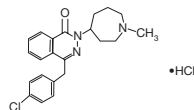


OPTIVAR®

(azelastine hydrochloride ophthalmic solution), 0.05%

DESCRIPTION

OPTIVAR® (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-(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride and is represented by the following chemical structure:



Empirical chemical structure: C₂₂H₂₄ClN₃O•HCl

Each mL of OPTIVAR® 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 osmolality of approximately 271 to 312 mOsmol/L.

Up to \$25 off OPTIVAR!

MedPointe Pharmaceuticals will reimburse you the out-of-pocket cost for your OPTIVAR prescription up to \$25. To receive your refund, mail this certificate, along with all of the required information, to the address indicated on reverse. Include your OPTIVAR prescription label and the cash register receipt for your OPTIVAR prescription. Refund will be issued only to the patient or to the parent or guardian of the patient submitting this form. This form may not be reproduced. Limited to one refund per prescription.

Not responsible for lost, damaged, or misdirected mail.

Expiration date: March 31, 2006.

Void where prohibited by law for prescriptions reimbursed under Medicare, Medicaid, or other government programs and in states that prohibit patient rebates if a third party pays any of the prescription price. Subject to all applicable federal, state, and local laws. Applicant represents that the amount to be refunded has not been reimbursed by any third-party insurance and that it will comply with the requirements of this refund offer and its health plan, and MedPointe Pharmaceuticals relies on this representation.

medPointe
pharmaceuticals
medPointe Healthcare Inc.
Somerset, New Jersey 08873

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December 2004

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 OPTIVAR® 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, OPTIVAR® was more effective than its vehicle in preventing itching associated with allergic conjunctivitis. OPTIVAR® 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 OPTIVAR® for two to eight weeks. In these studies, OPTIVAR® was more effective than its vehicle in relieving itching associated with allergic conjunctivitis.

INDICATIONS AND USAGE

OPTIVAR® is indicated for the treatment of itching of the eye associated with allergic conjunctivitis.

CONTRAINDICATIONS

OPTIVAR® is contraindicated in persons with known or suspected hypersensitivity to any of its components.

WARNINGS

OPTIVAR® 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. Keep bottle tightly closed when not in use. This product is sterile when packaged.

Patients should be advised not to wear a contact lens if their eye is red. OPTIVAR® should not be used to treat contact lens related irritation. The preservative in OPTIVAR®, 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 OPTIVAR® 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 rec-

ommended 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. OPTIVAR® 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 OPTIVAR® 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 AND ADMINISTRATION

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

HOW SUPPLIED

OPTIVAR® (azelastine hydrochloride ophthalmic solution), 0.05% is supplied as follows: 6 mL (NDC# 0037-7025-60) solution in a translucent 10 mL HDPE container with a LDPE dropper tip, and a white HDPE screw cap.

Storage

Store UPRIGHT between 2° and 25°C (36° and 77°F)

Rx only

U.S. Patent 5,164,194

Manufactured by: Vetter Pharma Fertigung GmbH & Co. KG, Germany

Distributed by:

medPointe
pharmaceuticals
medPointe Healthcare Inc.
Somerset, New Jersey 08873

Made in Germany

Issued July 2003 AN0143-05 56199040

Real-Eyes Relief™ with OPTIVAR



If you suffer from itchy allergy eyes:

- Complete the allergy eye checklist
- Discover if OPTIVAR is right for you
- Save up to \$25 on your OPTIVAR prescription

OPTIVAR®
azelastine hydrochloride
ophthalmic solution, 0.05%
Real-Eyes Relief™



WHAT'S CAUSING YOUR ALLERGY EYES?

When allergens such as pollen, dust, and pet dander get into your eye, they trigger a reaction called allergic conjunctivitis (also known as allergy eyes). It usually starts with bothersome or intense itching. Other symptoms include: redness, burning, tearing, puffy/swollen eyelids, and a white, mucus-like discharge.

Depending on your allergies, symptoms may strike during certain seasons or throughout the year. If you're allergic to specific grass, tree, or other pollens (eg, ragweed), allergy eyes may hit you in the fall or spring. If you're allergic to dust, mold, or other "indoor" allergens, you could suffer all year long.

An important first step to relief is talking to your doctor about your allergy eye symptoms.

ALLERGY EYE CHECKLIST

Complete the checklist and share the results with your healthcare provider.

Do you experience any of these symptoms?

Symptom	Mild	Moderate	Severe
Itching			
Redness			
Burning			
Tearing			
Puffy/swollen eyelids			
White, mucus-like discharge			

Do you experience these symptoms?

(check all that apply)

<input type="checkbox"/> IN THE SPRING
<input type="checkbox"/> IN THE SUMMER
<input type="checkbox"/> IN THE FALL
<input type="checkbox"/> IN THE WINTER
<input type="checkbox"/> ALL YEAR LONG

Have you ever used:

(check all that apply)

	Past	Present
Optivar®	<input type="radio"/>	<input type="radio"/>
Elestat™	<input type="radio"/>	<input type="radio"/>
Claritin®	<input type="radio"/>	<input type="radio"/>
Clarinex®	<input type="radio"/>	<input type="radio"/>
Allegra®	<input type="radio"/>	<input type="radio"/>
Zyrtec®	<input type="radio"/>	<input type="radio"/>
Astelin®	<input type="radio"/>	<input type="radio"/>
Patanol®	<input type="radio"/>	<input type="radio"/>
Zaditor™	<input type="radio"/>	<input type="radio"/>
Visine®	<input type="radio"/>	<input type="radio"/>
Other _____	<input type="radio"/>	<input type="radio"/>

Elestat (epinastine HCl ophthalmic solution) 0.05% is a trademark of Allergan, Inc. Claritin (loratadine) and Clarinex (desloratadine) are registered trademarks of Schering Corporation.

Allegra (fexofenadine HCl) is a registered trademark of Aventis Pharmaceuticals Inc.

Zyrtec (cetirizine HCl) and Visine (tetrahydrozoline HCl) are registered trademarks of Pfizer Inc.

Patanol (olopatadine hydrochloride ophthalmic solution) is a registered trademark of Alcon Laboratories, Inc.

Zaditor (ketotifen fumarate ophthalmic solution, 0.025%) is a trademark of Novartis Ophthalmic.

ASK YOUR DOCTOR IF OPTIVAR IS RIGHT FOR YOU.

Prescription OPTIVAR eye drops give fast, effective itch relief from allergy eyes.

- Relieves itch within 3 minutes and lasts 8-10 hours
- Proven to be effective and well tolerated
- Contains the soothing lubricant, HPMC

In controlled clinical studies some patients experienced brief eye burning/stinging, headache, and bitter taste. Less than 1% of patients stopped using OPTIVAR because of these effects. OPTIVAR should not be used if you are sensitive to any of the medication's components.

ALLERGY EYE TIPS

- Take prescription medications as directed
- Avoid rubbing your eyes
- Minimize exposure to what's causing your allergies; for example, stay inside on heavy pollen days
- Apply a cool compress to your eyes for temporary relief
- Avoid overuse of over-the-counter medications

Please see full product information on reverse side.

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For more information,
please visit

www.OPTIVAR.com

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ophthalmic solution, 0.05%
Real-Eyes Relief™



Get up to **\$25** off your prescription for **OPTIVAR**

(please print)

Name

Address

City State ZIP Code

Telephone - -

E-mail Address

We will notify you by email of the status of your rebate submission.

Pharmacy

City State ZIP Code

Please send me information about OPTIVAR.

\$_____ Out-of-pocket cost of my prescription for OPTIVAR

I have filled my prescription for OPTIVAR as directed by my doctor, and I am enclosing the OPTIVAR prescription label and the cash register receipt for my OPTIVAR prescription.

Offer expires March 31, 2006.

Note to patients: When fully completed, this certificate entitles you to a refund of your out-of-pocket cost for OPTIVAR up to \$25. Please attach the prescription label and cash register receipt for OPTIVAR and this completed form. MedPointe Pharmaceuticals relies on this representation. To track the status of your rebate, visit www.rebateshq.com or by calling 1-888-641-4114.

Please see reverse for important information.

For a prompt refund, mail to: OPTIVAR
Dept. 04-79228, PO Box 028542
Miami, FL 33102-8542