AZELASTINE b (Nasal)

Introduction

VA CLASSIFICATION (Primary)¾NT400

Commonly used brand name(s):Astelin.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

b Not commercially available in Canada.

Category

Antihistaminic (H 1-receptor), nasal.

Indications

Accepted

Rhinitis, seasonal allergic (treatment)¾Azelastine is indicated for symptomatic treatment of seasonal allergic rhinitis, including rhinorrhea, sneezing, and nasal pruritus, in adults and children 5 years of age and older 1.
2

Rhinitis, vasomotor (treatment)¾Azelastine is indicated for symptomatic treatment of vasomotor rhinitis including rhinorrhea, nasal congestion, and post nasal drip in adults and children 12 years of age and older. 2

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Chemical group¾Phthalazinone derivative 1.

Molecular weight¾418.37 1

pH¾Saturated solution: 5 to 5.4 1.

Commercial product: 6.8 ± 0.3 1.
Solubility¾Sparingly soluble in water, methanol, and propylene glycol and slightly soluble in ethanol, octanol, and glycerine 1.

Mechanism of action/Effect:

Azelastine acts by competing with histamine for H 1-receptor sites on effector cells 1.

Absorption:

Systemic bioavailability is approximately 40% after nasal administration [1].

Distribution:

Vol D¾14.5 liters per kg of body weight [1].

Protein binding:

Azelastine¾High (88%) [1].

Desmethylazelastine¾Very high (97%) [1].

Biotransformation:

Hepatic, by oxidation via the cytochrome P450 enzyme system [1].

The exact cytochrome P450 isoenzyme involved has not been determined, but a nonspecific P450 inhibitor (cimetidine) was found to raise mean concentrations of azelastine significantly; no pharmacokinetic interaction could be demonstrated with a known CYP3A4 inhibitor (erythromycin) [1].

The major metabolite, desmethylazelastine, also has H 1-receptor antagonist activity [1].

Desmethylazelastine is undetectable in plasma following single intranasal doses of azelastine but concentrations range from 20 to 50% of azelastine concentrations at the steady-state [1].

Half-life:

Elimination¾ Azelastine (after intravenous or oral administration)¾22 hours [1].

Desmethylazelastine (after oral administration of azelastine)¾54 hours [1].

Note:
According to limited data, the metabolite profile is similar for oral and intranasal administration of azelastine [1].

Onset of action:

In dose-ranging trials, nasal azelastine was found to produce a statistically significant decrease in allergic symptoms within 3 hours after the initial dose [1].

Time to peak concentration:

Plasma¾2 to 3 hours [1].

Peak plasma concentration

Oral administration of azelastine produces linear responses in the maximum plasma concentration (C max) and area under the plasma concentration-time curve (AUC) 1.

However, administration of intranasal doses of more than 2 sprays per nostril for 29 days has been found to produce greater than proportional increases in the C max and AUC 1.

In oral, single-dose studies, renal insufficiency (creatinine clearance less than 50 mL per minute) resulted in a 70 to 75% increase in the C max and AUC compared with those in normal subjects, although the time to peak plasma concentration was unchanged 1.

Duration of action:

12 hours 1.

Elimination:

Fecal¾75% (less than 10% unchanged) after oral administration 1.

Precautions to Consider

Carcinogenicity

Studies in rats and mice given oral doses of up to 30 and 25 mg per kg of body weight (mg/kg) per day, respectively (240 and 100 times the maximum recommended human daily intranasal dose on a mg per square meter of body surface area [mg/m 2] basis, respectively), found no evidence of carcinogenicity 1.

Mutagenicity

No evidence of mutagenicity caused by azelastine was found in the Ames test, DNA repair test, mouse lymphoma forward mutation assay, mouse micronucleus test, or chromosomal aberration test in rat bone marrow 1.

Pregnancy/Reproduction

Fertility¾Studies in rats given oral doses of azelastine of up to 30 mg/kg per day (240 times the maximum recommended human daily intranasal dose on a mg/m 2 basis) found no effects on male or female fertility 1.

However, at doses of 68.6 mg/kg per day (550 times the maximum recommended human daily intranasal dose on a mg/m 2 basis), 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, but the implantation ratio was not affected 1.

Pregnancy¾Adequate and well-controlled studies in humans have not been done 1.

Studies in mice given an oral dose of 68.6 mg/kg per day (280 times the maximum recommended human daily intranasal dose on a mg/m 2 basis) found azelastine to be embryotoxic, fetotoxic, and teratogenic (external and skeletal abnormalities). Studies in rats given an oral dose of 30 mg/kg per day (240 times the maximum recommended human daily intranasal dose on a mg/m 2 basis) found delayed ossification (undeveloped metacarpus) and an increased incidence of 14th rib. At 68.6 mg/kg per day (550 times the maximum recommended human daily intranasal dose on a mg/m 2 basis), azelastine caused abortion and fetotoxic effects in rats. 1

It is recommended that risk-benefit be considered before using azelastine during pregnancy 1.

FDA Pregnancy Category C 1.

Breast-feeding

It is not known whether azelastine is distributed into breast milk 1.

Pediatrics

Appropriate studies performed to date have not demonstrated pediatrics-specific problems that would limit the usefulness of azelastine in children 5 years of age and older. 2

Geriatrics

Although studies on the relationship of age to the effects of azelastine have not been performed in the geriatric population, placebo-controlled clinical trials included a small number of patients over 60 years of age, and adverse effects in this group were similar to those in younger individuals 1.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
>> Alcohol or

>> CNS depression-producing medications, other (see Appendix II)

(concurrent use may potentiate the CNS depressant effects of either these medications or azelastine 1)

>> Cimetidine

(concurrent use with azelastine results in significantly increased plasma concentrations of azelastine, as a result of inhibition of cytochrome P450 by cimetidine 1)

Ketoconazole

(interferes with measurement of plasma azelastine concentrations 1)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Alanine aminotransferase (ALT [SGPT])

(serum values may rarely be increased 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

Renal function impairment

(plasma concentrations may be increased 1)

Sensitivity to azelastine 1

Side/Adverse Effects

Note: No significant effect on QT interval has been found in studies of orally or nasally administered azelastine at therapeutic doses 1.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence rare

Allergic reaction 1 (skin rash, hives, or itching); bronchospasm 1 (shortness of breath, tightness in chest, troubled breathing, or wheezing); cough 1; eye problems or pain 1 (eye pain or redness or blurred vision or other change in vision); hematuria 1 (blood in urine); stomatitis 1 (sores in mouth or on lips); tachycardia 1 (rapid heartbeat)
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Bitter taste 1¾incidence 19.7%; somnolence 1 (drowsiness or sleepiness)
Incidence less frequent

Burning inside the nose 1; dizziness 1; dryness of mouth 1; epistaxis (bloody mucus or unexplained nosebleeds); fatigue (unusual tiredness or weakness); headache 1; myalgia 1 (muscle aches or pain); nausea 1; pharyngitis 1 (sore throat); sneezing, paroxysmal 1 (sudden outbursts of sneezing); weight gain 1

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

There have been no reported incidents of azelastine overdose in humans; however, acute overdose would not be expected to result in clinically significant adverse effects other than increased somnolence, since one bottle contains 17 mg of azelastine hydrochloride and single oral doses of up to 16 mg have not produced serious adverse effects 1.

In mice, oral doses of greater than 120 mg per kg of body weight (mg/kg) (480 times the maximum recommended human daily intranasal dose on a mg per square meter of body surface area [mg/m 2] basis) produced significant mortality, preceded by tremor, convulsions, decreased muscle tone, and salivation. In dogs, single doses as high as 10 mg/kg (270 times the maximum recommended human daily intranasal dose on a mg/m 2 basis) were well tolerated, but single doses of 20 mg/kg were lethal 1.

Treatment of overdose

General supportive measures 1.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Azelastine (Nasal)¾Introductory Version .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to azelastine
Pregnancy¾Risk-benefit should be considered; teratogenic in animals
Use in children¾Safety and efficacy not established in children up to 5 years of age
Other medications, especially alcohol or other CNS depressants or cimetidine
Proper use of this medication

Reading patient instructions carefully before using

Clearing nasal passages by blowing nose before use

Proper administration technique; reading patient directions carefully before use; before initial use, priming the pump with four sprays or until a fine mist appears; if not used for 3 or more days, priming the pump with two sprays or until a fine mist appears

Preventing contamination: Wiping tip of applicator with clean, damp tissue; replacing cap right after use

>> Importance of not using more medication than the amount prescribed

>> Proper dosing
Missed dose: Using as soon as possible; if almost time for next dose, skipping missed dose and going back to regular dosing schedule; not doubling doses
>> Proper storage; storing upright at room temperature with pump tightly closed
Precautions while using this medication

>> Avoiding use of alcohol or other CNS depressants

>> Caution if dizziness or drowsiness occurs

>> Avoiding spraying in the eyes

Side/adverse effects

Signs of potential side effects, especially allergic reaction, bronchospasm, cough, eye problems or pain, hematuria, stomatitis, or tachycardia

General Dosing Information

Before initial use, the pump should be primed with four sprays or until a fine mist appears. If not used for 3 or more days, the pump should be primed with two sprays or until a fine mist appears. 1

Prior to administration of azelastine, the nasal passages should be cleared.
Azelastine is dispensed in a package consisting of two bottles of medication (for a total of 200 metered sprays) and one pump assembly 1.

Nasal Dosage Forms

AZELASTINE HYDROCHLORIDE NASAL SOLUTION

Usual adult and adolescent dose

Rhinitis, seasonal allergic¾Intranasal, 2 sprays in each nostril two times a day 1, 2.

Rhinitis, vasomotor¾Intranasal, 2 sprays in each nostril two times a day 2

Usual pediatric dose

Rhinitis, seasonal allergic¾Children 12 years of age and older: See Usual adult and adolescent dose 1.

Children 5 to 11 years of age: Intranasal, 1 spray in each nostril twice daily. 2

Children up to 5 years of age: Safety and efficacy have not been established. 2

Rhinitis, vasomotor¾Children 12 years of age and older: See Usual adult and adolescent dose 2

Children up to 12 years of age: Safety and efficacy have not been established 2.

Strength(s) usually available

U.S.¾137 mcg per metered spray (1 mg per mL; 100 metered sprays per bottle) (Rx)[Astelin 1 (benzalkonium chloride 125 mcg per mL) (edetate disodium) (hydroxypropyl methylcellulose) (citric acid) (dibasic sodium phosphate) (sodium chloride) (purified water)]

Note: Azelastine is dispensed in a package consisting of two bottles of medication (for a total of 200 metered sprays) and one pump assembly 1.

Packaging and storage:

Store between 20 and 25 °C (68 and 77 °F) 1.

Protect from freezing 1.

Stability:

The expiration date on the bottles applies to the unopened bottles 1.

Once the pump assembly has been inserted into the first bottle of the dispensing package, the pump assembly (and any unused portion of either bottle) should be discarded after 3 months, but not to exceed the original expiration date 1.

Auxiliary labeling:

· Avoid spraying in eyes 1.

· For the nose.

References

1 Astelin package insert (Wallace Laboratories¾US), Rev 10/96, Rec 1/27/97.

2 Product Information: AstelinÒ, azelastine. Wallace Laboratories, Cranbury, NJ. (PI Revised 08/2000) PI Reviewed 01/2001