID in adults (on a mg/m² 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 HCl caused structural abnormalities (oligo- and brachydactylia), delayed ossification, and skeletal variations, in the absence of maternal toxicity, at approximately 270 times the MRHDID in adults (on a mg/m² basis at a maternal oral dose of 30 mg/kg/day). Azelastine HCl caused embryo-fetal death and decreased fetal weight and severe maternal toxicity at approximately 610 times the MRHDID (on a mg/m² basis at a maternal oral dose of 68.6 mg/kg/day). Neither fetal nor maternal effects occurred at approximately 20 times the MRHDID (on a mg/m² 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 HCl caused abortion, delayed ossification and decreased fetal weight and severe maternal toxicity at approximately 530 times the MRHDID in adults (on a mg/m² basis at a maternal oral dose of 30 mg/kg/day). Neither fetal nor maternal effects occurred at approximately 5 times the MRHDID (on a mg/m² 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 HCl produced no adverse developmental effects on pups at maternal doses up to approximately 270 times the MRHDID (on mg/m² basis at a maternal dose of 30 mg/kg/day).

8.2 Lactation

Risk Summary

There are no data on the presence of azelastine HCl in human milk, the effects on the breastfed infant, or the effects on milk production. Breastfed infants should be monitored for signs of milk rejection during azelastine HCl use by lactating women (see *Clinical Considerations*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for azelastine HCl nasal spray, 0.1% and any potential adverse effects on the breastfed infant from azelastine HCl nasal spray, 0.1% or from the underlying maternal condition.

Clinical Considerations

Monitoring for Adverse Reactions

Breastfed infants of lactating women treated with azelastine HCl nasal spray, 0.1% should be monitored for possible signs of milk rejection related to the bitter taste of azelastine HCl.

8.4 Pediatric Use

The safety and effectiveness of azelastine HCl nasal spray, 0.1% for the treatment of symptoms of seasonal allergic rhinitis have been established for patients 5 years and older [see *Adverse Reactions (6.1)* and *Clinical Studies (14.1)*]. The safety and effectiveness of azelastine HCl nasal spray, 0.1% for the treatment of vasomotor rhinitis have been established for patients 12 years and older [see *Adverse Reactions (6.1)* and *Clinical Studies (14.2)*]. The safety and effectiveness of azelastine HCl nasal spray, 0.1% in pediatric patients below the age of 5 years with seasonal allergic rhinitis and in pediatric patients below the age of 12 years with vasomotor rhinitis have not been established.

8.5 Geriatric Use

Clinical trials of azelastine HCl nasal spray, 0.1% did not include sufficient numbers of patients aged 65 and over 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.

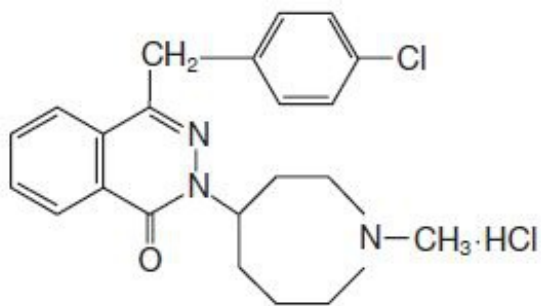
10 OVERDOSAGE

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

11 DESCRIPTION

Azelastine HCl nasal spray, 0.1%, 137 micrograms (mcg), is an antihistamine formulated as a metered-spray solution for intranasal administration. Azelastine HCl, USP 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:



Azelastine HCl nasal spray, 0.1% contains 0.1% azelastine HCl, USP in an aqueous solution at $pH\ 6.8 \pm 0.3$. It also contains benzalkonium chloride (125 mcg/mL), citric acid, dibasic sodium phosphate, edetate disodium, hypromellose, purified water (pH 6.8) and sodium chloride.

After priming [see *Dosage and Administration (2.3)*], each metered spray delivers a 0.137 mL mean volume containing 137 mcg of azelastine HCl, USP (equivalent to 125 mcg of azelastine base). The bottle can deliver 200 metered sprays.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Azelastine HCl, a phthalazinone derivative, exhibits histamine H_1 -receptor antagonist activity in isolated tissues, animal models, and humans. Azelastine HCl nasal spray, 0.1% 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 Electrophysiology:

In a placebo-controlled study (95 subjects with allergic rhinitis), there was no evidence of an effect of azelastine HCl nasal spray, 0.1% (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 HCl and erythromycin or ketoconazole were conducted. These drugs had no effect on QTc based on analysis of serial electrocardiograms. At a dose approximately 8 times the maximum recommended dose, azelastine HCl does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption: After intranasal administration, the systemic bioavailability of azelastine HCl is approximately 40%. Maximum plasma concentrations (C_{max}) are achieved in 2 to 3 hours.

Azelastine HCl administered intranasally at doses above two sprays per nostril twice daily for 29 days resulted in greater than proportional increases in C_{max} and area under the curve (AUC) for azelastine.

Distribution: Based on intravenous and oral administration, the steady-state volume of distribution 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 intranasal dosing of azelastine HCl to steady-state, plasma concentrations of desmethylazelastine range from 20% to 50% of azelastine concentrations. Limited data indicate that the metabolite profile is similar when azelastine HCl is administered via the intranasal or oral route.

Elimination: Based on intravenous and oral administration, the elimination half-life and plasma clearance are 22 hours and 0.5 L/h/kg, respectively. Approximately 75% of an oral dose of radiolabeled azelastine HCl 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% to 75% higher C_{max} and AUC compared to normal 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: No significant pharmacokinetic interaction was observed with the co-administration of orally administered azelastine (4 mg twice daily) with erythromycin (500 mg three times daily for 7 days). In this study, co-administration of orally administered azelastine with erythromycin 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.

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%. No pharmacokinetic interaction was observed with co-administration of orally administered azelastine (4 mg twice daily)

with ranitidine hydrochloride (150 mg twice daily). Oral co-administration of azelastine with ranitidine resulted in C_{max} of 8.89 ± 3.28 ng/mL and AUC of 88.22 ± 40.43 ng•h/mL for azelastine, whereas, azelastine when administered alone resulted in C_{max} of 7.83 ± 4.06 ng/mL and AUC of 80.09 ± 43.55 ng•h/mL for azelastine.

Theophylline: No significant pharmacokinetic interaction was observed with the co-administration of an oral 4 mg dose of azelastine HCl 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 CrI:CD(SD)BR rats and NMRI mice were conducted to assess the carcinogenic potential of azelastine HCl. No evidence of tumorigenicity was observed in rats at doses up to 30 mg/kg (approximately 270 and 240 times the MRHDID for adults and children, respectively, on a mg/m² basis). No evidence for tumorigenicity was observed in mice at doses up to 25 mg/kg (approximately 110 and 100 times the MRHDID for adults and children, respectively, on a mg/m² basis).

Azelastine HCl 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 270 times the MRHDID in adults on a mg/m² basis). At 68.6 mg/kg (approximately 610 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.

14 CLINICAL STUDIES

14.1 Seasonal Allergic Rhinitis

Two Sprays Per Nostril Twice Daily

The efficacy and safety of azelastine HCl nasal spray, 0.1% were evaluated in three placebo-controlled clinical trials of azelastine HCl nasal spray, 0.1% including 322 patients with seasonal allergic rhinitis who received two sprays per nostril twice a day for up to 4 weeks. These trials included 55 pediatric patients ages 12 to 16 years. Assessment of efficacy was based on the 12-hour reflective Total Symptom Complex (TSC) and Major Symptom Complex (MSC). The MSC was calculated as the average of individual symptoms of nose blows, sneezes, runny nose/sniffles, itchy nose, and watery eyes as assessed by patients on a 0 to 5 categorical scale. Azelastine HCl nasal spray, 0.1% two sprays per nostril twice daily demonstrated a greater decrease in the MSC than placebo (Table 3).

Table 3: Mean Change from Baseline in Reflective MSC* in Adults and Adolescents ≥ 12 Years with Seasonal Allergic Rhinitis Treated with Azelastine HCl Nasal Spray, 0.1% Two Sprays Per Nostril Twice Daily Versus Placebo

	Treatment	N	Baseline LS Mean (SD)	Change from Baseline (SD)	Treatment Difference	P-value
Trial 1: 12 Hour AM and PM Reflective MSC						
	Azelastine HCl Nasal Spray, 0.1%	63	11.48 (4.13)	-3.05 (3.51)	1.98	<0.01
	Placebo Nasal Spray	60	10.84 (4.53)	-1.07 (3.52)		
Trial 2: 12 Hour AM and PM Reflective MSC						
	Azelastine HCl Nasal Spray, 0.1%	63	12.50 (4.5)	-4.10 (3.46)	2.03	<0.01
	Placebo Nasal Spray	63	12.18 (4.64)	-2.07 (4.01)		
Trial 3: 12 Hour AM and PM Reflective MSC						
	Azelastine HCl Nasal Spray, 0.1%	66	12.04 (4.03)	-3.31 (3.74)	1.35	0.04
	Placebo Nasal Spray	66	11.66 (3.96)	-1.96 (3.57)		
* Major Symptom Complex (MSC): Average of individual symptoms of nose blows, sneezes, runny nose/sniffles, itchy nose, and watery eyes as assessed by patients on a 0 to 5 categorical scale.						

In dose-ranging trials, administration of azelastine HCl nasal spray, 0.1% two sprays per nostril twice daily resulted in a statistically significant decrease in symptoms compared to saline placebo within 3 hours after initial dosing and persisted over the 12-hour dosing interval.

One Spray Per Nostril Twice Daily

The efficacy and safety of azelastine HCl nasal spray, 0.1% were evaluated in two placebo-controlled clinical trials of azelastine HCl nasal spray, 0.1% including 275 patients with seasonal allergic rhinitis who received one spray per nostril twice a day for up to 2 weeks. Assessment of efficacy was based on the 12-hour reflective Total Nasal Symptom Score [rTNSS]. rTNSS is calculated as the sum of the patients scoring of four individual nasal symptoms (runny nose, sneezing, itchy nose, and nasal congestion) as assessed by patients on a 0 to 3 categorical scale. The primary efficacy endpoint was the change from Baseline to Day 14 in rTNSS. The mean change from baseline in rTNSS was greater in patients receiving azelastine HCl nasal spray, 0.1% one spray per nostril twice daily than those receiving placebo (Table 4).

Table 4: Mean Change from Baseline in Reflective TNSS* in Adults and Adolescents ≥12 years with Seasonal Allergic Rhinitis Treated with Azelastine HCl Nasal Spray, 0.1% One Spray Per Nostril Twice Daily Versus Placebo

	Treatment	N	Baseline LS Mean (SD)	Change from Baseline (SD)	Treatment Difference	P-value
Trial 4: 12 Hour AM and PM Reflective TNSS						
	Azelastine HCl Nasal Spray, 0.1%	138	16.34 (4.22)	-2.69 (4.79)	1.38	0.01
	Placebo Nasal	141	17.21 (4.22)	-1.21 (4.20)		

Spray	141	17.21 (4.52)	-1.51 (4.29)		
Trial 5: 12 Hour AM and PM Reflective TNSS					
Azelastine HCl Nasal Spray, 0.1%	137	16.62 (4.20)	-3.68 (4.16)	1.18	0.02
Placebo Nasal Spray	136	16.84 (4.77)	-2.50 (4.01)		
* Total Nasal Symptom Score (TNSS): Average of individual symptoms of runny nose, sneezing, itchy nose, and nasal congestion as assessed by patients on a 0 to 3 categorical scale.					

Two-week studies comparing the efficacy (and safety) of azelastine HCl nasal spray, 0.1% two sprays per nostril twice daily versus one spray per nostril twice daily were not conducted.

14.2 Vasomotor Rhinitis

The efficacy and safety of azelastine HCl nasal spray, 0.1% were evaluated in two placebo-controlled clinical trials of azelastine HCl nasal spray, 0.1% including 216 patients with vasomotor rhinitis who received two sprays per nostril twice a day for up to 4 weeks. These patients had vasomotor rhinitis for at least one year, negative skin tests to indoor and outdoor aeroallergens, negative nasal smears for eosinophils, and negative sinus X-rays. Azelastine HCl nasal spray, 0.1% demonstrated a significantly greater decrease in a symptom complex comprised of rhinorrhea, post nasal drip, nasal congestion, and sneezing compared to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Azelastine HCl nasal spray 0.1%, 137 mcg, is supplied as a 30-mL package (NDC 65162-676-84) 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 white safety clip and a white or clear plastic dust cover. The net content of the bottle is 30 mL (net weight 30 g of solution). Each bottle contains 30 mg (1 mg/mL) of azelastine HCl, USP. 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 HCl, USP. 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. Azelastine HCl nasal spray, 0.1% should not be used after the expiration date "EXP" printed on the medicine label and carton.

Storage:

Store upright at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from freezing.

17 PATIENT COUNSELING INFORMATION

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

Activities Requiring Mental Alertness

Somnolence has been reported in some patients taking azelastine HCl nasal spray, 0.1%. Caution patients against engaging in hazardous occupations requiring complete mental alertness and motor coordination such as driving or operating machinery after administration of azelastine HCl nasal spray, 0.1% [see *Warnings and Precautions (5.1)*].

Concurrent Use of Alcohol and other Central Nervous System Depressants

Instruct patients to avoid concurrent use of azelastine HCl nasal spray, 0.1% 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 azelastine HCl nasal spray, 0.1% may lead to adverse reactions, which include bitter taste, headache, somnolence, dysesthesia, rhinitis, nasal burning, pharyngitis, epistaxis, sinusitis, paroxysmal sneezing, nausea, dry mouth, fatigue, dizziness, and weight increase [see *Adverse Reactions (6.1)*].

Priming

Instruct patients to prime the pump before initial use and when azelastine HCl nasal spray, 0.1% 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 azelastine HCl nasal spray, 0.1% into their eyes.

Keep Out of Children's Reach

Instruct patients to keep azelastine HCl nasal spray, 0.1% out of the reach of children. If a child accidentally ingests azelastine HCl nasal spray, 0.1%, seek medical help or call a poison control center immediately.

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Bridgewater, NJ 08807

Rev. 10-2018-02

PATIENT INFORMATION

Azelastine Hydrochloride (ay" ze las' teen hye" droe klor' ide) Nasal Spray, 0.1%

Important: For use in your nose only.
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What is azelastine HCl nasal spray, 0.1%?

- Azelastine HCl nasal spray, 0.1% is a prescription medicine used to treat symptoms of seasonal allergic rhinitis in people age 5 and older and vasomotor rhinitis in people age 12 and older.

- Azelastine HCl nasal spray, 0.1% may help to reduce your nasal symptoms including stuffy nose, runny nose, itching and sneezing.

It is not known if azelastine HCl nasal spray, 0.1% is safe and effective in children with seasonal allergic rhinitis under 5 years of age or in children with vasomotor rhinitis under 12 years of age.

What should I tell my healthcare provider before using azelastine HCl nasal spray, 0.1%?

Before using azelastine HCl nasal spray, 0.1%, tell your healthcare provider if you are:

- allergic to any of the ingredients in azelastine HCl nasal spray, 0.1%. See the end of this leaflet for a complete list of ingredients in azelastine HCl nasal spray, 0.1%.
- pregnant, or plan to become pregnant.
- breastfeeding, or plan to breastfeed. It is not known if azelastine HCl passes into your breast milk. You and your healthcare provider should decide if you will use azelastine HCl nasal spray, 0.1% 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. Azelastine HCl nasal spray, 0.1% and other medicines may affect each other, causing side effects.

How should I use azelastine HCl nasal spray, 0.1%?

- Read the **Instructions for Use** at the end of this leaflet for information about the right way to use azelastine HCl nasal spray, 0.1%.
- Spray azelastine HCl nasal spray, 0.1% in **your nose only. Do not spray it into your eyes or mouth.**
- Use azelastine HCl nasal spray, 0.1% exactly as your healthcare provider tells you to use it.
- **Do not** use more than your healthcare provider tells you.
- Throw away your azelastine HCl 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.
- If you use too much or a child accidentally swallows azelastine HCl nasal spray, 0.1%, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while using azelastine HCl nasal spray, 0.1%?

Azelastine HCl nasal spray, 0.1% can cause sleepiness:

- **Do not** drive, operate machinery, or do other dangerous activities until you know how azelastine HCl nasal spray, 0.1% affects you.
- **Do not** drink alcohol or take other medicines that may cause you to feel sleepy while using azelastine HCl nasal spray, 0.1%. It may make your sleepiness worse.

What are the possible side effects of azelastine HCl nasal spray, 0.1%?

The most common side effects of azelastine HCl nasal spray, 0.1% include:

- unusual bitter taste
- headache

- sleepiness
- nose burning, pain or discomfort
- runny nose
- scratchy or sore throat
- nosebleeds
- inflammation or swelling of the sinuses
- sneezing
- nausea
- dry mouth
- fatigue
- dizziness
- weight increase

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 azelastine HCl nasal spray, 0.1%. 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 azelastine HCl nasal spray, 0.1%?

- Keep azelastine HCl nasal spray, 0.1% upright at 68° to 77°F (20° to 25°C).
- Do not freeze azelastine HCl nasal spray, 0.1%.
- Do not use azelastine HCl nasal spray, 0.1% after the expiration date “EXP” on the medicine label and box.

Keep azelastine HCl nasal spray, 0.1% and all medicines out of reach of children.

General information about the safe and effective use of azelastine HCl nasal spray, 0.1%.

Medicines are sometimes prescribed for conditions other than those listed in a Patient Information leaflet. Do not use azelastine HCl nasal spray, 0.1% for a condition for which it was not prescribed. Do not give azelastine HCl nasal spray, 0.1% 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 azelastine HCl nasal spray, 0.1%. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about azelastine HCl nasal spray, 0.1% that is written for health professionals.

For more information call 1-877-835-5472.

What are the ingredients in azelastine HCl nasal spray, 0.1%?

Active ingredient: Azelastine HCl, USP

Inactive ingredients: Benzalkonium chloride, citric acid, dibasic sodium phosphate, edetate disodium, hypromellose, purified water (pH 6.8) and sodium chloride.

* Trademarks are the property of their respective owners.

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Rev. 10-2018-02

Instructions for Use

Azelastine Hydrochloride (ay" ze las' teen hye" droe klor' ide) 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 azelastine HCl nasal spray, 0.1% pump

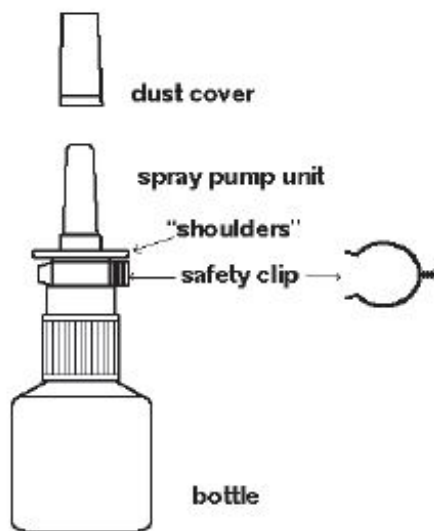


Figure A

Before you use azelastine HCl nasal spray, 0.1% for the first time, you will need to prime the bottle.

Priming your azelastine HCl nasal spray, 0.1%

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

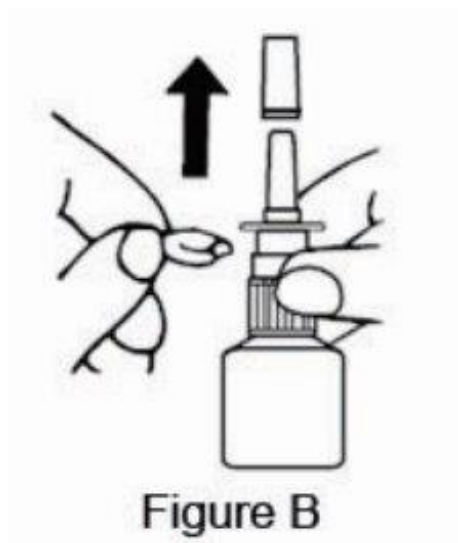


Figure B

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 4 sprays or less.

Now your pump is primed and ready to use.

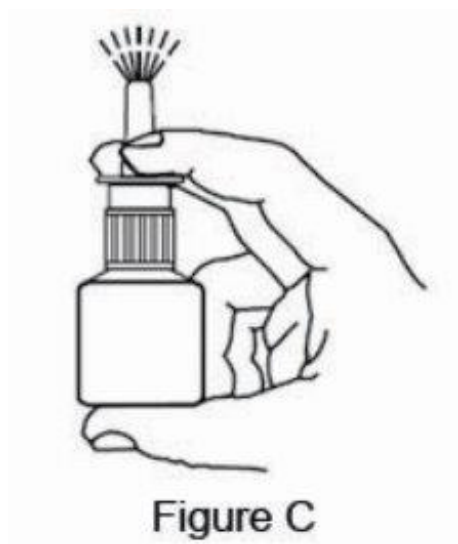


Figure C

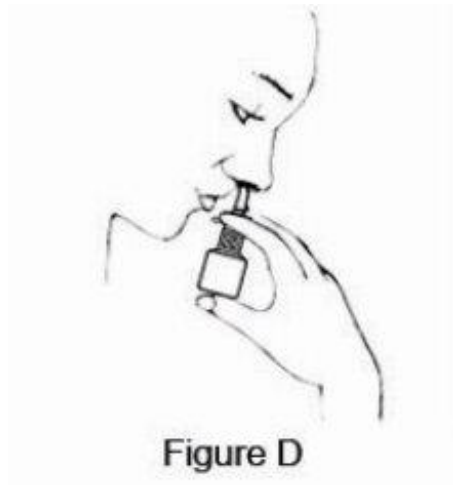
- **Do not** use azelastine HCl nasal spray, 0.1% unless you see a fine mist after you do the priming sprays. If you do not see a fine mist, clean the tip of the spray nozzle. See the **“Cleaning the Spray Tip of your azelastine HCl nasal spray, 0.1%”** section below.
- If you do not use azelastine HCl nasal spray, 0.1% for 3 or more days, you will need to prime the pump with 2 sprays or until you see a fine mist.
Using your azelastine HCl nasal spray, 0.1%

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 $\frac{1}{4}$ inch to $\frac{1}{2}$ inch into 1 nostril. Hold bottle upright and aim the

spray tip toward the back of your nose (**See 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**).



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 azelastine HCl nasal spray, 0.1%. This will help to keep the medicine from going into your throat.

Step 8. When you finish using your azelastine HCl nasal spray, 0.1%, 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 azelastine HCl nasal spray, 0.1%

- 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

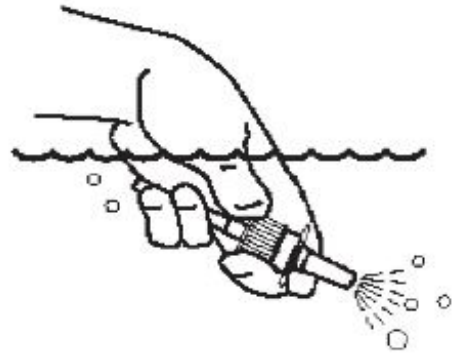


Figure G

- 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.

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Rev. 10-2018-02

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

IMPORTANT: READ ACCOMPANYING DIRECTIONS CAREFULLY BEFORE USE.

Each mL contains 1 mg azelastine HCl, USP. Each spray delivers 0.137 mL (137 mcg as azelastine HCl, USP equivalent to 125 mcg of azelastine base).
Usual Dosage: See accompanying full prescribing information. Initial priming is 4 sprays; use 2 sprays or until a fine mist appears to reprime.
Store upright at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from freezing.
Keep bottle upright, tightly closed, and away from children. Also contains citric acid, benzalkonium chloride, dibasic sodium phosphate, edetate disodium, hypromellose, purified water (pH 6.8) and sodium chloride.

NDC 65162-676-84

Azelastine HCl Nasal Spray, 0.1% 137 mcg per spray

200 Metered Sprays
FOR INTRANASAL USE ONLY
DO NOT SPRAY IN EYES

Rx only
Net Contents: 30 mL

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LOT:
EXP:

0.95" x 0.5"
Non-Varnish Area
For Lot & Exp



2.73" x 1.64"
Non-Varnish Area
For Lot & Exp
and Serialization

Azelastine HCl Nasal Spray, 0.1%
137 mcg per spray

NDC 65162-676-84

Azelastine HCl Nasal Spray, 0.1%

137 mcg per spray



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Rev. 06-2017-00



Antihistamine Nasal Spray
200 Metered Spray
Dispensing Package

Patient: See the Enclosed How to Use Instructions

FOR INTRANASAL USE ONLY
DO NOT SPRAY IN EYES

Each spray delivers 0.137 mL (137 mcg azelastine hydrochloride, USP).
Keep bottle tightly closed and away from children.

Net Contents: 30 mL

Rx only



Azelastine HCl Nasal Spray, 0.1%
137 mcg per spray



Each mL contains 1 mg azelastine HCl, USP. Each spray delivers 0.137 mL (137 mcg as azelastine HCl, USP equivalent to 125 mcg of azelastine base).

Also contains citric acid, benzalkonium chloride, dibasic sodium phosphate, edetate disodium, hypromellose, purified water (pH 6.8) and sodium chloride.

IMPORTANT: Dispense with enclosed patient instructions for use.

Initial priming is 4 sprays; use 2 sprays or until a fine mist appears to reprime.

Store upright at 20° to 25°C (68° to 77°F)[see USP Controlled Room Temperature]. Protect from freezing.

Azelastine HCl Nasal Spray, 0.1%

137 mcg per spray



Dosing Instructions:

- ▶ Blow nose gently
- ▶ Tilt head slightly forward (look at toes)
- ▶ Inhale gently (do not breathe in forcefully or tilt your head back)



Usual dosage:
See enclosed full Prescribing Information.

For assistance call 1-877-835-5472



2.73" x 1.64"
Non-Varnish Area
For Lot & Exp
and Serialization



AZELASTINE HYDROCHLORIDE

azelastine spray, metered

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:65162-676
Route of Administration	NASAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AZELASTINE HYDROCHLORIDE (UNII: 0L591QR10I) (AZELASTINE - UNII:ZQI909440X)	AZELASTINE HYDROCHLORIDE	1 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	
SODIUM PHOSPHATE (UNII: SE337SVY37)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
WATER (UNII: 059QF0KO0R)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	

Product Characteristics

Color	white (clear)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65162-676-84	1 in 1 CARTON	09/05/2017	
1		30 mL in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204660	09/05/2017	

Labeler - Amneal Pharmaceuticals LLC (123797875)**Establishment**

Name	Address	ID/FEI	Business Operations
Amneal Pharmaceuticals, LLC		963900878	analysis(65162-676) , label(65162-676) , manufacture(65162-676) , pack(65162-676)

Revised: 10/2018

Amneal Pharmaceuticals LLC