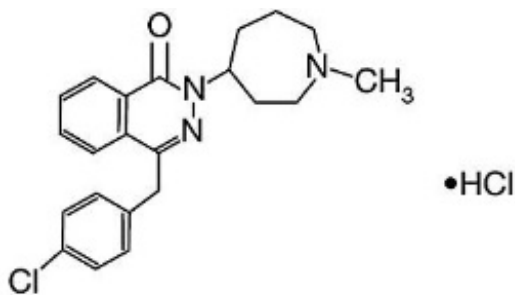


AZELASTINE HYDROCHLORIDE OPHTHALMIC SOLUTION 0.05% - azelastine hydrochloride ophthalmic solution 0.05% solution/ drops
Alembic Pharmaceuticals Inc.

Azelastine Hydrochloride Ophthalmic Solution 0.05%

DESCRIPTION

Azelastine Hydrochloride Ophthalmic Solution 0.05% is a sterile ophthalmic solution containing azelastine hydrochloride, a relatively selective H₁-receptor antagonist for topical administration to the eyes. Azelastine hydrochloride is a white crystalline powder with a molecular weight of 418.37. Azelastine hydrochloride is sparingly soluble in water, methanol and propylene glycol, and slightly soluble in ethanol, octanol, and glycerine. Azelastine hydrochloride is a racemic mixture with a melting point of 225°C. The chemical name for azelastine hydrochloride is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride and is represented by the following chemical structure:



Structural formula: C₂₂H₂₄ClN₃O•HCl

Each mL of Azelastine Hydrochloride Ophthalmic Solution 0.05% contains: **Active:** 0.5 mg azelastine hydrochloride, equivalent to 0.457 mg of azelastine base; **Preservative:** 0.125 mg benzalkonium chloride; **Inactives:** disodium edetate dihydrate, hypromellose, sorbitol solution, sodium hydroxide and water for injection. It has a pH of approximately 5.0 to 6.5 and an osmolarity of approximately 271 to 312 mOsmol/L.

CLINICAL PHARMACOLOGY

Azelastine Hydrochloride is a relatively selective histamine H₁ antagonist and an inhibitor of the release of histamine and other mediators from cells (e.g. mast cells) involved in the allergic response. Based on *in-vitro* studies using human cell lines, inhibition of other mediators involved in allergic reactions (e.g. leukotrienes and PAF) has been demonstrated with azelastine hydrochloride. Decreased chemotaxis and activation of eosinophils has also been demonstrated.

Pharmacokinetics and Metabolism:

Absorption of azelastine following ocular administration was relatively low. A study in symptomatic patients receiving one drop of Azelastine Hydrochloride Ophthalmic Solution 0.05% in each eye two to four times a day (0.06 to 0.12 mg azelastine hydrochloride) demonstrated plasma concentrations of

azelastine hydrochloride to generally be between 0.02 and 0.25 ng/mL after 56 days of treatment. Three of nineteen patients had quantifiable amounts of N-desmethylazelastine that ranged from 0.25–0.87 ng/mL at Day 56.

Based on intravenous and oral administration, the elimination half-life, steady-state volume of distribution and plasma clearance were 22 hours, 14.5 L/kg and 0.5 L/h/kg, respectively. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was excreted in the feces with less than 10% as unchanged azelastine. Azelastine hydrochloride is oxidatively metabolized to the principal metabolite, N-desmethylazelastine, by the cytochrome P450 enzyme system. *In-vitro* studies in human plasma indicate that the plasma protein binding of azelastine and N-desmethylazelastine are approximately 88% and 97%, respectively.

Clinical Trials:

In a conjunctival antigen challenge study, Azelastine Hydrochloride Ophthalmic Solution 0.05% was more effective than its vehicle in preventing itching associated with allergic conjunctivitis. Azelastine Hydrochloride Ophthalmic Solution 0.05% had a rapid (within 3 minutes) onset of effect and a duration of effect of approximately 8 hours for the prevention of itching.

In environmental studies, adult and pediatric patients with seasonal allergic conjunctivitis were treated with Azelastine Hydrochloride Ophthalmic Solution 0.05% for two to eight weeks. In these studies, Azelastine Hydrochloride Ophthalmic Solution 0.05% was more effective than its vehicle in relieving itching associated with allergic conjunctivitis.

INDICATIONS & USAGE

Azelastine Hydrochloride Ophthalmic Solution 0.05% is indicated for the treatment of itching of the eye associated with allergic conjunctivitis.

CONTRAINDICATIONS

Azelastine Hydrochloride Ophthalmic Solution 0.05% is contraindicated in persons with known or suspected hypersensitivity to any of its components.

WARNINGS

Azelastine Hydrochloride Ophthalmic Solution 0.05% is for ocular use only and not for injection or oral use.

PRECAUTIONS

INFORMATION FOR PATIENTS

To prevent contaminating the dropper tip and solution, care should be taken not to touch any surface, the eyelids, or surrounding areas with the dropper tip of the bottle or single-use container. Keep bottle tightly closed when not in use. Discard single-use container immediately after use. This product is sterile when packaged.

Patients should be advised not to wear a contact lens if their eye is red. Azelastine Hydrochloride Ophthalmic Solution 0.05% should not be used to treat contact lens related irritation. The preservative in Azelastine Hydrochloride Ophthalmic Solution 0.05%, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and **whose eyes are not red**, should be instructed to wait at least ten minutes after instilling Azelastine Hydrochloride Ophthalmic Solution 0.05% before they insert their contact lenses.

CARCINOGENESIS & MUTAGENESIS & IMPAIRMENT OF FERTILITY

Azelastine hydrochloride administered orally for 24 months was not carcinogenic in rats and mice at doses up to 30 mg/kg/day and 25 mg/kg/day, respectively. Based on a 30 µL drop size, these doses were approximately 25,000 and 21,000 times higher than the maximum recommended ocular human use level of 0.001 mg/kg/day for a 50 kg adult.

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 of up to 25,000 times the maximum recommended ocular human use level. At 68.6 mg/kg/day (57,000 times the maximum recommended ocular human use level), the duration of the estrous cycle was prolonged and copulatory activity and the number of pregnancies were decreased. The numbers of corpora lutea and implantations were decreased; however, the implantation ratio was not affected.

PREGNANCY

Teratogenic Effects: Pregnancy Category C. Azelastine hydrochloride has been shown to be embryotoxic, fetotoxic, and teratogenic (external and skeletal abnormalities) in mice at an oral dose of 68.6 mg/kg/day (57,000 times the recommended ocular human use level). At an oral dose of 30 mg/kg/day (25,000 times the recommended ocular human use level), delayed ossification (undeveloped metacarpus) and the incidence of 14th rib were increased in rats. At 68.6 mg/kg/day (57,000 times the maximum recommended ocular human use level) azelastine hydrochloride caused resorption and fetotoxic effects in rats. The relevance to humans of these skeletal findings noted at only high drug exposure levels is unknown.

There are no adequate and well-controlled studies in pregnant women. Azelastine Hydrochloride Ophthalmic Solution 0.05% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 Azelastine Hydrochloride Ophthalmic Solution 0.05% is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 3 have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

ADVERSE REACTIONS

In controlled multiple-dose studies where patients were treated for up to 56 days, the most frequently reported adverse reactions were transient eye burning/stinging (approximately 30%), headaches (approximately 15%) and bitter taste (approximately 10%). The occurrence of these events was generally mild.

The following events were reported in 1–10% of patients: asthma, conjunctivitis, dyspnea, eye pain, fatigue, influenza-like symptoms, pharyngitis, pruritus, rhinitis and temporary blurring.

Some of these events were similar to the underlying disease being studied.

DOSAGE & ADMINISTRATION

The recommended dose is one drop instilled into each affected eye twice a day.

HOW SUPPLIED

Azelastine Hydrochloride Ophthalmic Solution 0.05% is supplied as follows:

Azelastine Hydrochloride Ophthalmic Solution 0.05% 6 mL (NDC#62332-506-06) solution in a 10 mL LDPE container with LDPE nozzle and a white HDPE screw cap.

Storage

Azelastine Hydrochloride Ophthalmic Solution 0.05% : Store UPRIGHT between 2° and 25°C (36° and 77°F).

Rx only

Manufactured for:

Alembic Pharmaceutical, Inc.

750 Route 202, Bridgewater, NJ 08807

USA

Made in India



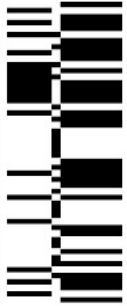
Manufactured by:

Gland Pharma Limited,

Hyderabad-500 043, India (IND)

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Azelastine Hydrochloride Ophthalmic Solution 0.05%- Bottle Label

<p>Rx only 6 mL</p> <p>Each mL contains: azelastine hydrochloride 0.5 mg</p> <p>STORAGE: STORE UPRIGHT between 2° and 25°C (36° and 77°F).</p> <p>Usual Dosage: 1 drop per affected eye(s) twice daily. See package insert for full prescribing information.</p>	<p>NDC 62332-506-06</p> <p>Azelastine Hydrochloride Ophthalmic Solution 0.05%</p> <p>FOR USE IN THE EYES ONLY</p>  	<p>Manufactured for: Alembic Pharmaceuticals, Inc. 750 Route 202, Bridgewater, NJ 08807 USA</p> <p>Made in India.</p> <p>LAB-020313-00 02/2019</p> <p>M.L.No. 103/AP/RR/97/F/R</p>  <p>(01)0 0362332 506 06 4</p>	<p>LOT:</p> <p>EXP:</p>
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Azelastine Hydrochloride Ophthalmic Solution 0.05%- Carton Label



Revised 03/2019

AZELASTINE HYDROCHLORIDE OPHTHALMIC SOLUTION 0.05%

azelastine hydrochloride ophthalmic solution 0.05% solution/ drops

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:62332-506
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AZELASTINE HYDROCHLORIDE (UNII: 0L591QR10I) (AZELASTINE - UNII:ZQI909440X)	AZELASTINE HYDROCHLORIDE	0.5 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
SORBITOL (UNII: 506T60A25R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0K00R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:62332-506-06	1 in 1 CARTON	03/20/2019	
1		6 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA209620	03/20/2019	

Labeler - Alembic Pharmaceuticals Inc. (079288842)**Establishment**

Name	Address	ID/FEI	Business Operations
Gland Pharma Limited		918601238	MANUFACTURE(62332-506)

Revised: 3/2019

Alembic Pharmaceuticals Inc.