CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-688 / S-003

Trade Name: Patanol

Generic Name: olopatadine

Sponsor: Alcon Laboratories

Approval Date: May 29, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-688 / S-003

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Labeling	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-688 / S-003

APPROVAL LETTER

NDA 20-688/S-003

Alcon Laboratories
Attention: Susan H. Caballa
Associate Director, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134

MAY 29 1998

Dear Ms. Caballa:

Please refer to your supplemental new drug application dated March 2, 1998, received March 25, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PATANOL™ (olopatadine hydrochloride ophthalmic solution) 0.1%. Please also refer to our letter dated June 26, 1997.

We acknowledge receipt of your submissions dated March 19 and 20, 1998.

The supplemental application provides for revised draft labeling of the package insert.

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated March 2, 1998, with the revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter. As discussed by telephone on April 1, 1998, between Cheryl Anderson of Alcon and Joanne Holmes of this Division, the revisions are as follows:

1. The [redacted] will be added to the Description section.

2. The second sentence of the Carcinogenesis subsection of the Precautions sections will begin "[redacted]" rather than "Based on a 40 l drop size..."

These revisions are terms of the supplemental NDA approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 20-688/S-003. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Joanne M. Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

MAC 5/29/98
Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
NDA 20-688
HFD-550/Div. files
HFD-550/MO/Bull (with labeling)
HFD-550/Dep Dir/Chambers (with labeling) 4/1/98
HFD-550/Clin Rev/Holmes (with labeling)
HFD-550/Proj Mgr/Gorski (with labeling) 4/2/98
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)

Drafted by: jh/March 31, 1998/20688s3.ap
Initialed by:
final:

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

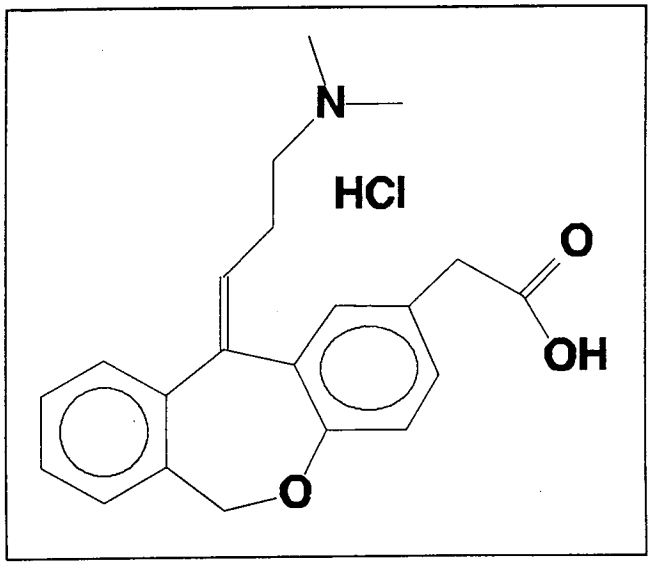
20-688 / S-003

LABELING

PATANOL™ (olopatadine hydrochloride ophthalmic solution) 0.1%

DESCRIPTION

PATANOL™ (olopatadine hydrochloride ophthalmic solution) 0.1% is a sterile ophthalmic solution containing olopatadine, a relatively selective H_1-receptor antagonist and inhibitor of histamine release from the mast cell for topical administration to the eyes. Olopatadine hydrochloride is a white, crystalline, water-soluble powder with a molecular weight of 373.88. The chemical structure is presented below:



Chemical Name: 11-[(Z)-3(Dimethylamino)propylidene]-6-11-dihydrodibenz[b,e] oxepin-2-acetic acid hydrochloride

Each mL of PATANOL contains: **Active:** 1.11 mg olopatadine hydrochloride equivalent to 1 mg olopatadine. **Preservative:** benzalkonium chloride 0.01%. **Inactives:** dibasic sodium phosphate; sodium chloride; hydrochloric acid/sodium hydroxide (adjust pH); and purified water.

CLINICAL PHARMACOLOGY

Olopatadine is an inhibitor of the release of histamine from the mast cell and a relatively selective histamine H1-antagonist that inhibits the *in vivo* and *in vitro* type 1 immediate hypersensitivity reaction. Olopatadine is devoid of effects on alpha-adrenergic, dopamine, muscarinic type 1 and 2, and serotonin receptors.

Following topical ocular administration in man, olopatadine was shown to have low systemic exposure. Two studies in normal volunteers (totalling 24 subjects) dosed bilaterally with olopatadine 0.15% ophthalmic solution once every 12 hours for 2 weeks demonstrated plasma concentrations to be generally below the quantitation limit of the assay (<0.5 ng/mL). Samples in which olopatadine was quantifiable were typically found within 2 hours of dosing and ranged from 0.5 to 1.3 ng/mL. The half-life in plasma was approximately 3 hours, and elimination was predominantly through renal excretion. Approximately 60-70% of the dose was recovered in the urine as parent drug. Two metabolites, the mono-desmethyl and the N-oxide, were detected at low concentrations in the urine.

Results from conjunctival antigen challenge studies demonstrated that PATANOL, when subjects were challenged with antigen both initially and up to 8 hours after dosing, was significantly more effective than its vehicle in preventing ocular itching associated with allergic conjunctivitis.

INDICATIONS AND USAGE

PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1% is indicated for the temporary prevention of itching of the eye due to allergic conjunctivitis.

CONTRAINDICATIONS

PATANOL is contraindicated in persons with a known hypersensitivity to olopatadine hydrochloride or any components of PATANOL.

WARNINGS

PATANOL is for topical 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 the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

Patients should be instructed not to wear a contact lens if their eye is red. PATANOL should not be used to treat contact lens related irritation. The preservative in PATANOL, 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 PATANOL before they insert their contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 40 l drop size, these doses were 78,125 and 31,250 times higher than the maximum recommended ocular human dose (MROHD). No mutagenic potential was observed when olopatadine was tested in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* mammalian chromosome aberration assay or an *in vivo* mouse micronucleus test. Olopatadine administered to male and female rats at oral doses of 62,500 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of 7,800 times the maximum recommended ocular human use level

Pregnancy: Pregnancy Category C. Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 93,750 times the MROHD and rabbits treated at 400 mg/kg/day, or 62,500 times the MROHD, during organogenesis showed a decrease in live fetuses. There are, however, no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

Nursing Mothers: Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PATANOL is administered to a nursing mother.

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

ADVERSE REACTIONS

Headaches were reported at an incidence of 7%. The following adverse experiences were reported in less than 5% of patients: Asthenia, burning or stinging, cold syndrome, dry eye, foreign body sensation, hyperemia, keratitis, lid edema, pharyngitis, pruritus, rhinitis, sinusitis, and taste perversion. Some of these events were similar to the underlying disease being studied.

DOSAGE AND ADMINISTRATION

The recommended dose is one to two drops in each affected eye two times per day at an interval of 6 to 8 hours.

HOW SUPPLIED

PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1% is supplied as follows: 5, 10 and 15 mL in plastic DROP-TAINER® dispensers.

5 mL:	NDC 0065-0271-05
10 mL:	NDC 0065-0271-10
15 mL:	NDC 0065-0271-15

Storage:
Store at 39° F to 86° F (4° C to 30° C)

Rx only.

Alcon Ophthalmic Logo
Alcon Laboratories, Inc.
Fort Worth, Texas 76134 USA

February 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-688 / S-003

MEDICAL REVIEW(S)

Clinical Review of NDA 20-688
Labeling Supplement

APR 1 1998

NDA 20-688/S-003

Submission Dates:	3/2/98, 3/19/98, 3/20/98
Receipt Dates:	3/25/98, 3/24/98, 3/25/98
Review Date:	4/1/98

Applicant:

Alcon Laboratories
6201 South Freeway
Fort Worth, TX 76134-2099

Applicant's Representative:

Susan H. Caballa
Associate Director, Regulatory Affairs
(817) 568-6296

Drug:

PATANOL™ (olopatadine hydrochloride ophthalmic solution) 0.1%

Pharmacologic Category:

Selective H1-receptor agonist and mast cell stabilizer

Submitted:

Revised draft labeling of the package insert to make it more consistent with he package insert of Emadine (NDA 20-706).

Following is the labeling submitted by the company. Reviewer recommended deletions are noted by ~~strikeout~~ and additions by shading within the review.

PATANOL™ (olopatadine hydrochloride ophthalmic solution) 0.1%

DESCRIPTION

PATANOL™ (olopatadine hydrochloride ophthalmic solution) 0.1% is a sterile ophthalmic solution containing olopatadine, a relatively selective H_1-receptor antagonist and inhibitor of histamine release from the mast cell for topical administration to the eyes. Olopatadine hydrochloride is a white, crystalline, water-soluble powder with a molecular weight of 373.88. The chemical structure is presented below:

[Structural Formula]

Chemical Name: 11-[(Z)-3-(Dimethylamino)propylidene]-6-11-dihydrodibenz[b,e] oxepin-2-acetic acid hydrochloride

Each mL of PATANOL contains: **Active:** 1.11 mg olopatadine hydrochloride equivalent to 1 mg olopatadine. **Preservative:** benzalkonium chloride 0.01%. **Inactives:** dibasic sodium phosphate; sodium chloride; hydrochloric acid/sodium hydroxide (adjust pH); and purified water.

Reviewer's comments: *The established name, [(olopatadine hydrochloride ophthalmic solution) 0.1%] after the trademark has been deleted in several places, so that it appears only in the Description and Indications sections. Acceptable.*
It was requested in the June 26, 1997 Acknowledge and Retain letter that the [redacted] be added to the Description section. This was not done.

CLINICAL PHARMACOLOGY

Olopatadine is an inhibitor of the release of histamine from the mast cell and a relatively selective histamine H_1-antagonist that inhibits the *in vivo* and *in vitro* type 1 immediate hypersensitivity reaction. Olopatadine is devoid of effects on alpha-adrenergic, dopamine, muscarinic type 1 and 2, and serotonin receptors.

Following topical ocular administration in man, olopatadine was shown to have low systemic exposure. Two studies in normal volunteers (totaling 24 subjects) dosed bilaterally with olopatadine 0.15% ophthalmic solution once every 12 hours for 2 weeks demonstrated plasma concentrations to be generally below the quantitation limit of the assay (<0.5 ng/mL). Samples in which olopatadine was quantifiable were typically found within 2 hours of dosing and ranged from 0.5 to 1.3 ng/mL. The half-life in plasma was approximately 3 hours, and elimination was predominantly through renal excretion. Approximately 60-70% of the dose was recovered in the urine as parent drug. Two metabolites, the mono-desmethyl and the N-oxide, were detected at low concentrations in the urine.

Results from conjunctival antigen challenge studies demonstrated that PATANOL, when challenged with antigen both initially and up to 8 hours after dosing, was significantly more effective than its vehicle in preventing ocular itching associated with allergic conjunctivitis.

INDICATIONS AND USAGE
PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1% is indicated for the temporary prevention of itching of the eye due to allergic conjunctivitis.

CONTRAINDICATIONS
PATANOL is contraindicated in persons with a known hypersensitivity to olopatadine hydrochloride or any component of PATANOL.

Reviewer's comments: *The Contraindications section was revised so the wording would be consistent with that for Emadine. Acceptable.*

WARNINGS
PATANOL is for topical use only and not for injection or oral use.

Reviewer's comments: *The Warnings section was revised so the wording would be consistent with that for Emadine. This includes moving the statement on contact lens wear to Precautions. Acceptable.*

PRECAUTIONS
Information for Patients: To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

Patients should be instructed not to wear a contact lens if their eye is red. PATANOL should not be used to treat contact lens related irritation. The preservative in PATANOL, 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 PATANOL before they insert their contact lenses.

Reviewer's comments: *The Information for Patients subsection was revised so the wording on contact lens wear would be consistent with that for Emadine. Acceptable.*

Carcinogenesis, Mutagenesis, Impairment of Fertility: Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 40 µl drop size, these doses were 78,125 and 31,250 times higher than the maximum recommended ocular human dose (MROHD). No mutagenic potential was observed when olopatadine was tested in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* mammalian chromosome aberration assay or an *in vivo* mouse micronucleus test. Olopatadine administered to male and female rats at oral doses of 62,500 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of 7,800 times the maximum recommended ocular human use level.

Pregnancy: Pregnancy Category C. Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 93,750 times the MROHD and rabbits treated at 400 mg/kg/day, or 62,500 times the MROHD, during organogenesis showed a decrease in live fetuses. There are, however, no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

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

ADVERSE REACTIONS:

Headaches were reported at an incidence of 7%. The following adverse experiences were reported in less than 5% of patients: Asthenia, burning or stinging, cold syndrome, dry eye, foreign body sensation, hyperemia, keratitis, lid edema, pharyngitis, pruritus, rhinitis, sinusitis, and taste perversion. Some of these events were similar to the underlying disease being studied.

Reviewer's comments: *The Adverse Reactions section was revised to combine the ocular and nonocular experiences, since they were both at less than 5%. "Some of these events were similar to the underlying disease being studied" was added for consistency to Emadine. Acceptable.*

DOSAGE AND ADMINISTRATION

The recommended dose is one to two drops in each affected eye two times per day at an interval of 6 to 8 hours.

HOW SUPPLIED

PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1% is supplied as follows: 5, 10 and 15 mL in plastic DROP-TAINER® dispensers.

5 mL:	NDC 0065-0271-05
10 mL:	NDC 0065-0271-10
15 mL:	NDC 0065-0271-15

Storage

Store at 39°F to 86°F (4°C to 30°C)

Rx only.

Reviewer's comments: *The statement "Caution: Federal law prohibits dispensing without prescriptions" has been replaced with "Rx only." Acceptable.*

Alcon Ophthalmic Logo
Alcon Laboratories, Inc.
Fort Worth, Texas 76134 USA

~~February~~April 1998

Recommendations:

The revisions are acceptable. In a telephone conversation on April 1, 1998, Cheryl Anderson agreed that the following changes would be made:

1. The osmolality and pH will be added to the Description section.

2. In the Carcinogenesis subsection of Precautions, the second sentence will begin "Based on a 40 µl drop size...," rather than "Based on a 40 l drop size..."

An approval letter may be issued, requesting FPL with the revisions noted above.

Joanne M. Holmes

Wiley A. Chambers, M.D.

cc:
NDA 20-688
HFD-550 Div files
HFD-550/Dep Dir/Chambers
HFD-550/MO/Bull
HFD-550/Clin Rev/Holmes
HFD-550/Proj Mgr/Gorski
HF-2/MedWatch