CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-545

MEDICAL REVIEW

Deputy Division Director's Review of NDA 21-545

Amendment

Submission Dates:	December 17, 2004
Review Completed:	December 21, 2004
Established Name:	Olopatadine HCl ophthalmic solution 0.2%
Chemical Name:	11-[(Z)-3-(Dimethylamino) propylidene]-6-11-dihydrodibenz[b,e] oxepin-2-acetic acid, hydrochloride
Molecular Formula:	$C_{21}H_{23}NO_3 \bullet HCl$
Molecular Weight:	373.88
Sponsor:	Alcon, Inc. P.O. Box 62 Bosch 69 CH-6331 Hunenberg Switzerland Alcon Research, Ltd. 6201 S. Freeway Fort Worth, TX 76134-2099 (817) 551-4933
Pharmacologic Category:	Antihistamine and mast cell stabilizer
Proposed Indication:	Allergic conjunctivitis
Dosage Form:	Ophthalmic solution
Route of Administration:	Topical ocular
NDA Drug Classification:	3S
Related IND:	IND 60,991
Related NDA:	NDA 20-688 (Patanol)

Deputy Division Director's Review of NDA 21-545

Executive Summary of the Primary Clinical Review

I. Recommendations

A. Recommendation on Approvability

NDA 21-545 is recommended for approval of the treatment of ocular itching associated with allergic conjunctivitis.

B. Recommendation on Postmarketing Studies and/or Risk Management Steps

No postmarketing studies are recommended. No risk management steps are recommended.

II. Summary of Findings

A. Brief Overview of Clinical Program

Olopatadine hydrochloride ophthalmic solutions 0.1% and 0.2%, are relatively selective histamine-1 receptor inhibitors and mast cell stabilizers. They have been studied for their safety and efficacy —

See Previous Reviews. This submission contains no new clinical information.

B. Efficacy

Olopatadine hydrochloride ophthalmic solution 0.1% has demonstrated in adequate and well controlled studies that it is effective

The 0.2% concentration is effective in treating itching associated with allergic conjunctivitis when dosed once a day,

C. Safety

There is not new safety information in this amendment. Overall, there were no significant adverse events that warrant special monitoring; they were relatively few in number, mild, resolved without treatment, and rarely resulted in discontinuation of participation in a trial.

In sum, the clinical trials met the Division's safety recommendations for minimum number of exposures, duration, and patient monitoring. It is likely that the similarity of adverse events reported in trials for the two olopatadine concentrations is predictive of those anticipated in a post-marketing patient population using olopatadine 0.2%.

D. Dosing, Regimen, and Administration

It is recommended that one ——— drops of olopatadine 0.2% be administered once daily to the eye.

E. Drug-Drug Interactions

Drug-drug interactions were not studied because the drug was dosed alone. However, if patients follow the standard dropping procedure ———
——— there is no obvious reason to believe that interactions warranting serious concern would occur.

F. Special Populations

Both genders were approximately equally represented, but all studies included predominantly Caucasian patients.

Of the total number of pediatric subjects exposed to olopatadine 0.2%, 26 were between the ages of 3 and 5, and 38 were between 6 and 11 years of age; the pediatric and adult safety profiles were similar. There is no reason to believe that drug efficacy would differ as a function of age. Pregnant women were excluded from all studies, and the Sponsor has revealed no plans to address use in this population.

In summary, there is no reason to recommend a dose modification for special populations.

G. Chemistry/Manufacturing Controls

Review of the manufacturing and control information has been reviewed. The application has been recommended for approval. All Manufacturing facilities have been inspected and found to be in compliance with cGMP. An acceptable recommendation was listed from the Office of Compliance.

H. Pharmacology/Toxicology

Review of the nonclinical studies was completed. The application was recommended for approval. No additional nonclinical studies were recommended. There are no outstanding issues.

I. Conclusions

Olopatadine hydrochloride ophthalmic solutions 0.1% and 0.2% have demonstrated in adequate and well controlled studies that

The 0.2% concentration is effective in treating itching associated with allergic conjunctivitis when dosed once a day.

J. Recommendations

From a clinical perspective, NDA 21-545 is recommended for approval of the treatment of ocular itching associated with allergic conjunctivitis when dosed once a day.

K. Labeling

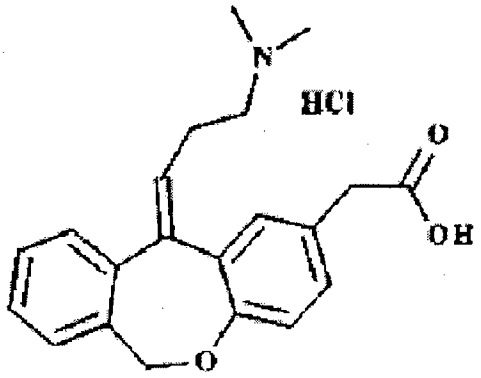
The following draft package insert was submitted for review. Reviewer recommended additions are identified by double underlining and reviewer recommended deletions are identified by single strikeout lines.

Olopatadine Hydrochloride Ophthalmic Solution, 0.2%

DESCRIPTION

Olopatadine Hydrochloride Ophthalmic Solution is a sterile ophthalmic solution containing olopatadine for topical administration to the eyes.

Olopatadine hydrochloride is a white, crystalline, water-soluble powder with a molecular weight of 373.88 and a molecular formula of $C_{21}H_{23}NO_3 \bullet HCl$. The chemical structure is presented below:



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_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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Wiley Chambers
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MEDICAL OFFICER

Medical Officer's Clinical Review of NDA 21-545

Amendment

Submission Dates:	November 5 & 19, 2004
Review Completed:	November 23, 2004
Proposed	—
Established Name:	Olopatadine HCl ophthalmic solution 0.2%
Chemical Name:	11-[(Z)-3-(Dimethylamino) propylidene]-6-11-dihydrodibenz[b,e] oxepin-2-acetic acid, hydrochloride
Molecular Formula:	$C_{21}H_{23}NO_3 \bullet HCl$
Molecular Weight:	373.88
Sponsor:	Alcon, Inc. P.O. Box 62 Bosch 69 CH-6331 Hunenberg Switzerland Alcon Research, Ltd. 6201 S. Freeway Fort Worth, TX 76134-2099 (817) 551-4933
Pharmacologic Category:	Antihistamine and mast cell stabilizer
Proposed Indication:	Allergic conjunctivitis
Dosage Form:	Ophthalmic solution
Route of Administration:	Topical ocular
NDA Drug Classification:	3S
Related IND:	IND 60,991
Related NDA:	NDA 20-688 (Patanol)

Executive Summary of the Primary Clinical Review

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective, NDA 21-545 is recommended for approval of —

If olopatadine hydrochloride is administered once a day, it is only effective for ocular itching —

B. Recommendation on Postmarketing Studies and/or Risk Management Steps

No postmarketing studies are recommended. No risk management steps are recommended.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Olopatadine hydrochloride ophthalmic solutions 0.1% and 0.2%, are relatively selective histamine-1 receptor inhibitors and mast cell stabilizers. They have been studied for their safety and efficacy in —

See Previous Reviews. This submission contains no new clinical information.

B. Efficacy

Olopatadine hydrochloride ophthalmic solution 0.1% has demonstrated in adequate and well controlled studies that —

The 0.2% concentration is effective in treating itching associated with allergic conjunctivitis when dosed once a day

C. Safety

There is not new safety information in this amendment. Overall, there were no significant adverse events that warrant special monitoring; events were relatively few in number, mild, resolved without treatment, and rarely resulted in discontinuation of participation in a trial.

In sum, the clinical trials met the Division's safety recommendations for minimum number of exposures, duration, and patient monitoring. It is likely that the similarity of adverse events reported in trials for the two olopatadine concentrations is predictive of those anticipated in a post-marketing patient population using olopatadine 0.2%.

D. Dosing, Regimen, and Administration

It is recommended that one —— drops of olopatadine 0.2% be administered —— daily to the eye.

E. Drug-Drug Interactions

Drug-drug interactions were not studied because the drug was dosed alone. However, if patients follow the standard dropping procedure ( ), there is no obvious reason to believe that interactions warranting serious concern would occur.

F. Special Populations

Both genders were approximately equally represented, but all studies included predominantly Caucasian patients.

Of the total number of pediatric subjects exposed to olopatadine 0.2%, 26 were between the ages of 3 and 5, and 38 were between 6 and 11 years of age; the pediatric and adult safety profiles were similar. There is no reason to believe that drug efficacy would differ as a function of age. Pregnant women were excluded from all studies, and the Sponsor has revealed no plans to address use in this population.

In summary, there is no reason to recommend a dose modification for special populations.

Clinical Review

I. Introduction and Background
The submitted drug product is [redacted] a histamine antagonist and mast cell stabilizer proposed for the [redacted] in patients over the age of 3 years old as a once-daily topical ocular drop.

The predominant forms of allergic conjunctivitis include perennial allergic conjunctivitis (typically year-round and caused by house dust or animal dander), and seasonal allergic conjunctivitis (typically appearing during pollen season). The pathogenesis common to both involves a local and systemic immunological hypersensitivity reaction; through multiple mechanisms, contact of the ocular surface with environmental (usually airborne) allergens leads to mast cell degranulation and release of chemical mediators such as histamine. This release sparks a cascade of molecular events that manifest clinically as the hallmark signs and symptoms of allergic conjunctivitis: itching, conjunctival hyperemia, tearing, eyelid edema, chemosis, and rhinitis. The clinical presentation may vary, depending on the weather (worse in warm, dry climate) and the patient's exposure to allergens.

Current therapeutic modalities attempt to improve the patient's quality of life by removing the offending allergen and/or modifying the inflammatory response. Initial management combines cold compresses, lubrication and an avoidance of allergens. If conservative therapy fails, the use of topical and oral medications is considered.

A. State of Armamentarium for Indication

There are several effective drug products used for allergic conjunctivitis, some available over the counter and others by prescription. Olopatadine 0.1%, the lower concentration of the submitted drug product with recommended twice-daily dosing, is a frequently prescribed drug product in this category. None of the currently approved drug products are approved for once-daily dosing with daylong duration of action.

Drug products that are used in the treatment of patients with allergic conjunctivitis or related symptoms, include antihistamine, mast cell inhibitors, vasoconstrictors, non-steroidal anti-inflammatories and steroidal anti-inflammatories.

B. Important Milestones in Product Development
See previous reviews.

C. Other Relevant Information
Olopatadine hydrochloride ophthalmic solution 0.2% is not currently marketed in any country. It has not been withdrawn from marketing in any country due to safety and efficacy concerns either.

D. Important Issues with Pharmacologically Related Agents

Orally administered drugs with anti-histamine effects, terfenadine and astemizole, were withdrawn from the market after post-marketing studies revealed that these drugs delayed cardiac repolarization. This is manifest as a prolongation of the QT interval on an electrocardiogram, and creates a potentially dangerous electrophysiological environment that permits the development of cardiac arrhythmias. These effects are dose related and have not been shown to occur with ophthalmologically administered products. The Sponsor conducted one study using the oral dosage form of the drug and demonstrated that olopatadine had no effect on QT interval when compared to placebo.

II. Significant Findings from Chemistry, Animal Pharmacology and Toxicology, and/or Microbiology

There were no significant findings from the Chemistry, Non-clinical Pharmacology or Toxicology reviews that are likely to affect the clinical outcome.

III. Human Pharmacokinetics and Pharmacodynamics

See Previous Reviews. There is no new information submitted that is likely to affect the safety or efficacy of this product.

IV. Description of Clinical Data and Sources

A. Sources of Clinical Data

This amendment consisted of one clinical volume.

B. Overview of Clinical Trials

See Previous Reviews. There is no new information submitted that is likely to affect the safety or efficacy of this product.

In the Safety Update, dated November 19, 2004, it was noted that no new safety or efficacy information has become available to the applicant.

C. Postmarketing Experience

Olopatadine 0.2% is not currently marketed in any country. However, olopatadine hydrochloride ophthalmic solution 0.1% is currently marketed in over 30 countries, including the U.S. and Canada (as Patanol) and the European Union (as Opatanol) for the treatment of the signs and symptoms of allergic conjunctivitis when dosed twice-daily.

The most commonly reported adverse events included ocular discomfort, ocular hyperemia, ocular pain, ocular edema, ocular irritation, lid edema, and blurred vision; non-ocular events included no drug effect, headache, and reaction aggravation.

D. Literature Review

The medical reviewer conducted a Pubmed electronic literature search to supplement the submitted review of the relevant literature.

V. Clinical Review Methods

A. Describe How Review was Conducted

All submitted studies were reviewed separately and subsequently assessed in aggregate.

B. Overview of Materials Consulted in Review

In addition to the originally submitted electronic and paper copies of NDA 21-545, IND 60,911 was also consulted, as well as the medical officer's review from NDA 20-688 (olopatadine ophthalmic solution) 0.1%, the Original Medical Officer's review of NDA 21-545, and the Medical Officer's review of amendments to NDA 21-545.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No special methods used.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

All trials were conducted under the review of approved Institutional Review Board committees. Investigators used an informed consent form that was appropriate for the respective trials.

E. Evaluation of Financial Disclosure

There is no evidence to suggest that the results of the studies were impacted by any financial payments.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The drug demonstrated efficacy in reducing ocular itching in patients with allergic conjunctivitis at onset and at 16 hours after dosing relative to placebo. C

B. General Approach to Review of the Efficacy of the Drug

See Previous Reviews. There is no new information submitted that is likely to affect the safety or efficacy of this product.

VII. Integrated Review of Safety

A. Brief Statement of Findings

Olopatadine 0.2% administered once daily is safe and well-tolerated in pediatric and adult subjects with seasonal allergic conjunctivitis, based on a review of adverse events and an assessment of ocular parameters. Adverse events in the overall treatment population were mostly non-serious and mild to moderate, generally resolved without treatment, and usually did not interrupt subject continuation in the studies.

B. Materials Utilized in the Review

The overall experience using olopatadine 0.2% ophthalmic solution was evaluated in 7 clinical trials. In addition, one clinical trial using an oral formulation of olopatadine contributed to the safety data set. The 4 CAC studies provided short-term data, the environmental and topical safety study provided long-term data, and the oral study provided oral systemic data.

C. Description of Patient Exposure

Two natural exposure and one safety study provided up to 12 weeks exposure. The rest of the studies provided only a single administration.

D. Safety Findings from Clinical Studies

Overall, ocular adverse events were similar regardless of contact lens use, iris color, race/ethnicity or gender. The findings in the studies presented in this review are not markedly changed from the first review.

E. Literature Review for Safety

No additional relevant information.

F. Postmarketing Surveillance

Discussed in a previous section.

G. Safety Update

No significant new information reported as of November 19, 2004.

H. Drug Withdrawal, Abuse, and Overdose Experience

No reports of overdose, drug abuse, or withdrawal/rebound phenomena were submitted. There is no foreseen potential for abuse and dependence.

I. Adequacy of Safety Testing

Overall, the safety data generated by the clinical studies was adequate. The drug was dosed in over 300 patients for at least 6 weeks—the length of a typical allergy season. It included an adequate number of children and an even representation of most demographic groups, with the exception of Caucasians representing 76% of subjects with long term exposure to the study drug. Ocular and systemic testing parameters were appropriately chosen and relevant.

J. Labeling Safety Issues and Postmarketing Commitments

Safety signals that need to be highlighted in the drug's labeling are consistent with those found in the olopatadine 0.1% label.

VIII. Dosing, Regimen, and Administration Issues

Reviewed in previous section.

IX. Use in Special Populations

A. Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity.

Based on a review of adverse events by age in the subjects with long term exposure to the drug, there are no apparent trends or safety concerns. Similarly, an analysis of adverse events by gender, race/ethnicity, and eye color revealed no notable, clinically relevant differences.

B. Pediatric Program (e.g., pediatric waivers, deferrals, written requests)

The Sponsor requested a waiver regarding the use of Olopatadine HCl Ophthalmic Solution (0.2% as base) in pediatric patients under the age of 3 years. The division does not consider allergic conjunctivitis to exist in a substantial population below the age of 3 years and therefore recommends granting the waiver.

C. Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

The drug product has negligible systemic absorption and therefore information in patients with renal or hepatic compromise is not necessary.

X. Conclusions, Recommendations, and Labeling

A. Conclusions

Olopatadine hydrochloride ophthalmic solutions 0.1% and 0.2% have demonstrated in adequate and well controlled studies [redacted]. The 0.2% concentration is effective in treating itching associated with allergic conjunctivitis when dosed once a day, [redacted]

B. Recommendations

From a clinical perspective, NDA 21-545 is recommended for approval of the [redacted]

Alternatively, NDA 21-545 could be recommended for approval of once-daily dosing in the [redacted]

C. Labeling

The following draft package insert was submitted for review. Reviewer recommended additions are identified by double underlining and reviewer recommended deletions are identified by single strikeout lines.

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Wiley Chambers
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William Boyd
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MEDICAL OFFICER

Medical Officer's Clinical Review of NDA 21-545

Amendment

Submission Date:	December 11, 2003
Review Completed:	June 2, 2004
Proposed Trademark:	———
Established Name:	Olopatadine HCl ophthalmic solution 0.2%
Chemical Name:	11-[(Z)-3-(Dimethylamino) propylidene]-6-11-dihydrodibenz[b,e] oxepin-2-acetic acid, hydrochloride
Molecular Formula:	$C_{21}H_{23}NO_3 \bullet HCl$
Molecular Weight:	373.88
Sponsor:	Alcon, Inc. P.O. Box 62 Bosch 69 CH-6331 Hunenberg Switzerland Alcon Research, Ltd. 6201 S. Freeway Fort Worth, TX 76134-2099 (817) 551-4933
Pharmacologic Category:	Antihistamine and mast cell stabilizer
Proposed Indication:	Allergic conjunctivitis
Dosage Form:	Ophthalmic solution
Route of Administration:	Topical ocular
NDA Drug Classification:	3S
Related IND:	IND 60,991
Related NDA:	NDA 20-688 (Patanol)

Executive Summary of the Primary Clinical Review

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective, NDA 21-545 is not recommended for approval of the

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NDA 21-545 is recommended for approval of once-daily dosing in the — of ocular itching due to allergic conjunctivitis.

A labeling review is deferred until data is submitted to support the proposed indication.

B. Recommendation on Postmarketing Studies and/or Risk Management Steps

No postmarketing studies are recommended. No risk management steps are recommended.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The study drug, olopatadine hydrochloride ophthalmic solution 0.2%, is a relatively selective histamine-1 receptor inhibitor and mast cell stabilizer. It was studied for its safety and efficacy in — , in patients with a confirmed history of the condition when administered once daily to the eye.

Two additional clinical studies have been submitted. This is in addition to the original 6 trials which involved a total 493 patients who were exposed to topical dosing of the drug product, 300 of whom were exposed daily for at least 6 weeks.

B. Efficacy

Of the 6 primary studies designed to test the drug's efficacy, 4 were conjunctival allergen challenge (CAC) studies and two were natural exposure studies.

In the 4 CAC studies, investigators instilled one drop of the drug or vehicle into the eye of patients with confirmed allergic conjunctivitis. These patients were then challenged with an inciting antigen during at least two separate visits: the first to test the drug effect at its onset of action (27 minutes), and the second to test its effect after a typical day (16 hours after instillation).

Overall, the drug demonstrated relative efficacy in reducing itching symptoms at both time points. This effect was moderate in magnitude, less evident at 16 hours, and relatively uniform within each study; however, the effect was variable between studies. One natural exposure study did not demonstrate drug efficacy for any endpoint; the other demonstrated relief of itching — during the day but did not establish effectiveness throughout the day.

None of the studies demonstrated a clinically meaningful reduction of any evaluated signs and symptoms other than itching, and there were no studies directly comparing the drug to other treatments.

C. Safety

The 4 CAC studies provide limited supportive safety data because subjects were exposed to no more than 3 drops of the drug, each separated by multiple days. The natural exposure study randomized several hundred patients to 12 weeks of daily drug exposure and included 64 children ranging from 3 to 11 years of age.

Safety data from these 2 relatively long-term studies are generally amenable to extrapolation.

Overall, there were no significant adverse events that warrant special monitoring; they were relatively few in number, mild, resolved without treatment, and rarely resulted in discontinuation of participation in a trial.

One safety study tested a 5 mg oral form of the drug versus placebo in 102 patients. As expected, this dose resulted in higher plasma concentrations than those expected with topical administration. There was no evidence of drug effect on cardiac repolarization and no clinically relevant treatment-related changes in laboratory parameters or vital signs relative to placebo.

In sum, the clinical trials met the Division's safety recommendations for minimum number of exposures, duration, and patient monitoring. It is likely that the similarity of adverse events reported in trials for the two olopatadine concentrations is predictive of those anticipated in a post-marketing patient population using olopatadine 0.2%.

D. Dosing, Regimen, and Administration

In the clinical studies evaluating the topical formulation, one drop of olopatadine 0.2% was administered once daily to the eye. This concentration and dosing regimen was based on several factors, including data from a pre-clinical dose-response study, the efficacy and safety demonstrated for the marketed product (olopatadine 0.1%) when instilled BID, and solubility considerations.

E. Drug-Drug Interactions

Drug-drug interactions were not studied because the drug was dosed alone. However, if patients follow the standard dropping procedure [redacted], there is no obvious reason to believe that interactions warranting serious concern would occur.

F. Special Populations

Both genders were approximately equally represented, but all studies included predominantly Caucasian patients.

Of the total number of pediatric subjects exposed to olopatadine 0.2%, 26 were between the ages of 3 and 5, and 38 were between 6 and 11 years of age; the pediatric and adult safety profiles were similar. There is no reason to believe that drug efficacy would differ as a function of age. Pregnant women were excluded from all studies, and the Sponsor has revealed no plans to address use in this population.

In summary, there is no reason to recommend a dose modification for special populations.

Clinical Review

I. Introduction and Background
The submitted drug product is [redacted] a histamine antagonist and mast cell stabilizer proposed for the [redacted] in patients over the age of 3 years old as a once-daily topical ocular drop.

The predominant forms of allergic conjunctivitis include perennial allergic conjunctivitis (typically year-round and caused by house dust or animal dander), and seasonal allergic conjunctivitis (typically appearing during pollen season). The pathogenesis common to both involves a local and systemic immunological hypersensitivity reaction; through multiple mechanisms, contact of the ocular surface with environmental (usually airborne) allergens leads to mast cell degranulation and release of chemical mediators such as histamine. This release sparks a cascade of molecular events that manifest clinically as the hallmark signs and symptoms of allergic conjunctivitis: itching, conjunctival hyperemia, tearing, eyelid edema, chemosis, and rhinitis. The clinical presentation may vary, depending on the weather (worse in warm, dry climate) and the patient's exposure to allergens.

Current therapeutic modalities attempt to improve the patient's quality of life by removing the offending allergen and/or modifying the inflammatory response. Initial management combines cold compresses, lubrication and an avoidance of allergens. If conservative therapy fails, the use of topical and oral medications is considered.

A. State of Armamentarium for Indication

There are several effective drug products used for allergic conjunctivitis, some available over the counter and others by prescription. Olopatadine 0.1%, the lower concentration of the submitted drug product with recommended twice-daily dosing, is a frequently prescribed drug product in this category. None of the currently approved drug products are approved for once-daily dosing with daylong duration of action.

Drug products that are used in the treatment of patients with allergic conjunctivitis or related symptoms, include antihistamine, mast cell inhibitors, vasoconstrictors, non-steroidal anti-inflammatories and steroidal anti-inflammatories.

B. Important Milestones in Product Development

At an End-of-Phase 2 meeting with the FDA on May 14, 2001, the Sponsor presented the results of the first CAC study. Various options for the clinical development of olopatadine 0.2% were discussed with the Agency, including: one CAC and one environmental study, two CAC studies, or two environmental studies. In addition, the agency explained that the proposed drug should be clinically superior to placebo for [redacted] to demonstrate efficacy for [redacted]

Given these options, the Sponsor planned to pursue the indication for the treatment of [redacted] by conducting one additional CAC study and one twelve-week environmental trial. The Agency also recommended that at least 300 patients be exposed to the study drug for at least 6 weeks; to reach that threshold, the Sponsor planned one 6-week, placebo-controlled safety study.

In previous discussions with the Agency, as documented in letters dated November 9, 2000, and January 11, 2001, and after completion of the first CAC trial with a "contralateral eye" design, the Sponsor was notified that a "totally randomized by-eye" study design was preferred for the trials. This design included randomizing subjects such that one group received active drug in both eyes, one group received placebo in both eyes, and one group received active drug in one eye and placebo in the contralateral eye. Thus, the two subsequent CAC trials were conducted using this totally randomized by-eye design. During discussions dated February 6, 2002, the Sponsor was notified that efficacy would be based on data from all study patients in the by-eye studies, not on the subset of patients who received active/placebo drops in contralateral eyes.

In discussions with the Agency dated October 10, 2001, the Sponsor was informed that the drug should demonstrate clinically meaningful efficacy; this was defined as superiority over vehicle by at least 1 unit for the majority of time points measured for each endpoint.

C. Other Relevant Information

Olopatadine hydrochloride ophthalmic solution 0.2% is not currently marketed in any country. It has not been withdrawn from marketing in any country due to safety and efficacy concerns either.

D. Important Issues with Pharmacologically Related Agents

Orally administered drugs with anti-histamine effects, terfenadine and astemizole, were withdrawn from the market after post-marketing studies revealed that these drugs delayed cardiac repolarization. This is manifest as a prolongation of the QT interval on an electrocardiogram, and creates a potentially dangerous electrophysiological environment that permits the development of cardiac arrhythmias. These effects are dose related and have not been shown to occur with ophthalmologically administered products. The Sponsor conducted one study using the oral dosage form of the drug, and demonstrated that olopatadine had no effect on QT interval when compared to placebo.

II. Significant Findings from Chemistry, Animal Pharmacology and Toxicology, and/or Microbiology

There were no significant findings from the Chemistry, Non-clinical Pharmacology or Toxicology reviews that are likely to affect the clinical outcome.

III. Human Pharmacokinetics and Pharmacodynamics

Summary of the Study 80:38610:0294: Fifteen normal, healthy subjects instilled 2 drops of Olopatadine Ophthalmic Solution 0.15% twice daily in each eye for 15 days. The study subjects ranged in age from 22 to 47 years, 7 males (47%) and 8 females (53%), 13 Caucasians (86%), 1 Asian (7%) and 1 "Classified as Other" (7%). Blood samples for were taken before dosing and at 0.25, 0.5, 1, 2, 4, 6 and 8 hours after ocular instillation on Days 1, 8 and 15. Plasma concentrations measured after 15 days of topical, ocular dosing were typically at or below 0.5 ng/mL quantitation limit with only 3 of 375 samples being above 1 ng/mL.

Summary of the Study 17:38570:0594: Nine normal, healthy male Japanese subjects instilled 2 drops of Olopatadine Ophthalmic Solution 0.15% twice daily in each eye for 14 days. Plasma samples were obtained before dosing and at 0.25, 0.5, 1, 2, 4, 6 and 8 hours after dosing on Days 1 and 15. Plasma samples were also obtained on Day 8 at 0.25, 0.5 and 1 hour postdose.

Plasma samples were analyzed by a validated GC/MS spectrometric method with a quantitation limit of 0.50 ng/mL. Plasma concentrations of olopatadine were typically below 0.5 ng/mL. Only 2 out of 180 total samples were above 1 ng/mL with the highest concentration being 1.28 ng/mL. The results of this study demonstrate a very low systemic exposure of olopatadine during a multiple topical ocular dosing regimen.

IV. Description of Clinical Data and Sources

A. Sources of Clinical Data

Electronic Submission of Volumes 1 through 17 of the NDA amendment for NDA 21-545.

B. Overview of Clinical Trials

Parameters	C-02-45	C-02-67
Study Design	randomized, double masked, contralateral eye comparison, active controlled	Randomized, double masked, parallel group, placebo controlled
Treatment Groups	Olopatadine 0.2%: 1 drop, topical ocular, one eye Olopatadine 0.1%: 1 drop, topical ocular, contralateral eye	Olopatadine 0.2%: 1 drop, topical ocular, both eyes, once-daily Placebo: 1 drop, topical ocular, both eyes, once-daily
Number of subjects	45	260
Duration	2 days	10 weeks

C. Postmarketing Experience

Olopatadine 0.2% is not currently marketed in any country. However, olopatadine hydrochloride ophthalmic solution 0.1% is currently marketed in over 30 countries, including the U.S. and Canada (as Patanol) and the European Union (as Opatanol) for the treatment of the signs and symptoms of allergic conjunctivitis when dosed twice-daily. Olopatadine HCl is marketed for oral use (2.5 or 5 mg twice-daily) in the treatment of allergic rhinitis, urticaria, and itching resulting from skin diseases such as eczema/dermatitis, prurigo, etc.

Since the product's approval in the United States in December 1996, and through December 2001, over ——— units have been sold. During the time period from January 1, 1997, to December 31, 2001, three hundred and ten (310) spontaneous adverse event reports associated with the use of Patanol have been received.

The most commonly reported adverse events included ocular discomfort, ocular hyperemia, ocular pain, ocular edema, ocular irritation, lid edema, and blurred vision; non-ocular events included no drug effect, headache, and reaction aggravation.

D. Literature Review

The medical reviewer conducted a Pubmed electronic literature search to supplement the submitted review of the relevant literature.

V. Clinical Review Methods

A. Describe How Review was Conducted

All submitted studies were reviewed separately and subsequently assessed in aggregate.

B. Overview of Materials Consulted in Review

In addition to the originally submitted electronic and paper copies of NDA 21-545, IND 60,911 was also consulted, as well as the medical officer's review from NDA 20-688 (olopatadine ophthalmic solution) 0.1% and the Original Medical Officer's review of NDA 21-545.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No special methods used.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

All trials were conducted under the review of approved Institutional Review Board committees. Investigators used an informed consent form that was appropriate for the respective trials.

E. Evaluation of Financial Disclosure

There is no evidence to suggest that the results of the studies were impacted by any financial payments.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The drug demonstrated efficacy in reducing ocular itching in patients with allergic conjunctivitis at onset and at 16 hours after dosing relative to placebo.

B. General Approach to Review of the Efficacy of the Drug

Efficacy data from four CAC studies and two natural exposure studies was reviewed in the original submission, one additional CAC and one additional natural exposure study was reviewed from this submission.

VII. Detailed Review of Trials

A. Study #7: Protocol C-02-45

Title: A Comparative Study of Olopatadine 0.2% Versus Olopatadine 0.1% in the Treatment of Allergic Conjunctivitis Using the Conjunctival Allergen Challenge (CAC) Model (C-02-45)

Investigator:
Jack V. Greiner, O.D., D.O., Ph.D.
Ophthalmic Research Associates
863 Turnpike Street
North, Andover, MA 01845
Phone: 978-685-8900
Fax: 978-689-0020

Subinvestigators:

Reviewer's Comments: *The investigators in this study also participated in other studies submitted to this NDA.*

Study Plan:
This study was a single-center, double-masked, randomized, contralateral eye comparison of Olopatadine 0.2% versus PATANOL in the treatment of allergen-mediated conjunctivitis using the conjunctival allergen challenge (CAC) model at 8 and 24 hours post-instillation. Study subjects were randomized in a 1:1 ratio to receive one of the following two therapy regimens: one drop of Olopatadine 0.2% in the left eye and one drop of PATANOL in the right eye; or, one drop of Olopatadine 0.2% in the right eye and one drop of PATANOL in the left eye. Eligible subjects were challenged with antigen at 24 hours (Visit 3) and at 8 hours (Visit 4) after dosing with masked medication. Ocular signs and symptoms of allergic conjunctivitis were evaluated both before dosing and after antigen challenge at each study visit. Efficacy and safety variables were assessed at 24 hours (Visit 3) and at 8 hours (Visit 4) after instillation of the study medication. The study population consisted of adult subjects with a history of clinically active allergic conjunctivitis, a positive diagnostic test (skin prick) for allergic disease, and a successful baseline challenge. 45 subjects were enrolled into the study. Forty-two (42) subjects completed. The primary efficacy variable was ocular itching. Secondary efficacy variables were scores for total redness (sum of conjunctival, ciliary, and episcleral redness), conjunctival redness, ciliary redness, episcleral redness, chemosis, eyelid swelling, and tearing. The evaluation of safety was conducted on all subjects who were randomized into the study and received at least one dose of study drug. The safety analysis was based on an evaluation of the extent of exposure to study drug, adverse events, visual acuity, ocular signs, and fundus parameters.

At the Screening Visit, subjects underwent a bilateral CAC test, based on the subject's own allergic sensitivity, until a positive reaction occurred as determined by a post-CAC assessment of ocular symptoms. All subjects were to have demonstrated a positive reaction to the CAC in order for them to continue in the study. A positive CAC reaction was defined as itching scores ≥ 2 in each eye, and ocular redness scores ≥ 2 in at least one of the three vessel beds (ciliary, conjunctival, or episcleral) in each eye, within 10 minutes of the last administered antigen dose. At Visit 2 (Confirmatory Challenge), subjects with no ocular itching, ocular redness scores < 1 before the antigen challenge, and a positive post-CAC assessment of ocular signs and symptoms (ocular redness and itching scores ≥ 2 in each eye in at least two assessment time-points) were eligible for Visit 3. At Visit 3, subjects with no ocular itching, and ocular redness scores < 1 before the antigen challenge, were enrolled in the study.

Procedures	Visit 1 Screening		Visit 2 Confirmatory Challenge 7 Days ±2 After Visit 1		Visit 3 24 Hour Assessment 14 Days ±3 After Visit 2		Visit 4 8 Hour Assessment 14 Days ±3 After Visit 3		Early Discontinuation
	Pre-CAC Titer	Post-CAC Titer	Pre-CAC	Post-CACa	Pre-CAC	Post-CACa	Pre-CAC	Post-CACa	
Informed Consent	X								
Medical History	X								
Concomitant Medications	X								
Changes in Health/Con Meds			X		X		X		X
Pregnancy Testb	X							X	X
Diagnostic (Skin prick)c Test	X								
Visual Acuity	X		X		Xd		Xd	Xd	X
Ocular Symptoms: Itching, Tearing	X	X	X	X	X	X	X	X	
Ocular Signs: Redness, Chemosis, Eyelid Swelling	X	X	X	X	X	X	X	X	
Slit Lamp: Cornea, Ant. Chamber, Iris, Lens	X		X		Xd		Xd	Xd	X
Fundus (Undilated) Exam	X							Xe	X
CAC	X		X		X		X		
Assign Subject Number					X				
Instill Drug					X		X		
Record Adverse Events					Xe	X	X	X	X
Complete Exit Form								X	X

Subjects: 45 subjects were enrolled in the study.

Discontinued Patients:

Investigator#	Subject #	Treatment	Sex	Age	Race	Reason
1957	1002	Olopat-Patanol	Female	52	Caucasian	Does Not Meet Criteriaa
1957	1015	Patanol-Olopat	Female	33	Caucasian	Noncompliance
1957	1044	Patanol-Olopat	Female	54	Caucasian	Does Not Meet Criteriaa

	Olopat-Patanol		**Patanol-Olopat**		
	N	**%**	**N**	**%**	**p-value**
Age					
02-11	0	0.0	0	0.0	1.0000
12-17	0	0.0	0	0.0	
18-64	22	95.7	21	95.5	
≥65	1	4.3	1	4.5	
Sex					
Male	6	26.1	7	31.8	0.6716
Female	17	73.9	15	68.2	
Race					
Caucasian	23	100.0	21	95.5	0.4889
Hispanic	0	0.0	1	4.5	
Iris Color					
Brown	11	47.8	16	72.7	0.1576
Hazel	2	8.7	1	4.5	
Green	2	8.7	3	13.6	
Blue	8	34.8	2	9.1	

Results:

Ocular Itching:

		24-Hr Duration CAC			8-Hr Duration CAC		
		3min	5min	7min	3min	5min	7min
Olopatadine 0.2%	Mean	0.77	0.82	0.76	0.37	0.42	0.37
	Std	0.72	0.70	0.73	0.54	0.51	0.43
	N	45	45	45	42	42	42
Patanol*	Mean	0.64	0.81	0.74	0.30	0.36	0.40
	Std	0.69	0.73	0.70	0.52	0.45	0.51
	N	45	45	45	42	42	42
Difference (Olopatadine 0.2% – Patanol)	Mean	0.12	0.01	0.01	0.07	0.06	-0.04
	Std	0.78	0.84	0.83	0.50	0.43	0.42
	N	45	45	45	42	42	42
	p-value	0.3017	0.9299	0.9288	0.3608	0.3755	0.5836

Applicant's report of previous Patanol studies

			8-Hr Duration-of-Action Assessment		
			3 min	10 min	20 min
Study C-94-10b	PATANOL	Mean	0.50	0.48	0.42
		Std	0.72	0.76	0.69
		N	25	25	25
Study C-94-39b	PATANOL	Mean	0.59	0.63	0.50
		Std	0.89	0.84	0.78
		N	53	53	53
Study C-94-58b	PATANOL	Mean	1.22	1.23	1.08
		Std	0.96	1.05	1.05
		N	30	30	30

Reviewer's Comments: *The data above represents a failed study. The values observed for the control group, Patanol, were less than those observed in the controlled studies which supported approval of Patanol. Olopatadine 0.2% failed to demonstrate superiority to Patanol.*

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical-_____

B. Study #8: Protocol C-02-67

Title: A Comparative Study of Olopatadine QD Versus Vehicle in Patients with Seasonal Allergic Conjunctivitis or Rhinoconjunctivitis (C-02-67)

Investigators:

Site Number	Name and Address	Subinvestigators	Number of subjects
3803	Mark Blecher, M.D. 1521 Locust Street, Suite 610 Philadelphia, PA 19102		34
2759	H. Jerome Crampton, M.D. Andover Eye Associates 138 Haverhill Street Andover, MA 01810		30
1128	Richard A. Eiferman, M.D. 6400 Dutchmans Pkwy. Suite 220 Louisville, KY 40205		15
3806	James C. Liu, M.D. Spectrum Eye Physicians 2577 Samaritan Dr., Suite 732 San Jose, CA 95124		32
1933	C. Thomas Moran, M.D. Kentucky Eye Care, PSC 6400 Dutchmans Pkwy, Suite 125 Louisville, KY 40205		14
1270	Francis W. Price, Jr., M.D. 9002 N. Meridian St., Suite 100 Indianapolis, IN 46260		27
1939	Howard Schenker, M.D. Rochester Ophthalmological Group 2100 S. Clinton Avenue Rochester, NY 14618		45

Site Number	Name and Address	Subinvestigators	Number of subjects
3815	Fred M. Shafrin, M.D. 5150 North Port Washington Rd. Suite 251 Milwaukee, WI 53217		0
3766	Christian Serdahl, M.D. 4925 J Street Sacramento, CA 95819		40
3807	Steven Silverstein, M.D. Silverstein Eye Centers 4240 Blue Ridge Blvd Suite 1000 Kansas City, MO 64133		23

Reviewer's Comments: *Site 2759 utilizes the same set of investigators as Study 1 in this review (C-02-45) and study sites in the previous Medical Officer's review.*

Study Plan: This was a 10 week, double-masked, randomized, placebo-controlled, multicenter, clinical trial. Two hundred sixty (260) subjects were seen for in-office visits (after the initial eligibility visit on Day 0) at Weeks 1, 2, 4, 6, 8, and 10. At these visits, subject self-assessments of the frequency of ocular and nasal symptoms over the 3 prior days were recorded, subjects self-assessed their current eyelid swelling, and visual acuity and slit-lamp evaluations were conducted; an undilated fundus exam and an IOP measurement were performed at both the entry (Day 0) and the exit visits (Week 10). Telephone contacts were conducted at Weeks 3, 5, 7, and 9 during which subject self-assessments of the frequency of ocular and nasal symptoms over the previous 3 days were collected. In addition, at all in-office visits and telephone contacts, adverse events, changes in medical history, concomitant medication use, and dosing compliance were recorded. Subjects also maintained a diary throughout the trial in which the worst daily, self-assessed severity of ocular itching and ocular redness was captured; the sites maintained a weekly pollen tracking log.

Reviewer's Comments: *There is strong disagreement with the validity of an endpoint which requires patients to recall events over the previous 3 days. This endpoint will not be accepted for the purposes of this review.*

As a general rule, safety examinations of the fundus should be conducted through a dilated pupil.

Schedule

Parameters	**Eligibility Visit Day 0**	**Office Visits Weeks 1, 2, 4, 6, 8** [Days 7, 14, 28, 42, 56 (±3 Days)]	**Telephone Contacts Weeks 3, 5, 7, 9** [Days 21, 35, 49, 63 (±3 Days)]	**Exit Visit, Week 10** [Day 70 (±3 Days) or the Last Office Visit (for patients who discontinue early)]
Informed Consent	X			
Medical History/Demographics	X			
Pregnancy Test[a]	X			X
Diagnostic Test (Skin prick)[b]	X			
Visual Acuity (logMAR)	X	X		X
Pt. Assessment of frequency of Itching, Redness, Tearing, and Nasal Symptoms	X	X	X	X
Pt. Assessment of Eyelid Swelling	X	X		X
Fundus Exam (Undilated)	X			X
Slit Lamp Evaluations	X	X		X
CAC / Pre- and Post-CAC Itching and Redness	X			
IOP Measurement	X			X
Dispense and/or Collect Study Medication (as needed)	X	X		
Record Adverse Events	X[c]	X	X	X
Update Medical History and Concomitant Medication Records		X	X	X
Issue / Collect Diary Card (as needed)	X	X		X
Record Missed Doses / Compliance Review		X	X	X
Collect Study Medication				X
Complete Exit Form				X

[a]A pregnancy test was performed at Day 0 and at the Exit Visit for all women of childbearing potential.
[b]If not obtained during the 24 months prior to Day 0.
[c]Adverse events that occurred after instillation of study medication were recorded.

Scales used in study:

Regional Redness (Ciliary, Episcleral and Conjunctival)
Evaluated for the CAC Test at Eligibility Visit (Day 0)
Determined using a slit-lamp (See Reference photographs for CAC)

0 = None.	A normal, quiet eye; some subjects will exhibit rare vessels which are naturally prominent either by location or a large normal vessel diameter.
1.0 = Mild.	Slight dilated blood vessels; color of vessels is typically pink; can be quadrantic.
2.0 = Moderate.	More apparent dilation of blood vessels; vessel color is more intense (redder); involves the vast majority of the vessel bed.
3.0 = Severe.	Numerous and obvious dilated blood vessels; in the absence of chemosis the color is deep red - in the presence of chemosis, the leaking interstitial fluid may make the color appear less red or even pinkish; is not quadrantic.
4.0 = Extremely severe.	Large, numerous, dilated blood vessels characterized by unusually severe deep red color, regardless of grade of chemosis, which involves the entire vessel bed.

NOTE: 0.5 increments were used in the CAC redness assessments when a vessel bed cannot be adequately and completely described by the definitions as stated above, but was between the two definitions.

Total Redness
Evaluated at all office visits after Eligibility (Day 0), and by the subjects in their daily diaries. Determined using a slit-lamp (See Reference photographs for Total Redness)
0 = Absent
0.5 = Between Absent and Trace
1.0 = Trace
1.5 = Between Trace and Mild
2.0 = Mild
2.5 = Between Mild and Moderate
3.0 = Moderate
3.5 = Between Moderate and Severe
4.0 = Severe

Itching
Day 0 CAC and Subject diary
0 = None
0.5 = An intermittent tickling sensation, possibly localized just in the corner of your eye.
1.0 = An intermittent tickling sensation, involving more than just in the corner of your eye.
1.5 = An intermittent all over tickling sensation.
2.0 = A mild continuous itch (can be localized), not requiring rubbing.
2.5 = A moderate, diffused, continuous itch, which you would like to rub.
3.0 = A severe itch, which you would like to rub.
3.5 = A severe itch, improved with minimal rubbing.
4.0 = An incapacitating itch, which requires significant eye rubbing.
NOTE: Subjects were not allowed to rub their eyes.

Chemosis
Determined using a slit-lamp at all Office Visits
0.0 = None
0.5 = Detectable only by slit-lamp beam; slight separation of conjunctiva from sclera.
1.0 = Detectable only by slit-lamp beam; definite separation of conjunctiva from sclera.
1.5 = Detectable with pen light illumination; localized microchemosis.
2.0 = Visible in normal room light; more diffuse edema.
2.5 = Conjunctiva elevated to and at the limbus; very diffuse.
3.0 = Conjunctival billowing at the limbus; very diffuse and noticeable.
3.5 = Large pocket of fluid localized anywhere in conjunctiva.

4.0 = Severe overall ballooning of conjunctiva.

Eyelid Swelling
Determined by the subject at all Office Visits
0.0 = None
1.0 = Mild – Detectable swelling of lower and/or upper lid.
2.0 = Moderate – Definite swelling of lower and/or upper lid.
3.0 = Severe – Swelling of upper and/or lower lid to a point that there is a decrease in the space between your upper and lower lids and/or a sensation of pressure.

Itching Frequency
Collected at all In-Office Visits and Telephone Contacts
The patient was asked, "*How often during the last three days did your eyes itch enough that you wanted to rub them?*" The term "wanted" was used instead of "did" since interviews with patients have indicated that women who wear makeup will not rub their eyes since rubbing would ruin their makeup.
0 = None. (Did not occur)
1 = Rarely. (Once)
2 = Occasionally (At least once on two days)
3 = Frequently (At least once every day)
4 = Very Frequently (Two or more times every day)
5 = Continuously (Virtually all the time over the past three days)

Redness Frequency
Collected at all In-Office Visits and Telephone Contacts
The patient was asked, "*How often during the last three days were your eyes noticeably more red than normal for you?*" The question was directed to redness suspected to be allergy-related.
0 = None. (Did not occur)
1 = Rarely. (Once)
2 = Occasionally (At least once on two days)
3 = Frequently (At least once every day)
4 = Very Frequently (Two or more times every day)
5 = Continuously (Virtually all the time over the past three days)

Tearing Frequency
Collected at all In-Office Visits and Telephone Contacts
The patient was asked, "*How often during the last three days did your eyes tear?*" The question was directed to tearing suspected to be allergy-related and not emotional or other tearing.
0 = None. (Did not occur)
1 = Rarely. (Once)
2 = Occasionally (At least once on two days)
3 = Frequently (At least once every day)
4 = Very Frequently (Two or more times every day)
5 = Continuously (Virtually all the time over the past three days)

Nasal Signs and Symptoms Frequency
Collected at all In-Office Visits and Telephone Contacts
The patient was asked, "*How often during the last three days did the following nasal signs and symptoms occur?*" The question was directed to nasal signs and symptoms suspected to be allergy-related.

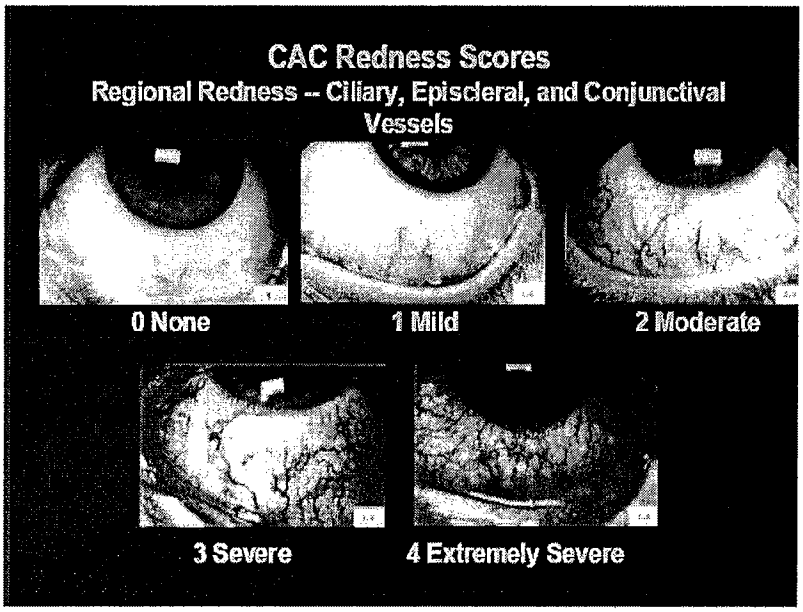
Stuffy Nose
0 = None. (Did not occur)
1 = Rarely. (Once)
2 = Occasionally (At least once on two days)
3 = Frequently (At least once every day)
4 = Very Frequently (Two or more times every day)
5 = Continuously (Virtually all the time over the past three days)

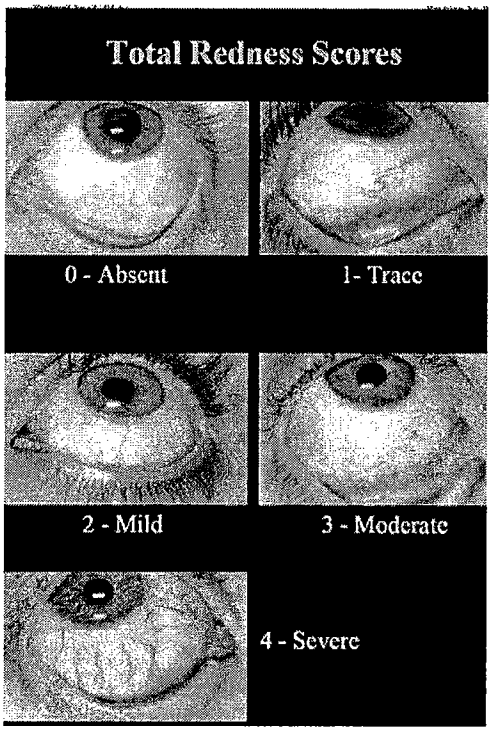
Sneezing
0 = None. (Did not occur)
1 = Rarely. (Once)
2 = Occasionally (At least once on two days)
3 = Frequently (At least once every day)
4 = Very Frequently (Two or more times every day)
5 = Continuously (Virtually all the time over the past three days)

Runny Nose
0 = None. (Did not occur)
1 = Rarely. (Once)
2 = Occasionally (At least once on two days)
3 = Frequently (At least once every day)
4 = Very Frequently (Two or more times every day)
5 = Continuously (Virtually all the time over the past three days)

Itchy Nose
0 = None. (Did not occur)
1 = Rarely. (Once)
2 = Occasionally (At least once on two days)
3 = Frequently (At least once every day)
4 = Very Frequently (Two or more times every day)
5 = Continuously (Virtually all the time over the past three days)

Postnasal Drip
0 = None. (Did not occur)
1 = Rarely. (Once)
2 = Occasionally (At least once on two days)
3 = Frequently (At least once every day)
4 = Very Frequently (Two or more times every day)
5 = Continuously (Virtually all the time over the past three days)

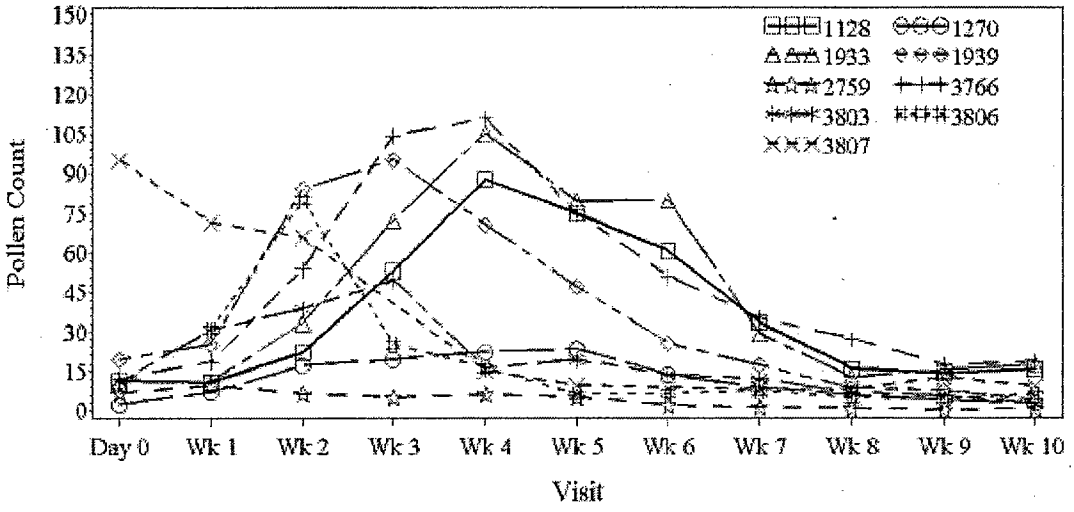




Study Population: The study population consisted of subjects, 10 years old or older with a history of seasonal allergic conjunctivitis or rhinoconjunctivitis, a positive response to grass (by diagnostic skin prick test performed within the past 2 years), and a positive CAC response to grass of the following magnitude:

• Redness (in at least one of the vessel beds – ciliary, episcleral, conjunctival – each measured separately on a scale ranging from 0 to 4) and itching scores ≥ 2 in each eye within 10 minutes following the antigen challenge for subjects with baseline redness and itching scores < 1; OR
• An increase of ≥ 1 score unit in redness (in at least one of the vessel beds – ciliary, episcleral, conjunctival – each measured separately on a scale of 0 to 4) and itching scores in each eye within 10 minutes following the antigen challenge for subjects with baseline itching and redness scores ≥ 1.

Pollen Counts:



APPEARS THIS WAY
ON ORIGINAL

Demographics

	Treatment Group				
	Olopatadine 0.2%		Vehicle		
	N	%	N	%	p-value
Age					
2-11	1	0.8	2	1.5	0.7192
12-17	14	10.9	11	8.4	
18-64	108	83.7	114	87.0	
≥65	6	4.7	4	3.1	
Age (≥65)					
65-74	4	66.7	4	100.0	0.4667
75-84	2	33.3	0	0.0	
Gender					
Male	61	47.3	62	47.3	0.9947
Female	68	52.7	69	52.7	
Race					
Caucasian	97	75.2	95	72.5	0.7817
Black	14	10.9	15	11.5	
Asian	6	4.7	7	5.3	
Japanese	5	3.9	3	2.3	
Hispanic	5	3.9	5	3.8	
Other	2	1.6	6	4.6	
Iris Color					
Brown	60	46.5	62	47.3	0.6513
Hazel	22	17.1	16	12.2	
Green	9	7.0	8	6.1	
Blue	38	29.5	44	33.6	
Grey	0	0.0	1	0.8	

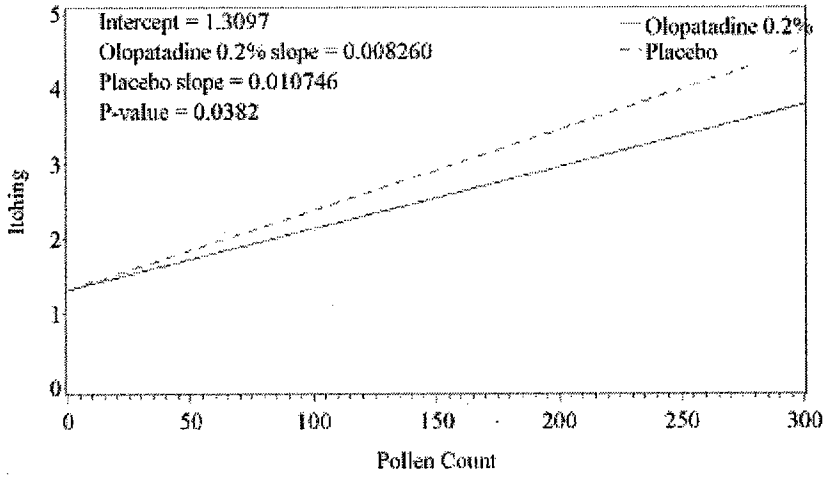
Per-Protocol Patient Numbers:

		Day 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
Available	Olopatadine 0.2%	127	125	124	120	122	122	122	121	117	118	117
	Placebo	128	122	123	124	125	121	120	121	118	121	117
Discontinued	Olopatadine 0.2%	0	0	1	1	1	3	3	4	4	4	5
	Placebo	0	0	2	3	3	4	4	6	7	7	7
Missing	Olopatadine 0.2%	0	0	1	5	2	1	1	1	5	3	0
	Placebo	0	2	2	0	0	2	2	1	3	0	0
Not Evaluable	Olopatadine 0.2%	0	2	1	1	2	1	1	1	1	2	5
	Placebo	0	4	1	1	0	1	2	0	0	0	4
Total	Olopatadine 0.2%	127	127	127	127	127	127	127	127	127	127	127
	Placebo	128	128	128	128	128	128	128	128	128	128	128
	Total	255	255	255	255	255	255	255	255	255	255	255

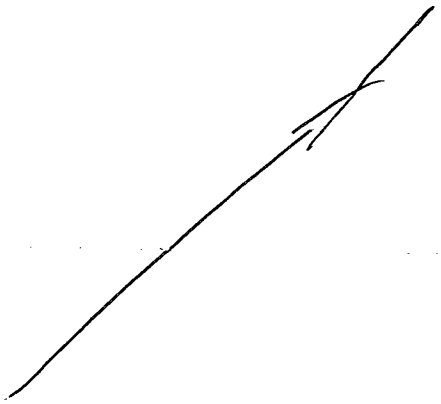
Discontinued:

Investigator	Treatment	Patient	Age	Gender	Race	Reason for Discontinuation
1128	Placebo	110	40	Female	Caucasian	Herpetic infection
3803	Placebo	400	20	Female	Black	Patient Decision
3803	Placebo	402	56	Male	Caucasian	Foreign body sensation following chemical accident exposure
3806	Placebo	615	69	Male	Caucasian	Used Allergy medications
3806	Placebo	619	39	Male	Hispanic	Missed multiple visits
1939	Placebo	709	34	Female	Caucasian	Treatment Failure
3766	Placebo	817	45	Female	Caucasian	Corneal abrasion
3807	Placebo	904	43	Male	Black	Work related travel
1270	Olopatadine 0.2%	326	23	Male	Caucasian	Ocular inflammation
3803	Olopatadine 0.2%	410	32	Male	Caucasian	Dermatitis
1939	Olopatadine 0.2%	707	75	Female	Caucasian	Noncompliance
3766	Olopatadine 0.2%	801	25	Female	Hispanic	Systemic allergy reaction- Asthma
3807	Olopatadine 0.2%	911	39	Male	Caucasian	Decreased visual acuity
3807	Olopatadine 0.2%	918	15	Male	Caucasian	Head congestion/Allergy/ Blurred vision

Ocular Itching Frequency by Pollen Count (grains/m3 of air) (Intent-to-Treat Data)

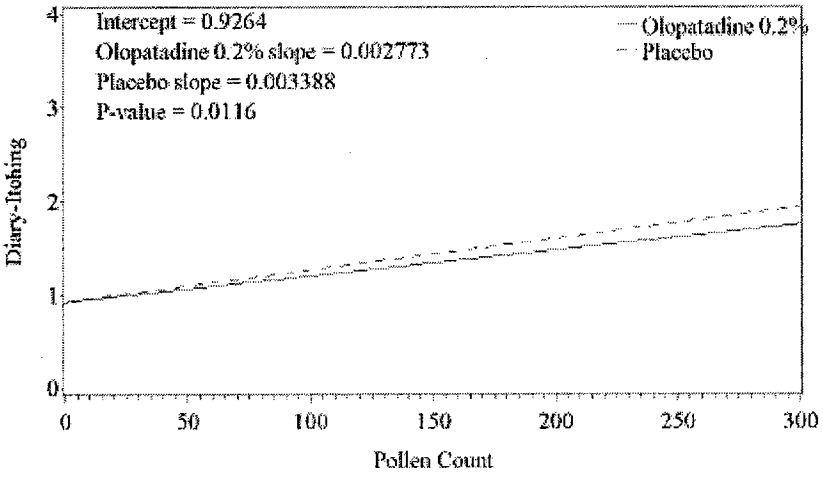


Ocular Redness Frequency by Pollen Count (grains/m3 of air) (Intent-to-Treat Data)

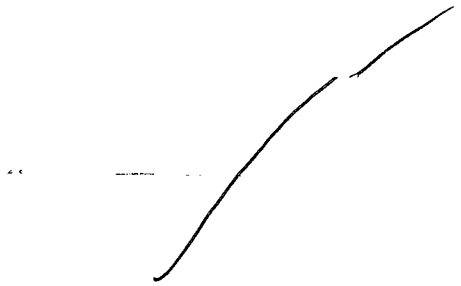


Reviewer's Comments: *This reviewer does not agree with the use of this type of analysis to demonstrate the clinical effectiveness of once a day therapy. The approval of olopatadine 1% bid established that olopatadine was more effective than vehicle at higher pollen counts. The use of a three day recall also diminishes the support for this indication. These results do not establish that once a day therapy of olopatadine 2% is clinically effective in*

Ocular Itching Severity by Pollen Count (grains/m^3 of air) (Intent-to-Treat Data)

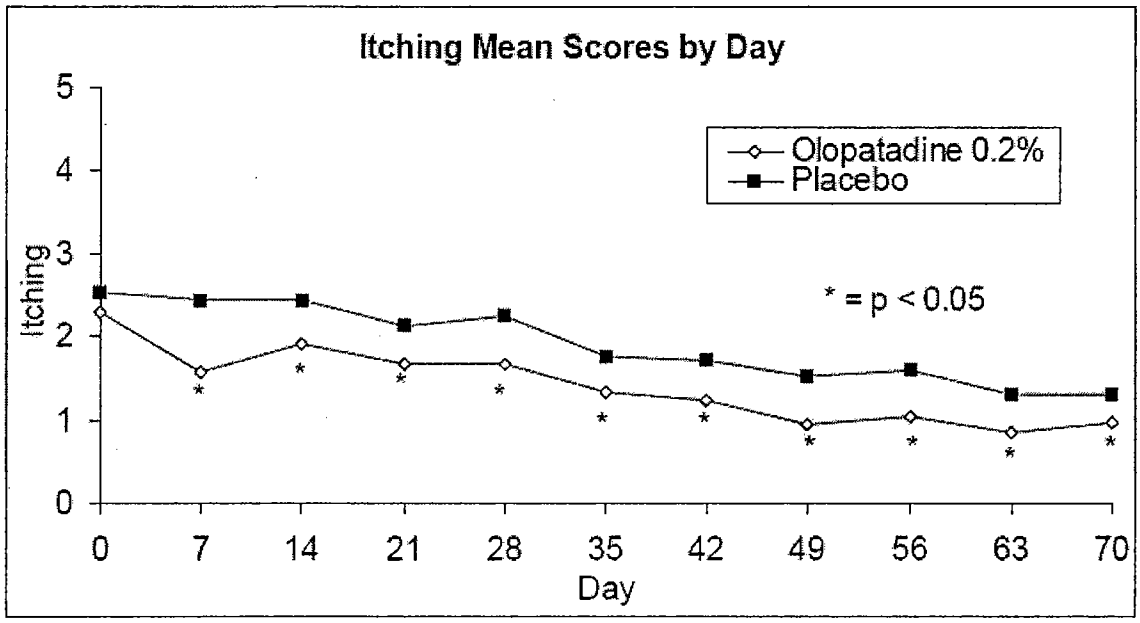


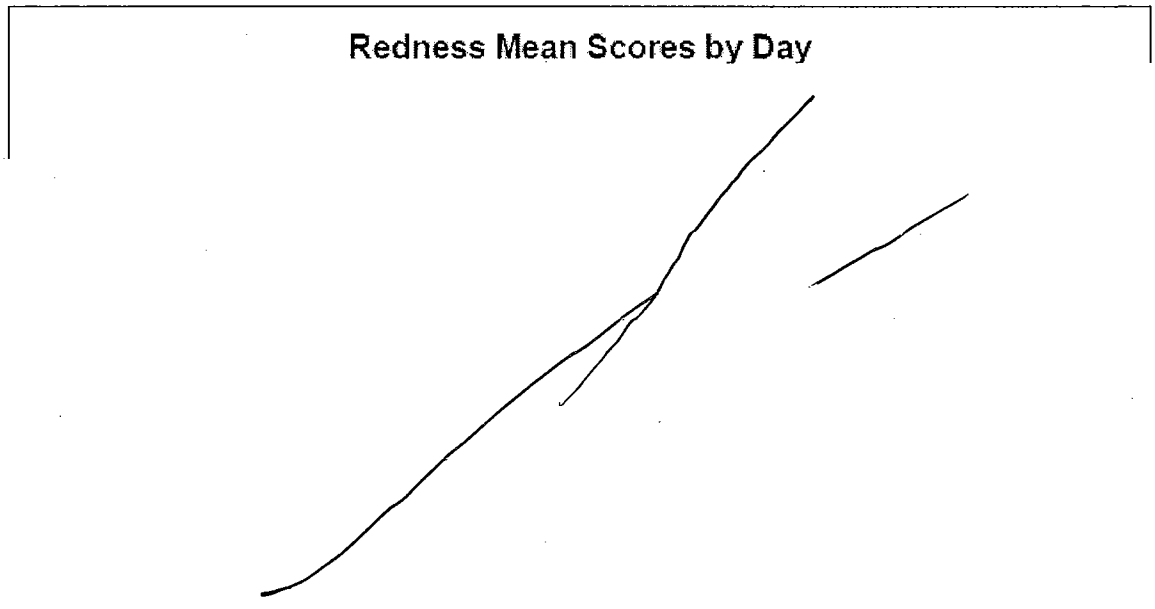
Ocular Redness Severity by Pollen Count (grains/m^3 of air) (Intent-to-Treat Data)



Reviewer's Comments: *This reviewer does not agree with the use of this type of analysis to demonstrate the clinical effectiveness of once a day therapy. The approval of olopatadine 1% bid established that olopatadine was more effective than vehicle at higher pollen counts. The use of a three day recall also diminishes the support for this indication. These results do not establish that once a day therapy of olopatadine 2% is clinically effective in*

Intent to Treat Analysis





Reviewer's Comments: *The values presented above are also based on 3-day recalls and therefore are of limited value.*

Itching and Redness Severity for the 14 Day Consecutive Period with the highest Mean Pollen Count (ITT)

Mean Itching

		Diary Itching	Diary Redness
Olopatadine 0.2%	Mean	1.10	
	Std	0.92	
	N	127	
Placebo	Mean	1.48	
	Std	1.04	
	N	129	
Difference		-0.38	
P-value (t-test)		0.0023	

Percentage of patients with clearing (score=0)

		Diary Itching
Olopatadine 0.2%	**0**	38 (30%)
	>0	90 (70%)
Vehicle	**0**	28 (22%)
	>0	101 (78%)
P (chi square test)		0.1431

Reviewer's Comments: *As noted in the table above, only a small percentage of patients obtain clearing of itching. The groups are not statistically different. Clearing throughout the day would be evidence of a continued effect of the drug product.*

Adverse Events:

Reviewer's Comments: *The primary reported adverse events were ocular pain, discomfort and blurring. They were reported in 1-3% of patients.*

VIII. Integrated Review of Safety

A. Brief Statement of Findings

Olopatadine 0.2% administered once daily is safe and well-tolerated in pediatric and adult subjects with seasonal allergic conjunctivitis, based on a review of adverse events and an assessment of ocular parameters. Adverse events in the overall treatment population were mostly non-serious and mild to moderate, generally resolved without treatment, and usually did not interrupt subject continuation in the studies.

B. Materials Utilized in the Review

The overall experience using olopatadine 0.2% ophthalmic solution was evaluated in 7 clinical trials. In addition, one clinical trial using an oral formulation of olopatadine contributed to the safety data set. The 4 CAC studies provided short-term data, the environmental and topical safety study provided long-term data, and the oral study provided oral systemic data.

C. Description of Patient Exposure

Two natural exposure and one safety study provided up to 12 weeks exposure. The rest of the studies provided only a single administration.

D. Safety Findings from Clinical Studies

Overall, ocular adverse events were similar regardless of contact lens use, iris color, race/ethnicity or gender. The findings in the studies presented in this review are not markedly changed from the first review.

E. Literature Review for Safety

No additional relevant information.

F. Postmarketing Surveillance

Discussed in a previous section.

G. Safety Update

No significant new information.

H. Drug Withdrawal, Abuse, and Overdose Experience

No reports of overdose, drug abuse, or withdrawal/rebound phenomena were submitted. There is no foreseen potential for abuse and dependence.

I. Adequacy of Safety Testing

Overall, the safety data generated by the clinical studies was adequate. The drug was dosed in over 300 patients for at least 6 weeks—the length of a typical allergy season. It included an adequate number of children and an even representation of most demographic groups, with the exception of Caucasians representing 76% of subjects with long term exposure to the study drug. Ocular and systemic testing parameters were appropriately chosen and relevant.

J. Labeling Safety Issues and Postmarketing Commitments

Safety signals that need to be highlighted in the drug's labeling are consistent with those found in the olopatadine 0.1% label.

IX. Dosing, Regimen, and Administration Issues

Reviewed in previous section.

X. Use in Special Populations

A. Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity.

Based on a review of adverse events by age in the subjects with long term exposure to the drug, there are no apparent trends or safety concerns. Similarly, an analysis of adverse events by gender, race/ethnicity, and eye color revealed no notable, clinically relevant differences.

B. Pediatric Program (e.g., pediatric waivers, deferrals, written requests)

The Sponsor requested a waiver regarding the use of Olopatadine HCl Ophthalmic Solution (0.2% as base) in pediatric patients under the age of 3 years. The division does not consider the disease to exist in a substantial population below the age of 3 years and therefore recommends granting the waiver.

C. Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

The drug product has negligible systemic absorption and therefore information in patients with renal or hepatic compromise is not necessary.

XI. Conclusions, Recommendations, and Labeling

A. Conclusions

In the 3 CAC studies, the drug demonstrated relative efficacy in reducing itching symptoms at onset and 16 hours after administration. This effect was moderate in magnitude, less evident at 16 hours, and relatively uniform within each study; however, the effect was variable between studies.

One natural exposure study did not demonstrate drug efficacy for any endpoint and the other natural exposure study was not designed to demonstrate efficacy throughout the day.

None of the studies demonstrated a clinically meaningful reduction of any evaluated signs and symptoms other than itching, and there were no studies directly comparing the drug to other treatments.

Overall, the clinical study designs met the Division's recommendations for replication and clinical significance, and the relative shortcomings in strength of efficacy results are offset by the minimal risk likely attributed to taking the drug.

The 3 CAC studies provide limited supportive safety data because subjects were exposed to no more than 3 drops of the drug, each separated by multiple days. Safety data from these 2 relatively long-term studies are generally amenable to extrapolation.

Overall, there were no significant adverse events that warrant special monitoring; they were relatively few in number, mild, resolved without treatment, and rarely resulted in discontinuation of participation in a trial.

One safety study tested a 5 mg oral form of the drug versus placebo in 102 patients. As expected, this dose resulted in higher plasma concentrations than those expected with topical administration. There was no evidence of drug effect on cardiac repolarization, and no clinically relevant treatment-related changes in laboratory parameters or vital signs relative to placebo.

B. Recommendations

NDA 21-545 is recommended for approval of once-daily dosing in the prevention of ocular itching due to allergic conjunctivitis with the labeling revisions listed in this review.

C. Labeling

A labeling review is deferred until data is submitted to support the proposed indication.

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/s/

Wiley Chambers
6/3/04 03:01:25 PM
MEDICAL OFFICER

William Boyd
6/3/04 03:16:03 PM
MEDICAL OFFICER
I concur with the analyses and conclusions reached in this Medical Officer's Clinical Review.

Medical Officer's Review of NDA 21-545
120-Day Safety Update

Submission Date:	December 13, 2002
Received Date:	December 18, 2002
Review Completed:	March 12, 2003
Proposed Trademark:	[redacted]
Generic Name:	Olopatadine HCl ophthalmic solution 0.2%
Chemical Name:	11-[(Z)-3-(Dimethylamino) propylidene]-6-11-dihydrodibenz[b,e] oxepin-2-acetic acid, hydrochloride
Molecular Formula:	$C_{21}H_{23}NO_3 \bullet HCl$
Molecular Weight:	373.88
Sponsor:	Alcon, Inc. P.O. Box 62 Bosch 69 CH-6331 Hunenberg Switzerland Alcon Research, Ltd. 6201 S. Freeway Fort Worth, TX 76134-2099 (817) 551-4933
Pharmacologic Category:	Antihistamine and mast cell stabilizer
Proposed Indication:	[redacted]
Dosage Form:	Ophthalmic solution
Route of Administration:	Topical ocular
NDA Drug Classification:	3S
Related IND:	IND 60,991
Related NDA:	NDA 20-688 (Patanol®)

Summary of Safety Data

The four-month safety update includes new safety data from one clinical study that has been completed since the filing of the olopatadine 0.2% NDA (21-545) in August, 2002, and one study which remains ongoing. These two studies include one environmental study (C-01-90: completed) providing long-term exposure to olopatadine 0.2% and one conjunctival allergen challenge (CAC) study (C-02-45: ongoing) providing short-term exposure.

Reported Adverse Events ≥ 1.0%

Adverse Events	At NDA Filing (all topical studies)						Post-NDA Filing					
							C-01-90				C-02-45	
	Drug-Drug N=390		Drug-Vehicle N=103		Vehicle - Vehicle N=271		Drug N=119		Vehicle N=121		Masked N=45	
	N	%	N	%	N	%	N	%	N	%	N	%
OCULAR												
Conjunctivitis	4	1.0			4	1.5			2	1.7		
Lid Margin Crusting	4	1.0	2		2	0.7						
Discomfort eye	2	0.5			5	1.8			2	1.7		
Hyperemia eye	4	1.0			1	0.4						
Tearing	2	0.5	1	1.0	2	0.7						
Discharge eye NOS	1	0.3	1	1.0	2	0.7						
Lid disease	1	0.3			3	1.1						
Pruritis eye	1	0.3	1	1.0	1	0.4						
Subconjunctival hem			1	1.0	1	0.4						
Dry eye	2	0.5							3	1.7		
Visual acuity dec.							2	1.7	4	3.3		
Chalazion							1	0.8	2	1.7		
Meibomitis							3	2.5				
Vision blurred							1	0.8	2	1.7		
NON-OCULAR												
Body as whole												
Cold Syndrome	13	3.3	2	1.9	10	3.7	3	2.5	4	3.3	2	4.4
Infection	11	2.8			7	2.6	3	2.5	1	0.8	3	6.7
Headache	10	2.6	1	1.0	7	2.6						
Injury Accidental	1	0.3	2	1.9								
Neck Rigid			2	1.9	1	0.4						
Pain Abdominal	1	0.3	1	1.0								
Flu Syndrome							4	3.4	1	0.8	2	4.4
Pain							2	1.7	3	2.5		
Pain Back	3	0.8					2	1.7				
Cardiovascular												
Tachycardia	1	0.3										
Digestive												
Abscess periodontal			1	1.0								
Gastritis			1	1.0								
Endocrine												
Diabetes Mell							2	1.7				
Metabolic / Nutritional												
Hypercholesterem							2	1.7				
Musculoskeletal												
Bone fracture, spontan.	1	0.3	1	1.0								

Adverse Events	At NDA Filing (all topical studies)						Post-NDA Filing					
							C-01-90				C-02-45	
	Drug-Drug N=390		Drug-Vehicle N=103		Vehicle - Vehicle N=271		Drug N=119		Vehicle N=121		Masked N=45	
Myalgia							1	0.8	2	1.7		
Respiratory												
Pharyngitis	11	2.8	1	1.0	5	1.8						
Rhinitis	8	2.1	2	1.9	1	0.4						
Cough increased	5	1.3			3	1.1					1	2.2
Sinusitis	5	1.3			3	1.1						
Epistaxis							3	2.5				
Skin, Appendages												
Herpes Simplex	1	0.3	1	1.0								
Special Senses												
Otitis Media	4	1.0			5							
Taste Perversion	6	1.5										
Urogenital												
Menopause			1	1.0								

Reviewer's comments: *Overall, most of the safety data observed in the completed environmental study (C-01-90) and the ongoing masked CAC study (C-02-45) are similar to the safety data filed in the NDA. A few additional adverse events have been noted (e.g., vision blurred, meibomitis, flu syndrome) and the label will be adjusted accordingly.*

Reviewer's recommendation: *Safety data from study C-02-45 should be submitted to the agency when available.*

Matthew Feinsod, M.D.
Medical Officer

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/s/

Matthew Feinsod
5/1/03 06:53:58 PM
MEDICAL OFFICER

Wiley Chambers
5/2/03 11:18:52 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-545

Original

Submission Date:	August 14, 2002
Received Date:	August 15, 2002
Review Completed:	February 17, 2003
Proposed Trademark:	——→
Generic Name:	Olopatadine HCl ophthalmic solution 0.2%
Chemical Name:	11-[(Z)-3-(Dimethylamino) propylidene]-6-11-dihydrodibenz[b,e] oxepin-2-acetic acid, hydrochloride
Molecular Formula:	$C_{21}H_{23}NO_3 \bullet HCl$
Molecular Weight:	373.88
Sponsor:	Alcon, Inc. P.O. Box 62 Bosch 69 CH-6331 Hunenberg Switzerland Alcon Research, Ltd. 6201 S. Freeway Fort Worth, TX 76134-2099 (817) 551-4933
Pharmacologic Category:	Antihistamine and mast cell stabilizer
Proposed Indication:	——
Dosage Form:	Ophthalmic solution
Route of Administration:	Topical ocular
NDA Drug Classification:	3S
Related IND:	IND 60,991
Related NDA:	NDA 20-688 (Patanol®)

Contents

The Executive Summary of the Primary Clinical Review

1. RECOMMENDATIONS

1.1. Recommendation on Approvability

From a clinical perspective, NDA 21-545 is recommended for approval of once-daily dosing in the — ocular itching due to allergic conjunctivitis with the labeling revisions listed in this review.

1.2. Recommendation on Postmarketing Studies and/or Risk Management Steps

It is recommended that the Sponsor conduct another environmental study with improved assay sensitivity to support the related claims.

2. SUMMARY OF CLINICAL FINDINGS

The Sponsor intends to optimize patient compliance and convenience by introducing a once-daily eye drop formulation for allergic conjunctivitis.

2.1. Brief Overview of Clinical Program

The study drug, olopatadine hydrochloride ophthalmic solution 0.2%, is a relatively selective histamine-1 receptor inhibitor and mast cell stabilizer. It was studied for its safety and efficacy — in patients with a confirmed history of the condition when administered once daily to the eye.
Four (4) primary clinical studies were conducted to test for both efficacy and safety, and 2 primary clinical studies were conducted to test for only safety (one topical, one oral formulation). Together, these 6 trials involved a total 493 patients who were exposed to the topical drug—over 300 of whom were exposed daily for at least 6 weeks.

2.2. Efficacy

Of the 4 primary studies designed to test the drug's efficacy, 3 were conjunctival allergen challenge (CAC) studies and one was an environmental study.

Ocular itching (a symptom) and conjunctival redness (a sign) are commonly regarded as clinically meaningful in patients with allergic conjunctivitis. The environmental trial and one CAC trial studied both as co-primary endpoints, but the other two CAC trials studied only ocular itching as a primary endpoint. Secondary endpoints included other ocular signs and symptoms of allergic conjunctivitis, such as tearing, chemosis, eyelid swelling, etc.

In the 3 CAC studies, investigators instilled one drop of the drug or vehicle into the eye of patients with confirmed allergic conjunctivitis. These patients were then challenged with an inciting antigen during at least two separate visits: the first to test the drug effect at its onset of action (27 minutes), and the second to test its effect after a typical day (16 hours after instillation). At both time points, the drug demonstrated relative efficacy in reducing itching symptoms. This effect was moderate in magnitude, less evident at 16 hours, and relatively uniform within each study; however, the effect was variable between studies.

The environmental study did not demonstrate drug efficacy for any endpoint.

None of the studies demonstrated a clinically meaningful reduction of any evaluated signs and symptoms other than itching, and there were no studies directly comparing the drug to other treatments.

Olopatadine 0.2% has demonstrated efficacy in the — itching — in contrast, olopatadine 0.1% has demonstrated efficacy in the prevention of redness as well as itching and is therefore approved for the signs and symptoms of allergic conjunctivitis. It is unclear how the Sponsor will adequately convey that distinction to the public and medical community.

Further, since the effect of olopatadine 0.2% on itching appears to diminish when measured at 16 hours relative to its effect at onset, it is plausible that a patient might prefer to use olopatadine 0.1% twice a day to achieve a more satisfying effect over time.

Overall, the clinical study designs met the Division's recommendations for replication and clinical significance, and the relative shortcomings in strength of efficacy results are offset by the minimal risk likely attributed to taking the drug.

2.3. Safety

The 3 CAC studies provide limited supportive safety data because subjects were exposed to no more than 3 drops of the drug, each separated by multiple days. Conversely, the environmental study randomized 119 patients to 12 weeks of daily drug exposure and the safety study randomized 236 patients to 6 weeks of daily drug exposure, totaling 355 patients that included 64 children ranging from 3 to 11 years of age.

Safety data from these 2 relatively long-term studies are generally amenable to extrapolation.

Overall, adverse events were relatively few in number, mild, resolved without treatment, and rarely resulted in discontinuation of participation in a trial. There were no significant adverse events that warrant special monitoring.

One safety study tested a 5 mg oral form of the drug versus placebo in 102 patients. As expected, this dose resulted in higher plasma concentrations than those expected with topical administration. There was no evidence of drug effect on cardiac repolarization, and no clinically relevant treatment-related changes in laboratory parameters or vital signs relative to placebo.

Significant off-label use of the study drug may occur, as physicians and patients may incorrectly assume that the newer formulation contains the same claims in its label as the lower concentration, despite the fact that the lower concentration holds a redness—and therefore, "signs and symptoms of allergic conjunctivitis"—claim. However, it is anticipated that the drug will be used primarily, if not exclusively, by patients with allergic conjunctivitis, and the non-serious safety data are similar for both the lower (0.1%) and higher (0.2%) concentration formulation in these patients.

All clinical studies were placebo-controlled; there were no studies comparing the safety profile of olopatadine 0.2% to other available treatments outside of its class.

Animal toxicology studies were conducted and the company referenced those from the approved product, olopatadine 0.1%.

In sum, the clinical trials met the Division's safety recommendations for minimum number of exposures, duration, and patient monitoring. It is likely that the similarity of adverse events reported in trials for the two olopatadine concentrations is predictive of those anticipated in a post-marketing patient population using olopatadine 0.2%.

2.4. Dosing, Regimen, and Administration

In the clinical studies evaluating the topical formulation, one drop of olopatadine 0.2% was administered once daily to the eye. This concentration and dosing regimen was based on several factors, including data from a pre-clinical dose-response study, the efficacy and safety demonstrated for the marketed product (olopatadine 0.1%) when instilled BID, and solubility considerations.

2.5. Drug-Drug Interactions

Drug-drug interactions were not studied because the drug was dosed alone. However, if patients follow the standard dropping procedure (, there is no obvious reason to believe that interactions warranting serious concern would occur.

2.6. Special Populations

Both genders were approximately equally represented, but all studies included predominantly Caucasian patients.

Of the total number of pediatric subjects exposed to olopatadine 0.2%, 26 were between the ages of 3 and 5, and 38 were between 6 and 11 years of age; the pediatric and adult safety profiles were similar. Children were not studied in the CAC studies, because of the inability to get accurate subjective responses. However, there is no reason to believe that drug efficacy would differ as a function of age.

Pregnant women were excluded from all studies, and the Sponsor has revealed no plans to address use in this population.

Drug-disease interaction analyses were conducted but the number of subjects enrolled was inadequate to draw conclusions.

In sum, there is no reason to recommend a dose modification for special populations.

Clinical Review

1. INTRODUCTION AND BACKGROUND

The submitted drug product is [redacted] a histamine antagonist and mast cell stabilizer proposed for [redacted] in patients over the age of 3 years old as a once-daily topical ocular drop.

The predominant forms of allergic conjunctivitis include "perennial" allergic conjunctivitis (typically year-round and caused by house dust or animal dander), and "seasonal" allergic conjunctivitis (typically appearing during pollen season). The pathogenesis common to both involves a local and systemic immunologic hypersensitivity reaction—through multiple mechanisms, contact of the ocular surface with environmental (usually airborne) allergens leads to mast cell degranulation and release of chemical mediators such as histamine. This release sparks a cascade of molecular events that manifest clinically as the hallmark signs and symptoms of allergic conjunctivitis: itching, conjunctival hyperemia, tearing, eyelid edema, chemosis, and rhinitis. The clinical presentation may vary, depending on the weather (worse in warm, dry climate) and the patient's allergens exposure.

Current therapeutic modalities attempt to improve the patient's quality of life by removing the offending allergen and/or modifying the inflammatory response. Initial management combines cold compresses, lubrication and an avoidance of allergens. If conservative therapy fails, the use of topical and oral medications is considered.

1.1. State of Armamentarium for Indication

There are several effective drug products used for allergic conjunctivitis, some available over the counter and others by prescription. Olopatadine 0.1%, the lower concentration of the submitted drug product with recommended twice-daily dosing, is a frequently prescribed drug product in this category. None of the currently approved drug products are approved for once-daily dosing with daylong duration of action.

Drug products that are used in the treatment of patients with allergic conjunctivitis or related symptoms include antihistamines, mast cell stabilizers, vasoconstrictors, non-steroidal anti-inflammatories and steroidal anti-inflammatories.

1.2. Important Milestones in Product Development

At an End-of-Phase 2 meeting with the FDA on May 14, 2001, the Sponsor presented the results of the first CAC study. Various options for the clinical development of olopatadine 0.2% were discussed with the Agency, including: a) one CAC and one environmental study, b) two CAC studies, or c) two environmental studies. In addition, the agency explained that the proposed drug should be clinically superior to placebo for [redacted]

Given these options, the Sponsor planned to pursue the indication for the treatment of the [redacted] by conducting one additional CAC study and one twelve-week environmental trial. The Agency also recommended that at least 300 subjects be exposed to the study drug for at least 6 weeks; to reach that threshold, the Sponsor planned one 6-week, placebo-controlled safety study.

In previous discussions with the Agency, as documented in letters dated November 9, 2000, and January 11, 2001, and after completion of the first CAC trial with a "contralateral eye" design, the Sponsor was notified that a "totally randomized by-eye" study design was preferred for the trials. This design included randomizing subjects such that one group received active drug in both eyes, one group received placebo in both eyes, and one group received active drug in one eye and placebo in the contralateral eye. Thus, the two subsequent CAC trials were conducted using this totally randomized by-eye design. During discussions dated February 6, 2002, the Sponsor was notified that efficacy would be based on data from all study patients in the by-eye studies—not on the subset of patients who received active/placebo drops in contralateral eyes.

In discussions with the Agency dated October 10, 2001, the Sponsor was informed that the drug should demonstrate clinically meaningful efficacy; this was defined as superiority over vehicle by at least 1 unit of an approved grading system for the majority of time points measured for each endpoint.

1.3. Other Relevant Information

Olopatadine hydrochloride ophthalmic solution 0.2% is not currently marketed in any country. It has not been withdrawn from marketing in any country due to safety and efficacy concerns either.

1.4. Important Issues with Pharmacologically Related Agents

Orally administered drugs with anti-histamine effects, terfenadine and astemizole, were withdrawn from the market after post-marketing studies revealed that these drugs delayed cardiac repolarization. This delay is manifest as a prolongation of the QT interval on an electrocardiogram, and creates a potentially dangerous electrophysiological environment that permits the development of cardiac arrhythmias. These effects are dose-related and have not been shown to occur with ophthalmologically administered products. The Sponsor conducted one study using the oral dosage form of the drug, and demonstrated that olopatadine had no effect on QT interval when compared to placebo.

2. Significant Findings from Chemistry, Animal Pharmacology and Toxicology, and/or Microbiology

No clinically relevant findings noted.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1. Pharmacokinetics (PK)

The drug product does not produce systemically measurable blood levels. The assay limit of detection is 0.5 ng/mL.

3.2. Pharmacodynamics (PD)

The drug product does not produce systemically measurable blood levels. The assay limit of detection is 0.5 ng/mL.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Sources of Clinical Data

Clinical study reports in Volumes 1.1-1.3, 1.6-1.43 of NDA 21-545.

4.2. Overview of Clinical Trials

The Sponsor studied drug efficacy in one multi-center environmental trial, and in three "conjunctival allergen challenge" (CAC) trials, each performed at a different center. Two other trials were conducted to demonstrate safety: one with the topical formulation and the other with an oral formulation of the study drug.

On the following page is a table summarizing all 6 trials.

#	Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing Duration	Total # Subjects Exposed to Active Drug
1	C-00-36 (contralateral eye designed CAC study)	Prospective, contralateral eye randomized, placebo-controlled, double-masked	Subjects with history of allergic conjunctivitis and positive skin prick test	Olopatadine 0.2% Placebo	1 drop 1 drop	Visit 3 (onset-of-action) Visit 4 (24hr duration-of-action) Visit 5 (16hr duration-of-action) (3 non-consecutive days)	45
2	C-01-18 (totally randomized by eye designed CAC study)	Prospective, randomized, placebo-controlled, double-masked	Subjects with history of allergic conjunctivitis and positive skin prick test	Olopatadine 0.2% Placebo	1 drop 1 drop	Visit 3 (onset-of-action) Visit 4 (16hr duration-of-action) (2 non-consecutive days)	24
3	C-01-100 (totally randomized by eye designed CAC study)	Prospective, randomized, placebo-controlled, double-masked	Subjects with history of allergic conjunctivitis and positive skin prick test	Olopatadine 0.2% Placebo	1 drop 1 drop	Visit 3 (16hr duration-of-action) Visit 4 (onset-of-action) (2 non-consecutive days)	69
4	C-01-10 (environmental study)	Prospective, randomized, placebo-controlled, double-masked, parallel group	Patients ≥ 10 years of age with history of allergic conjunctivitis, positive skin prick test, and positive CAC for fall (ragweed) allergens	Olopatadine 0.2% Placebo	1 drop QD 1 drop QD	12 weeks	119
5	C-01-77 (6-week safety study)	Prospective, randomized, placebo-controlled, double-masked, parallel group	Subjects ≥ 3 years of age with asymptomatic eyes	Olopatadine 0.2% Placebo (2:1 randomization)	1 drop QD 1 drop QD	6 weeks	236
6	C-00-23 (PK/safety study)	Prospective, randomized, placebo-controlled, double-masked, two-way crossover	Subjects 18 to 75 years of age	5-mg orally dosed olopatadine Placebo	1 dose BID 1 dose BID	2.5 days (5 doses total)	(117)*
						Total Subject Exposure to Olopatadine 0.2%	**493**

* In this table, the subjects in C-00-23 are not included with the total number of subjects exposed to Olopatadine 0.2% as these subjects were exposed to 5-mg, oral doses of olopatadine hydrochloride.

There were several differences across trials. The environmental study (C-01-10) assessed the *frequency* of ocular itching and ocular redness as its primary efficacy variable (unlike the 3 CAC studies, which measured *severity*). In further contrast with the CAC studies, the environmental trial and the topical safety trial involved prolonged exposure to the topical formulation and included children.

Basic Differences Across All Clinical Trials

	6 CLINICAL TRIALS			
	CAC (3)	**Environmental**	**Safety—Topical**	**Safety—Oral**
TESTED:				
Efficacy	Yes	Yes	No	No
Long-term daily exposure (≥ 6-weeks)	No	Yes	Yes	No
Children	No	Yes	Yes	No
Primary endpoint measure of signs/symptoms	Severity	Frequency	N/A	N/A

Study Population Characteristics Across the 5 Topical Trials

		CAC #1 (C-00-36)	CAC #2 (C-01-18)	CAC #3 (C-01-100)	Environ. (C-01-10)	Safety (C-01-77)
Age	Mean (yrs.)	42.27	38.06	39.2	37.3	26.9
	Std dev.	11.0	9.83	12.5	12.4	17.0
	N	45	36	92	240	351
	Min (yrs.)	19	20	20	10	3
	Max (yrs.)	70	58	67	66	74
	0-27 days	NE*	NE	NE	NE	NE
	28 days-23 month	NE	NE	NE	NE	NE
	2-11 yrs.	NE	NE	NE	7	88
	12-17 yrs.	NE	NE	NE	9	38
	18-64 yrs.	43	36	90	221	218
	≥ 65 yrs.	2	0	2	3	7
Gender	Male	18	16	38	94	158
	Female	27	20	54	146	193
Race	Caucasian	42	33	85	215	233
	Black	2	0	3	17	34
	Asian	1	0	1	1	5
	Hispanic	0	0	3	0	77
	Other	0	3	0	7	2
Iris Color	Brown	15	19	49	90	188
	Hazel	10	6	16	37	53
	Green	2	2	10	24	26
	Blue	17	9	17	85	83
	Grey	1	0	0	3	1
	Missing	0	0	0	1	0

*NE: not eligible for study participation.

Reviewer comments: *Gender and common iris colors were relatively well-represented.*

4.3. Postmarketing Experience

Olopatadine 0.2% is not currently marketed in any country. However, olopatadine hydrochloride ophthalmic solution 0.1% is currently marketed in over 30 countries, including the U.S. and Canada (as Patanol), and has recently been approved in the European Union (as Opatanol) for the treatment of the signs and symptoms of allergic conjunctivitis when dosed twice-daily. Olopatadine HCl is marketed for oral use (2.5 or 5 mg twice-daily) in the treatment of allergic rhinitis, urticaria, and itching resulting from skin diseases such as eczema/dermatitis, prurigo, etc.

Since the product's approval in the United States in December 1996, and through December 2001, over units have been sold. During the time period from January 1, 1997, to December 31, 2001, three hundred ten spontaneous adverse event reports associated with the use of Patanol have been received.

The most commonly reported adverse events included ocular discomfort, ocular hyperemia, ocular pain, ocular edema, ocular irritation, lid edema, and blurred vision; non-ocular events included no drug effect, headache, and reaction aggravation.

4.4. Literature Review

The medical reviewer conducted a Pubmed search to supplement the submitted review of the relevant literature.

5. Clinical Review Methods

5.1. Describe How Review was Conducted

All submitted studies were reviewed separately and subsequently assessed in aggregate. Efficacy results from the 2 CAC studies using "by-eye" randomization were considered with higher weight than results from the CAC study with a contralateral eye design. Published literature was relied upon to supplement the validity of the conclusions drawn. Safety data was primarily derived from the 2 long-term (environmental and topical safety) trials.

5.2. Overview of Materials Consulted in Review

In addition to the originally submitted electronic and paper copies of NDA 21-545, IND 60,911 was also consulted (olopatadine ophthalmic solution 0.2%), as well as the medical officer's review from NDA 20-688 (olopatadine ophthalmic solution 0.1%).

5.3. Overview of Methods Used to Evaluate Data Quality and Integrity

No special methods used.

5.4. Were Trials Conducted in Accordance with Accepted Ethical Standards

All trials were conducted under the review of approved Institutional Review Board committees. Investigators used an informed consent form that was appropriate for the respective trials.

5.5. Evaluation of Financial Disclosure

Ophthalmic Research Associates managed most of the clinical studies and received a fee for its service. There is no evidence that the monetary payments were directly contingent upon certain study results.

6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

The drug demonstrated efficacy in reducing ocular itching in patients with allergic conjunctivitis at onset and at 16 hours after dosing relative to placebo.

6.2. General Approach to Review of the Efficacy of the Drug

Efficacy data from 3 CAC studies and one environmental study was reviewed.

6.3. Detailed Review of Trials

In all 4 efficacy studies, endpoints and their respective grading criteria were described prior to the initiation of the trials and were not altered thereafter. A summary review of the 3 CAC studies is presented first.

CAC Studies:

The conjunctival allergen challenge (CAC) model attempts to standardize the inciting allergic response and the pertinent variables used to measure it. The Sponsor used the CAC model to test the drug's efficacy at onset of action (CAC 27 minutes after instillation), and at duration of action (CAC 16 hours after instillation) to validate once-daily dosing.

Reviewer comments: *Using the CAC model, in conjunction with appropriate inclusion/exclusion criteria, adequate demographic representation, and data from other studies, results may be extrapolated to the overall target population. It is a known model system available for allergic conjunctivitis and has been validated as acceptable for regulatory purposes in past clinical trials.*

The 3 CAC trials were similar in many respects, with a few notable differences.

Overview of CAC Trials

Parameters	C-00-36	C-01-18	C-01-100
Study Design	Double-masked, vehicle controlled	Same as C-00-36	Same as C-00-36
Randomization	Contralateral eye randomized	Randomized by eye	Randomized by eye
Subjects	Adult volunteers with a history of allergic conjunctivitis, positive skin-prick test, and successful baseline CAC	Same as C-00-36	Same as C-00-36
Treatment Groups	Drug / Vehicle=45	Drug / Drug =12 Drug / Vehicle =12 Vehicle / Vehicle =12	Drug / Drug =23 Drug (OS) / Vehicle (OD) =23 Vehicle (OS) / Drug (OD) =23 Vehicle / Vehicle =23
Study Visits	1=Screening 2=Confirmatory CAC 3=Onset of action (27 min CAC) 4=Duration of action (24 hr CAC) 5=Duration of action (16hr CAC)	1=Screening 2=Confirmatory CAC 3=Onset of action (27 m CAC) 4=Duration of action (16h CAC)	1=Screening 2=Confirmatory CAC 3=Duration of action (16h CAC) 4=Onset of action (27 m CAC)
Dosing regimen	1 drop at Visits 3, 4, and 5	1 drop at Visits 3 and 4	1 drop at Visits 3 and 4
Post-CAC Assessment Time points	3, 10, 20 minutes – all parameters	3, 10, 20 minutes – all parameters	3, 5, 7 minutes – itching & redness 10, 15, 20 minutes – all other parameters
Primary endpoints	Itching AND Conjunctival Redness	Itching	Itching

Reviewer comments: *Note that during the Duration of Action (16 hour) Visits, drops were administered in the evening and CAC was performed the following morning. It is more likely that patients would instill this drug during waking hours (i.e., one drop in the morning to last all day). It is unclear whether sleeping for a large portion of the 16 hours has an effect on drug efficacy at the time of CAC.*

Basic Inclusion Criteria for CAC Studies:

1. Signed informed consent.
2. Adults, eighteen (18) years of age or older.
3. History of a seasonal allergic conjunctivitis within the previous two seasons.
4. Positive allergic history to cat hair/dander, ragweed, dust mites, grasses, and/or trees.
5. Corrected visual acuity of 0.6 logMAR or better in each eye as measured by ETDRS chart.
6. Positive diagnostic test (skin test) for allergic disease within the past 24 months.
7. Positive challenge results (≥2.0 itching in each eye and ≥2.0 redness in at least one of the three vessel beds [ciliary, conjunctival, episcleral] in each eye) at Visits 1 and 2.
8. Subjects receiving anti-allergy injections may have been enrolled, if their dosage remained stable for 3 months before Visit 1 and no changes are planned during the study.
9. Willing to avoid contact lens wear within 72 hours before Visit 1 and throughout the study.

Basic Exclusion Criteria for CAC Studies

1. Contraindications or hypersensitivity to the use of the study medications or their components (e.g., benzalkonium chloride (BAC), disodium EDTA, and povidone).
2. A known history or presence of dry eye syndrome, or presence of blepharitis, follicular conjunctivitis, iritis or preauricular lymphadenopathy, or any other ophthalmic abnormality.
3. Presumed or actual ocular infection (bacterial, viral or fungal) or history of ocular herpes in either eye as determined by subject history and/or examination.
4. History of moderate to severe allergic asthma reactions to the antigens used in this study.
5. Required use of any other topical ocular medication(s) during the study (other than the dose of an anti-allergic agent given at the office to relieve any immediate discomfort caused by the CAC procedure).
6. Any significant illnesses that could have interfered with the study, particularly any autoimmune disease such as rheumatoid arthritis, which may be associated with dry eye syndrome.
7. Subjects who were on systemic medication(s), used on a chronic dosing regimen, and who have been on this medication for less than one (1) month or who had changed dosage of this medication within the month prior to Visit 1.
8. Evidence of signs/symptoms of allergic conjunctivitis (greater than a score of 1 for redness in any of the three vessel beds [ciliary, conjunctival, episcleral] and/or any itching) at any baseline exam at any visit. Subjects who presented with signs/symptoms of allergic conjunctivitis as described above were discontinued from the study.
9. Therapy with another investigational agent within thirty (30) days of Visit 1, or during the study.
10. Women who were pregnant, nursing, or of childbearing potential who were not utilizing highly effective birth control measures.

Reviewer comments: *The Sponsor appropriately selected the subset of adult patients likely to benefit from the drug.*

Note that screening and confirmatory entrance criteria (≥ 2.0 OU for itching and redness) are lower than those in the olopatadine 0.1% CAC studies (i.e., C-96-79 and C-96-82 used ≥ 3.0 OU threshold). Therefore, patients with lower allergen sensitivities and milder allergic reactions were included here.

The grading criteria for itching, redness and chemosis were identical across all CAC studies. There were minor variations in the grading criteria used for other secondary endpoints. Only the first CAC trial measured mucous discharge and inflammation of the cornea, anterior chamber and iris.

CAC Grading System for Signs and Symptoms of Allergic Conjunctivitis

(taken from C-00-36, p.45/499; subjects were not allowed to rub their eyes)

Itching (as judged by patient)	
0.0	None
0.5	Intermittent tickling sensation; involving just corner of eye
1.0	Intermittent tickling sensation; involving more than corner of eye
1.5	Intermittent, all-over tickling sensation
2.0	Mild continuous itch (localized); no desire to rub
2.5	Moderate, diffused, continuous itch; desire to rub
3.0	Severe itch; desire to rub
3.5	Severe itch; improved with minimal rubbing
4.0	Incapacitating; requires significant eye rubbing
Regional Redness* (Ciliary, Episcleral, Conjunctival)**	
0.0	None. A normal quiet eye
1.0	Mild. Slightly dilated blood vessels. Color of vessels is typically pink.
2.0	Moderate. More apparent dilation of blood vessels. Color is redder.
3.0	Severe. Numerous and obviously dilated vessels. Color is deep red.
4.0	Extremely Severe. Large numerous dilated vessels. Severe deep red color.
Chemosis	
0.0	None
0.5	Detectable only by slit lamp; slight separation of conjunctiva from sclera
1.0	Detectable only by slit lamp, definite separation of conjunctiva from sclera
1.5	Detectable with penlight illumination; localized microchemosis
2.0	Visible in normal room light; more diffuse edema
2.5	Conjunctiva elevated to and at the limbus; very diffuse
3.0	Conjunctival billowing at the limbus; very diffuse and noticeable
3.5	Large pocket of fluid localized anywhere in conjunctiva
4.0	Severe overall ballooning of conjunctiva
Eyelid Swelling	
0.0	None
0.5	Any detectable change in lids
1.0	Edema in one quadrant of lids
1.5	Edema in two quadrants of lids
2.0	Definite alteration in lid folds
2.5	Loss of lid folds
3.0	Edema to lash margin
3.5	Ptosis
4.0	Lid closure
Tearing*	
0.0	None
1.0	Mild. Eyes feel slightly watery
2.0	Moderate. Blows nose occasionally
3.0	Severe. Tears rolling down cheeks
Mucus Discharge	
0.0	Absent
1.0	Present
Cornea	
0	Absence of active inflammation
1	Presence of active inflammation
Anterior chamber, Iris	
0	Absence of active inflammation
1	Presence of active inflammation

*0.5 increments were used when response was in between two grading definitions.

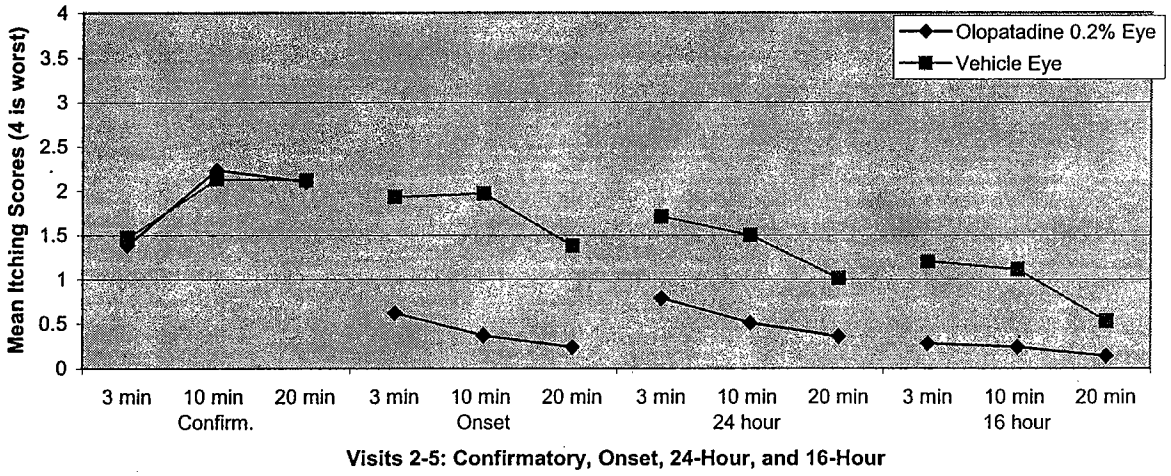
**Reference photos were used to determine redness scores and were the same for all CAC studies.

Reviewer comments: *Descriptions for each grade of the 4-point scale, particularly for the lower itching scores, are designed such that a difference in a score of 1 translates into a clinical benefit that is marginal at best. Further, by entering patients with lower threshold baseline CAC scores (mentioned above), the enrolled population is biased toward those lower grading scores, such that even the placebo mean itching scores are never higher than 2 in any of the CAC studies.*

APPEARS THIS WAY
ON ORIGINAL

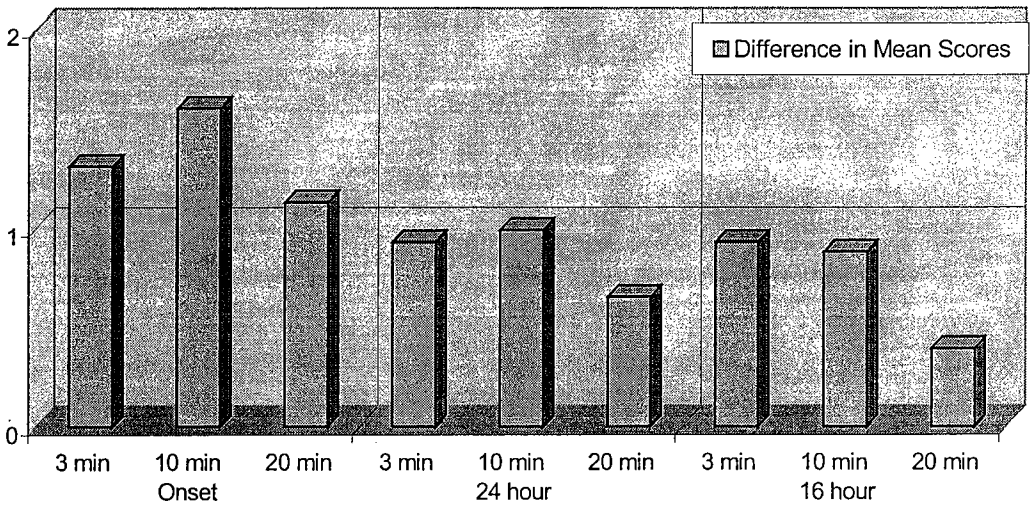
Efficacy Endpoint Outcomes of CAC Studies
Itching results from the 3 CAC studies, in chronological order:

Study C-00-36: Itching Scores (mean, intent to treat, contralateral eye), p.93/499



Visits 2-5: Confirmatory, Onset, 24-Hour, and 16-Hour

Study C-00-36: Difference in Mean Itching Score Between Drug and Placebo

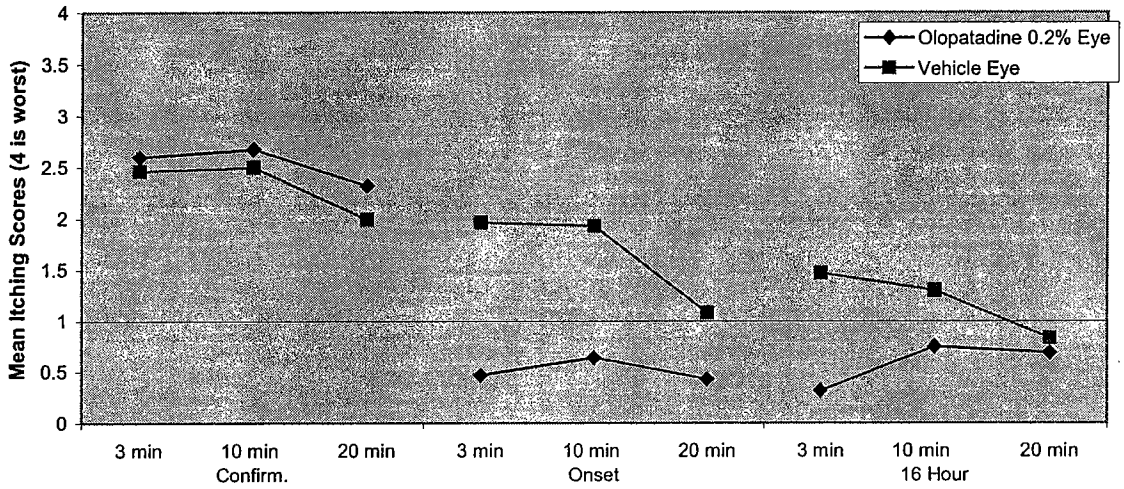


Visits 3-5: Onset, 24-Hour, and 16-Hour

Reviewer comments: *Efficacy in the —— itching is demonstrated; the difference in mean itching score is close to or exceeds one (1) at most time points, with statistical significance at all time points.*

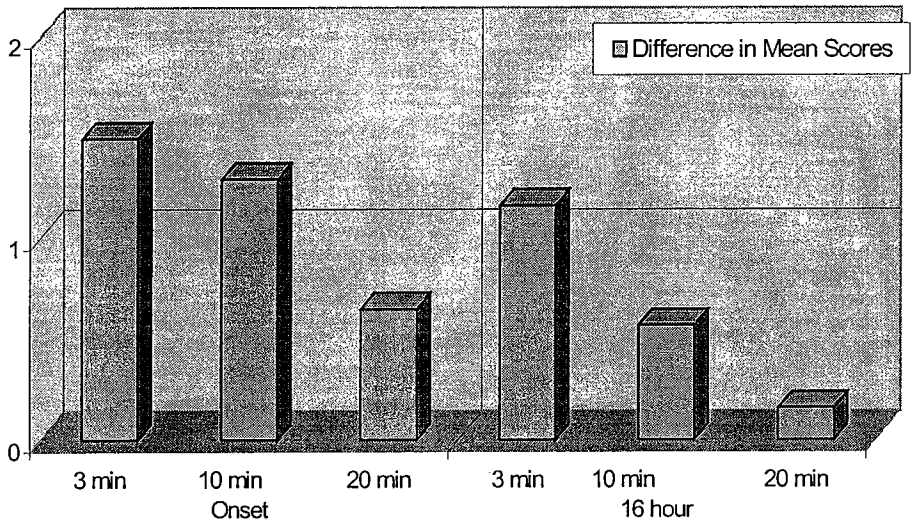
Effects at Onset are more convincing than at 16-hours, where both the vehicle and drug itching scores are relatively low. Scores from evaluations taken at three (3) and ten (10) minutes after CAC are more convincing than those taken at twenty (20) minutes, where the itching scores in both drug and placebo are much lower.

Study C-01-18: Itching Scores (mean, intent to treat, by-eye), p.109/684



Visits 2-4: Confirmatory, Onset, and 16-Hour

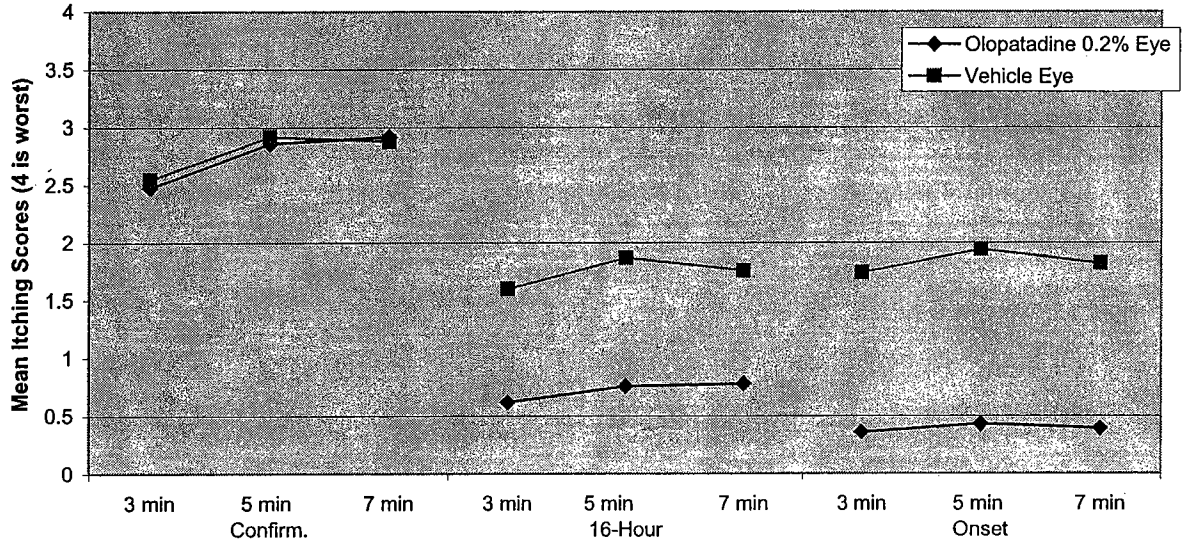
Study C-01-18: Difference in Mean Itching Score Between Drug and Placebo



Visits 3 & 4: Onset, 16-Hour

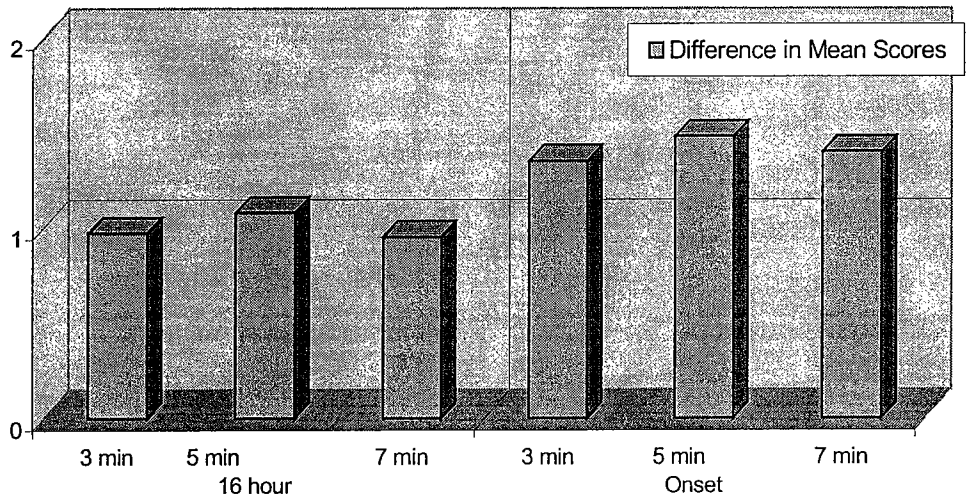
Reviewer comments: *Efficacy in the — itching is not demonstrated at the primary inference time point of 10 minutes post-CAC during the 16-hour visit, as the difference in mean itching score is not close to one (1). Difference in mean scores from the per-protocol data set are similar to those from the intent-to-treat analysis (0.57 in the ITT, 0.53 in the PP set at 10 minutes post-CAC) and smaller by 20 minutes.*

Study C-01-100: Itching Scores (mean, intent to treat, by-eye), p.114/612



Visits 2-4: Confirmatory, 16-Hour, Onset

CAC C-01-100: Difference in Mean Itching Score Between Drug and Placebo



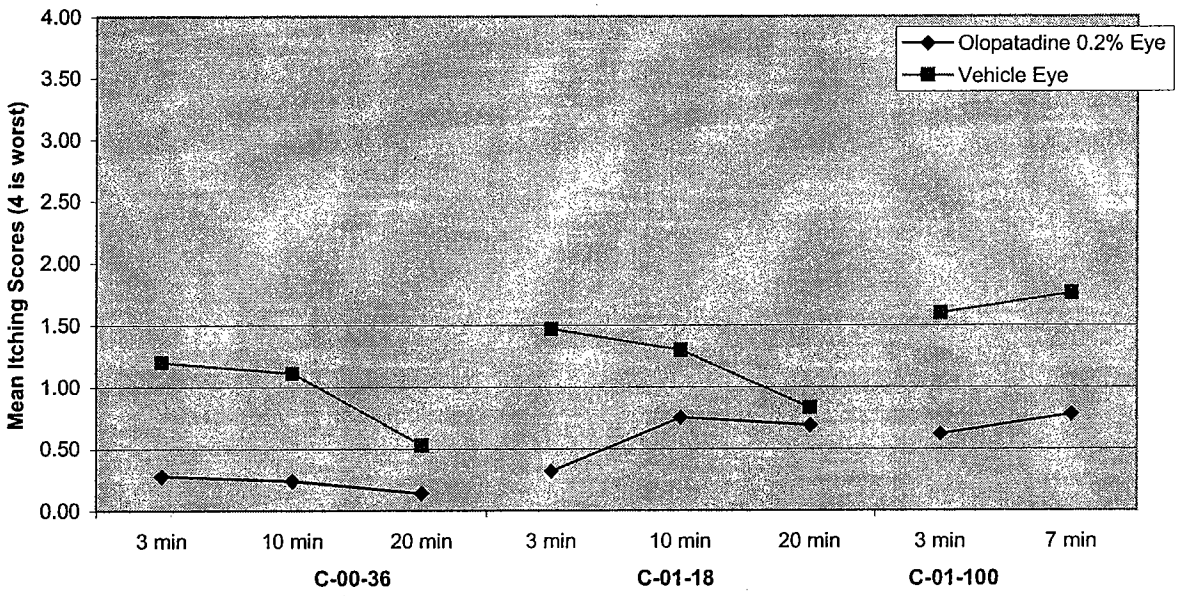
Visits 3 & 4: 16-Hour, Onset

Reviewer comments: *Efficacy in the __ itching at the duration of action (16-hour) visit is demonstrated at all post-CAC time points, as the difference in mean itching scores is close to one (1). Scores were recorded at 3, 5, and 7 minutes.*

Reviewer comments: *In C-00-36 and C-01-18, mean itching scores in the vehicle group steadily decreased with each subsequent visit. An explanation for this result is uncertain; the Sponsor speculates that this diminution of response is attributed to a refractory effect resulting from multiple allergen stimuli to the conjunctival mast cells over short time intervals. However, results in study C-01-100 contradicted this trend. Further, only one drop was administered at each visit, and visits were separated by 14 and 28 days, which should provide adequate time for washout.*

It is instructive to visualize and compare the itching results across the 3 CAC studies at the 16-hour visit, as this is the visit that assesses daylong efficacy. Note that in C-01-100, assessments were taken at 7 minutes, not at 10 and 20 minutes.

Itching Scores 16-Hours After Instillation; All 3 CAC Studies



Reviewer comments: *When tested 16-hours after instillation, the difference in itching scores appears to diminish after 7 minutes post-CAC.*

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical-_____

CAC Studies, Listed Individually:

Sponsor's protocol: C-00-36

Title: A Placebo-Controlled Study of Olopatadine QD in the Treatment of Allergic Conjunctivitis Using the Conjunctival Allergen Challenge (CAC) Model [conducted (10/27/00) to (1/12/01)]

Brief Description of Visits:

Visit 1: Screen
Subjects were screened for eligibility. The antigen and concentration that elicited a positive response was determined for each subject and was used at all subsequent visits for the "conjunctival allergen challenge" (CAC). A positive response was defined as redness (in at least one of the three vessel beds - conjunctival, episcleral, or ciliary) and itching scores of 2 or greater in each eye, within 10-minutes post-challenge.

Visit 2: Confirmatory
Investigators conducted a post-CAC assessment to confirm the subject's eligibility based upon the previously determined antigen and titer. Investigators then assessed ocular signs and symptoms at 3, 10, and 20 minutes and a positive result was defined as having redness (in at least one of the three vessel beds) and itching scores of 2 or greater in each eye, during at least one assessment time-point.

Visit 3: Onset of Action
- Randomized patient to one of the three groups
- Instilled one drop of drug, one drop of vehicle to each eye, respectively
- Administered CAC 27 minutes after drop
- Assessed signs/symptoms at 3, 10, and 20 minutes after CAC

Visit 4: Trough
- Administered CAC 24 hours after drop
- (otherwise same as Visit 3)

Visit 5: Duration of Action
- Administered CAC 16 hours after drop (the following morning)
- (otherwise same as Visit 3)

Study Plan

Procedures	Visit 1: Screening		Visit 2: Confirmatory Minimum of 7 Days After Visit 1		Visit 3: 27 Minute Minimum of 14 Days After Visit 2		Visit 4: 24 Hour Minimum of 14 Days After Visit 3		Visit 5: 16 Hour Minimum of 28 Days After Visit 4	
	Pre-CAC	Post-CAC	Pre-CAC	Post CAC (3, 10, 20 min)	Pre-CAC	Post CAC (3, 10, 20 min)	Pre-CAC	Post CAC (3, 10, 20 min)	Pre-CAC	Post CAC (3, 10, 20 min)[d]
Informed consent	X									
Medical history	X									
Pregnancy test[a]	X									X
Diagnostic Test (skin prick)	X									
Visual Acuity	X		X		X		X		X[b]	
Fundus Exam (undilated)	X								X[b]	
Ocular Sx: itching, tearing	X	X	X	X	X	X	X	X	X	X
SLE: cornea, A/C, iris	X		X		X		X		X[b]	
SLE: redness, chemosis, lid swelling	X	X	X	X	X	X	X	X	X	X
CAC	X		X		X		X		X	
Assign Randomization #					X					
Instill Drug[c]					X		X		X	
Record Adverse Events						X	X	X	X	X
Exit Form										X

[a]If necessary.
[b]Visual acuity and slit lamp examinations were performed pre- and post-dose (the post-dose exams were within 60 minutes prior to CAC) on Visit 5. Fundus examinations were performed post-dose only (again, within 60 minutes prior to the CAC) on Visit 5.
[c]Subjects meeting all qualifying criteria were randomized to receive either Olopatadine 0.2% or placebo in each respective eye.
[d]Drops were administered in the evening and post-CAC assessments made the following morning.

Statistical Plan:
With 45 subjects, the study had 90% power to detect differences between study drug and contralateral placebo greater than 0.5 unit in itching and conjunctival redness assuming a standard deviation = 1 (based on one-sample t-test with two-sided alpha = 0.05).

Reviewer comments: *Clinical significance was suggested by the FDA to be a minimum difference in mean scores of 0.5 unit at every time point, and of 1.0 at the majority of time points. This study was adequately powered, though the basis for the selected standard deviation was not explained.*

Subject Disposition:

Investigator

Number	Investigator	Address	Patients
1957	Jack V. Greiner, O.D., D.O., Ph.D.	Ophthalmic Research Associates 863 Turnpike Street North Andover, MA 01845 (978) 685-8900	45

Demographics

AGE	
Mean	42.3
Std	11
Min	19
Max	70
N	45

	N	%		N	%
AGE GROUP			**Iris Color**		
18-64	43	95.5	Brown	15	33.3
>=65	2	4.5	Hazel	10	22.2
			Green	2	4.5
SEX			Blue	17	37.8
Male	18	40	Gray	1	2.2
Female	27	60			
RACE					
Caucasian	42	93.3			
Black	2	4.5			
Asian	1	2.2			

Discontinued Subjects (p.53/499)
Of the 45 subjects enrolled, 5 did not complete the study (see chart, below). Three were lost-to-follow-up (#120, 144, 145), one subject (#124) decided for personal reasons not to continue (unrelated to adverse events), and one subject (#105) was discontinued at Visit 4 (24-hr. CAC visit) because of ocular redness >1 at the baseline exam prior to the CAC that day (below).

Discontinued Subjects

Subject #	Age	Sex	Race	Visit #	Reason for D/C
1 (#105)	56	F	C	4,5	Redness >1 prior to CAC
2 (#120)	37	F	C	4,5	Missed CAC; (lost to follow-up)
3 (#124)	39	F	C	5	Subject decision; unrelated to AE
4 (#144)	50	M	C	5	Missed CAC; (lost to follow-up)
5 (#145)	32	F	C	4,5	Missed Visit; (lost to follow-up)

Reviewer comments: *No patients discontinued for health-related reasons.*

Unscheduled Visits:
One subject (#133) presented with a subconjunctival hemorrhage exactly one week after visit #4 in the eye that received drug. This did not preclude the subject's continuation of the study.

Protocol Deviations (p.55/499)
There were eleven patients who returned for one of their visits one day early; none more than once. There were five patients who were late for their CAC exams, but none by a significant amount of time. The five patients who discontinued the study (table, above) did not have an exit fundus exam. There were no treatment compliance issues other than missed visits.

Conclusions Regarding Efficacy Data in Study:

Reviewer comments:
Of the two primary endpoints, efficacy in the [redacted] itching with once-daily dosing is demonstrated both at onset (27 minutes) and day-long duration (16-hour) time points, though data in the latter time point is less convincing. In fact, it is counter-intuitive and unclear as to why the data demonstrates a greater drug effect at 24-hours than at 16-hours.

Sponsor's Protocol: # C-01-18

Title: A Placebo-Controlled Study of Olopatadine QD in the Treatment of Allergic Conjunctivitis Using the Conjunctival Allergen Challenge (CAC) Model [Conducted 5/12/01 to 7/14/01]

Statistical Plan:

With 30 eyes per group (drug/placebo=10 patients, drug/drug=10 patients, and placebo/placebo=10 patients), the study had more than 90% power to detect a difference between Olopatadine 0.2% and placebo greater than 1 unit in itching, assuming a standard deviation = 1 (based on two-sample t-test with two-sided alpha=0.05).

Reviewer comment: *The Division defined clinical significance as a minimum difference in mean scores of 0.5 unit at all time points and of 1.0 at the majority of time points. This study was adequately powered, though the basis for the selected standard deviation was not explained.*

Subject Disposition:

Investigator

Number	Investigator	Address	Sub-investigator and Study Coordinator	Patients Enrolled
2873	Gerald P. Spindel, M.D.	Spindel Eye Assoc. Parkland Professional Bldg 43B Birch Street, Ste 5 Derry, NH 03038 (603) 434-4193	—	36

Study Monitor:
Clinical Research Group, Ltd
Kathleen Ripp, R.N., M.S.
7 Greenway View Trail
Kingwood, TX 77339

Demographics (Intent-to-treat):

Demographic Statistics by Treatment Group (Intent-to-Treat); p107/684

	Drug / Drug	Drug / Placebo	Placebo / Placebo	Total	p-value [a]
Age					
Mean	37.58	40.17	36.42	38.06	0.646
Std	9.31	11.82	8.55	9.83	
N	12	12	12	36	
Min	21	20	28	20	
Max	54	58	58	58	

[a] Based on analysis of variance

	Drug / Drug		Drug / Placebo		Placebo / Placebo		Total		
	N	%	N	%	N	%	N	%	p-value [b]
Age									
18-64	12	100.0	12	100.0	12	100.0	36	100.0	
Sex									0.894
Male	6	50.0	5	41.7	5	41.7	16	44.4	
Female	6	50.0	7	58.3	7	58.3	20	55.6	
Race									0.758
Caucasian	11	91.7	12	100.0	10	83.3	33	91.7	
Other	1	8.3	.	.	2	16.7	3	8.3	
Iris Color									0.908
Brown	5	41.7	6	50.0	8	66.7	19	52.8	
Hazel	3	25.0	2	16.7	1	8.3	6	16.7	
Green	1	8.3	1	8.3	.	.	2	5.6	
Blue	3	25.0	3	25.0	3	25.0	9	25.0	

[b] Based on chi-square or Fisher's Exact Test

Reviewer comments: *The racial homogeneity of the study group does not reflect the U.S. population. The distribution of iris color will contribute to the assessment of drug effect with regard to ocular pigment.*

Of 36 patients enrolled, 4 subjects discontinued the study before the 16-hour CAC visit; they were described as lost to follow up (below).

Discontinued Subjects (p.613/684)

Treatment: (vehicle or drug)	Patient	Age	Sex	Race	Reason	Missed Visit #
V-V	152	33	F	C	LTFU[a]	4
V-V	153	32	F	C	LTFU	4
D-D	166	28	M	C	LTFU	4
V-V	174	31	M	C	LTFU	4

[a] Lost to follow up

Reviewer comments: *Three of four discontinued patients were on vehicle-only. No patients discontinued for health-related reasons.*

Protocol Deviations (p.63/684)
One subject (#167) in the placebo/placebo treatment group was excluded from the per protocol efficacy analysis because the subject took Naproxen, an anti-inflammatory medication, during the study.

There were two patients who were late for their CAC exams at visit #4, but none by a significant amount of time. The four patients who discontinued the study did not have an exit eye exam.

Conclusions Regarding Efficacy Data in Study

Reviewer comments: *At the primary inference time point, efficacy in the — itching was demonstrated at onset (27 minutes), but not at 16 hours after instillation. These results do not support a claim for daylong efficacy. However, itching scores that were measured immediately (3 minutes) after CAC did demonstrate efficacy at the 16-hour visit.*

Sponsor's Protocol # C-01-100

Title: A Vehicle-Controlled Study of Olopatadine QD in the Treatment of Allergic Conjunctivitis Using the Conjunctival Allergen Challenge (CAC) Model [Conducted 2/10/02 to 4/7/02]

Statistical Plan:

With 80 eyes receiving Olopatadine 0.2% and 80 eyes receiving placebo (drug/placebo=20, placebo/drug =20, drug/drug =20, and placebo/placebo=20), the study had more than 99% power to detect a difference between Olopatadine 0.2% and placebo greater than 1 unit in itching assuming a standard deviation = 1 (based on two-sample t-test with two-sided alpha=0.05).

Reviewer comments: *The Division defined clinical significance as a minimum difference in mean scores of 0.5 unit at all time points and of 1.0 at the majority of time points. This study was adequately powered, though the basis for the selected standard deviation was not explained.*

Subject Disposition:

Investigator:

Number	Investigator	Sub-investigators and Study Coordinator	Patients Enrolled
3456	Clifford Michaelson, M.D. 198 Massachussetts Ave. North Andover, MA 018745 (978) 685-8900		92

Demographic Statistics by Treatment Group (Intent-to-Treat); p71/612

	Drug / Drug	Drug / Placebo	Placebo / Placebo	Placebo / Drug	Total	p-value [a]
AGE						
Mean	38.4	36.0	42.3	41.1	39.5	0.3270
Std	13.7	11.2	13.4	11.0	12.5	
N	23	22	23	22	90	
Min	20	21	21	25	20	
Max	63	60	66	67	67	

[a] Based on analysis of variance

	Drug / Drug		Drug / Placebo		Placebo / Placebo		Placebo / Placebo		Total		
	N	%	N	%	N	%	N	%	N	%	p-value [b]
Age											0.8679
18-64	23	100	22	100	22	95.7	21	95.5	88	97.8	
>=65	.	.	.	.	1	4.3	1	4.5	2	2.2	
Gender											0.5329
Male	11	47.8	9	40.9	10	43.5	6	27.3	36	40	
Female	12	52.2	13	59.1	13	56.5	16	72.7	54	60	
Race											0.7849
Caucasian	22	95.7	20	90.9	21	91.3	20	90.9	83	92.2	
Black	1	4.3	1	4.5	1	4.3	.	.	3	3.3	
Asian	.	.	.	.	1	4.3	.	.	1	1.1	
Hispanic	.	.	1	4.5	.	.	2	9.1	3	3.3	
Iris Color											0.3941
Brown	12	52.2	10	45.5	15	65.2	12	54.5	49	54.4	
Hazel	4	17.4	5	22.7	3	13	2	9.1	14	15.6	
Green	4	17.4	.	.	2	8.7	4	18.2	10	11.1	
Blue	3	13	7	31.8	3	13	4	18.2	17	18.9	

[b] Based on chi-square or Fisher's Exact Test

Of the 92 enrolled subjects, 7 discontinued the study (below):

Discontinued Subjects (p.65/612)

Treatment (Vehicle or Drug)	Patient	Age	Sex	Race	Reason	Missed Visits
D-V	3003	28	M	C	Patient decision	4 & exit
D-D	3012	23	F	C	LTFU*	4; exit done 5 days later
D-V	3021	36	F	C	LTFU	4 & exit
V-D	3028	41	F	C	Patient decision	4 & exit
V-D	3041	47	F	C	Did not meet criteria	4
D-V	3044	22	M	C	LTFU	4 & exit
V-D	3090	21	M	C	LTFU	4

* Lost to follow up

Two (#3003, 3090) of the above 7 patients were eligible for the safety analysis but ineligible for both the intent to treat and per protocol analyses because they discontinued without ever having an on-therapy CAC evaluation (they both had drops instilled during Visit 3 but missed the CAC and subsequent visits). Patient #3041 was discontinued for baseline itching at Visit 4.

Reviewer comments: *Six of seven discontinued patients were in the contralateral group. No patients discontinued for health-related reasons.*

Protocol Deviations (p.67/612)

The first five patients (#3001, 3002, 3003, 3004, 3005) missed Visit 3 evaluations because the investigator did not perform a 16-hour CAC. Three female patients missed their exit exams and did not have exit pregnancy tests (#3012, 3021, 3028). Several other minor deviations were present.

Reviewer comments: *It seems odd that the investigator failed to perform a 16 hour CAC in the first five patients of the study, since the CAC was intrinsic to the study design. The Sponsor does not elaborate as to what the reason was for this omission.*

Conclusions Regarding Efficacy Data in Study

Efficacy in the — itching was demonstrated at onset (27 minutes) and at 16 hours after instillation. These results do support a claim for daylong efficacy in the — itching in patients with allergic conjunctivitis.

Environmental Study:

Sponsor's Protocol # C-01-10

Title: A Comparative Study of Olopatadine QD vs. Placebo in Patients with Seasonal Allergic Conjunctivitis or Rhinoconjunctivitis; [conducted (7/27/01) to (12/01/01)]

Objective/Rationale:
The primary objective of this study was to demonstrate that Olopatadine 0.2% is superior to placebo in the treatment of the

Overall Design:
This study was a 12-week, double-masked, randomized, placebo controlled, parallel group, multi-center, environmental study comparing the efficacy of drug vs. placebo in the treatment

Population and Procedures:
The study population consisted of subjects 10 years of age or older, of both genders and any race, currently not using contraindicated topical or systemic medications. Subjects had a history of a seasonal allergic conjunctivitis or rhinoconjunctivitis, a positive diagnostic test for ragweed antigen (skin prick), and a positive response to ragweed in the CAC model. Two hundred forty (240) subjects were randomized and all received one drop of either drug or placebo once daily (in the morning) in both eyes during the 12-week period.

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Key Inclusion Criteria (p.56/1328):

1. History of a seasonal allergic conjunctivitis or rhinoconjunctivitis.
2. Corrected visual acuity of 0.6 logMAR or better in each eye as measured by ETDRS charts.
3. Positive skin prick test with ragweed antigen within the past 24 months.
4. A positive bilateral ocular response to ragweed pollen at the Eligibility Visit, as induced by the CAC model. The positive CAC response must meet one of the following criteria:
   - Redness (in at least one of the vessel beds–ciliary, episcleral, conjunctival–each measured separately on a scale ranging from 0 to 4) and itching scores =2 in each eye in at least one time point for subjects with baseline redness and itching scores <1 OR
   - An increase of =1 score unit in redness in at least one of the vessel beds (ciliary, episcleral, or conjunctival), each measured separately on a scale of 0 to 4 and itching scores in each eye on at least one time point for subjects with baseline itching and redness scores =1.
5. Willing and able to avoid any medication prior to the study start (Eligibility Visit on Day 1) that may interfere with the results of the study including the following:
   - Antihistamines (H1-blockers) 72 hours prior to Day 1
   - Steroids and mast cell stabilizers 14 days prior to Day 1
   - Immunotherapy and immunosuppressive agents two months prior to Day 1.

Reviewer comments: *The Sponsor selected patients with allergies specific to ragweed for this study. Overall, the above criteria demonstrate that the Sponsor recognized and attempted to control for potential patient risk. In addition, the Sponsor appropriately selected the subset of patients most likely to benefit from the drug, while minimizing confounding variables.*

Brief Description of Visits:

Eligibility Visit (Day 1)
Subjects underwent a CAC test with ragweed antigen. A positive response was defined as described in the inclusion criteria. A complete eye exam was performed, and subjects completed subjective allergic conjunctivitis and rhinoconjunctivitis quality of life questionnaires.

Office Visits: Weeks 1, 2, 4, 6, 8, 10
Frequency (during 3 days prior to visit; grading scale 0-5) and severity (during 24 hours prior to visit; grading scale 0-3) of ocular and nasal signs and symptoms of allergic conjunctivitis and rhinoconjunctivitis were rated by subjects. Adverse events and missed doses were recorded and an slit-lamp exam was performed.

At Week 2 only, the allergic conjunctivitis and rhinoconjunctivitis quality of life questionnaire was completed.

Telephone Contacts: Weeks 3, 5, 7, 9, 11
Frequency and severity of ocular and nasal signs and symptoms of allergic conjunctivitis and rhinoconjunctivitis were again rated by subjects (although fewer signs and symptoms than the number queried during the office visits). Adverse events and missed doses were recorded.

Exit Visit: Week 12 (+/-3 days) or Last Office Visit if discontinued prior to Week 12:
Similar to Week 2 visit, with the addition of a more comprehensive ocular exam, and a pregnancy test for women of childbearing age.

Pollen counts were obtained once per week during the 12 weeks.

Study Plan (p68/1328)

Parameters	Eligibility	Office Visits	Telephone Contacts	Exit Visit
	Day 1	Weeks 1, 2, 4, 6, 8, 10	Weeks 3, 5, 7, 9, 11	Week 12 (+/- 3 days) or last office visit if DC'd early
Informed Consent	X			
Medical hx/demographics	X			
Rhinoconjunctivitis Quality of Life Survey	X	X[b]		X
Pregnancy Test[a]	X			X
Diagnostic Test (skin prick)[c]	X			
Visual Acuity	X	X		X
Pt Assessment of Allergy Signs, Symptoms	X	X	X	X
Fundus Exam (undilated)	X			X
Slit Lamp Exam	X	X		X
Itch/redness pre-/post-CAC	X			
IOP	X			X
Allergic Conjunctivitis Quality of Life Survey	X	X[b]		X
Dispense/Collect Study Medication (as needed)	X	X		
Record Adverse Events[d]	X	X	X	X
Update Medical hx and Medical Records		X	X	X
Record Missed Doses		X	X	X
Collect Study Medication				X
Complete Exit Form				X

[a] A pregnancy test was performed at Day 1 and at the Exit Visit for all women of childbearing potential.
[b] The Rhinoconjunctivitis and the Allergic Conjunctivitis quality of life questionnaires were completed at Day 1, Week 2, and at the Exit Visit before any procedures were performed.
[c] If not performed within 24 months of Visit 1.
[d] Adverse events which occurred after instillation of study medication were recorded.

Evaluations/Endpoints:

All endpoints, primary and secondary, as well as their respective grading criteria, were described prior to the initiation of the trial, and were not altered thereafter. The primary efficacy variables were subject self-evaluations of the frequency of ocular itching and redness during the 3 days prior to each study visit. These were recorded as scores on a 6 unit scale (0=none; 1=rarely; 2=occasionally; 3=frequently; 4=very frequently; 5=continuously).

Secondary efficacy parameters included severity scores for ocular itching and redness, and frequency and severity scores for other signs and symptoms associated with allergic conjunctivitis and rhinoconjunctivitis.

All subjects who received drug and had at least one on-therapy visit qualified to be evaluated for the intent to treat analysis. All subjects who received drug, had at least one on-therapy visit, and satisfied inclusion/exclusion criteria were amenable to evaluation for the per protocol analysis.

Statistical Plan:

Repeated measures analysis of variance was used to compare treatment differences in the slopes of the regression lines for ocular itching and redness as a function of ragweed pollen counts. With 110 subjects amenable to evaluation per treatment group, the study had 85% power to detect a difference in slopes.

The sample size was based upon a simulation study with parameter estimates for the slope for Olopatadine (0.0012), the slope for placebo (0.0025), common intercept (0.85), between-subject variance (0.5872), and within-subject variance (0.5537) derived from a previous Alcon environmental allergy study (C-98-37, 15) of Olopatadine HCl Ophthalmic Solution 0.1%, versus placebo.

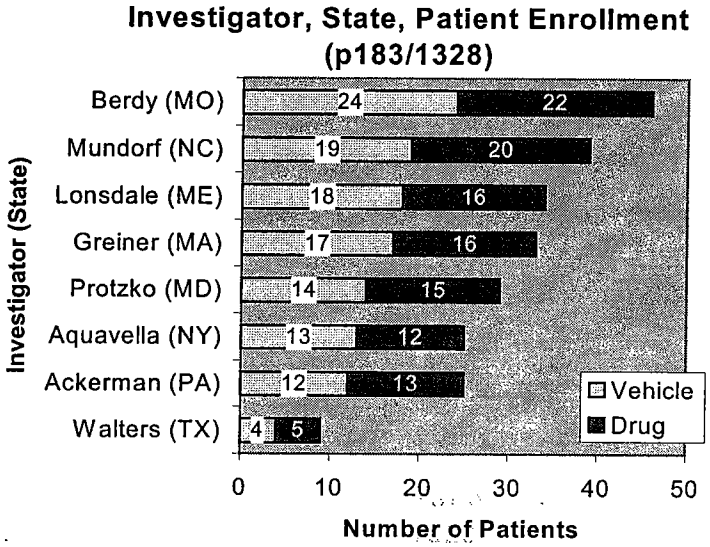
Reviewer comments: *The study was not powered to detect a mean difference in frequency scores between groups. The Sponsor neither quantified the difference in slopes it was powered to detect, nor explained the clinical significance of such a slope comparison.*

Subject Disposition:

The study was conducted at 8 investigational sites:

Principal Investigators:

Number	Investigator	Address	# Subjects/Group	
			Vehicle	Drug
3133	Stacey L. Ackerman, MD	Philadelphia Eye Associates 1703 Broad Street Philadelphia, PA 19148 (215) 339-8100	12	13
511	James V. Aquavella, MD	Genesee Valley Eye Institute 919 Westfall Road, Suite 201A Rochester, NY 14618 (716) 461-8409	13	12
1335	Greg Berdy, MD	Ophthalmology Associates 456 North New Ballas Road,, Suite 386 Creve Coeur, MO 63141 (314) 993-5000	24	22
1957	Jack V. Greiner, OD, DO, PhD	Ophthalmic Research Assoc. 863 Turnpike Street North Andover, MA 01845 (978) 685-8900	17	16
2573	John D. Lonsdale, MD	Central Maine Eye Care 181 Russell Street Lewiston, ME 04240 (207) 783-9670	18	16
1473	Thomas K. Mundorf, MD	Presbyterian Medical Center 1718 E. 4th Street Suite 703 Charlotte, NC 28204 (704) 334-3222	19	20
3132	Eugene E. Protzko, MD	Seidenberg Protzko Eye Assoc 520 Upper Chesapeake Drive Suite 401 Bel Air, MD 21041 (443) 643-4500	14	15
1007	Thomas R. Walters, MD	Texan Eye Care 1700 South Mopac Expressway Austin, TX 78746 (512) 732-7272	4	5



Patient Demographic Statistics by Treatment Group (Intent-to-Treat); (p182/1328)

	Vehicle	Drug	p-value
AGE:			0.6250
Mean	37.7	36.9	
Std	13.1	11.7	
N	121	119	
Min	10	10	
Max	66	66	

	Vehicle		Drug		p-value[a]
	N	%	N	%	
Age					1.0000
2-11	4	3.3	3	2.5	
12-17	5	4.1	4	3.4	
18-64	110	90.9	111	93.3	
≥65	2	1.7	1	0.8	
Sex					0.2454
Male	43	35.5	51	42.9	
Female	78	64.5	68	57.1	
Race					0.6803
Caucasian	110	90.9	105	88.2	
Black	7	5.8	10	8.4	
Asian	1	0.8	.	.	
Other	3	2.5	4	3.4	
Iris Color					0.8976
Missing	1	0.8	.	.	
Brown	44	36.4	46	38.7	
Hazel	18	14.9	19	16	
Green	14	11.6	10	8.4	
Blue	42	34.7	43	36.1	
Grey	2	1.7	1	0.8	

[a] Based on chi-square or Fisher's Exact Test

Of the 240 patients randomized, 11 discontinued the study—6 in the vehicle group and 5 in the drug group:

Discontinued Subjects (p.1210/1328)

On Vehicle or Drug)	Patient	Age	Sex	Race	Reason	Removed from Per Protocol
V	275	27	F	C	Patient revealed she had rosacea (exclusion criteria)	X
V	312	34	F	C	Discomfort: make-up running	
V	313	28	F	C	Otitis Media beginning on day of CAC	
V	583	35	F	C	Sinus infection	
V	614	33	M	C	Lost to follow up	X
V	627	44	F	C	Otitis media, Day 15	
D	322	56	F	C	Bacterial Conjunctivitis, Day 4 PVD with retinal tear OS, Day 69	
D	323	47	M	C	<15 minute episode of tachycardia Bad taste after instillation	
D	411	37	M	C	Worsening back pain Entered study	
D	568	45	F	C	Headache Dry eye	
D	640	21	M	C	Non-compliance	X

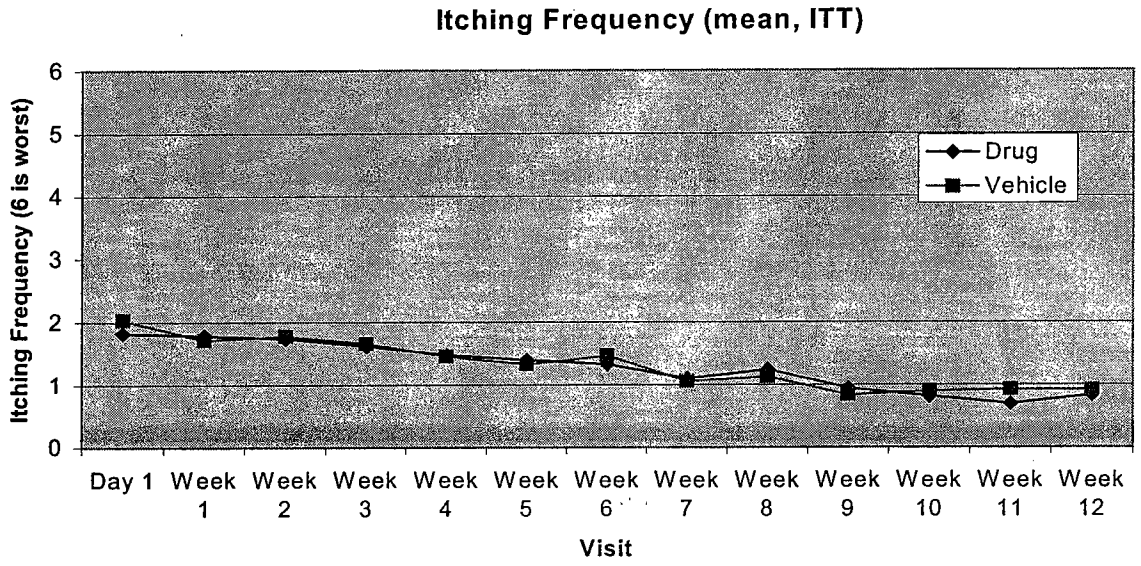
Protocol Deviations (p.99,1214/1328)
Fifty-three (53) patients deviated from the protocol, yielding 70 total deviations. Of the 10 patients not included in the per protocol analysis, 3 were on drug:

Protocol Deviations That Excluded Patients from Per Protocol Analysis	Patients on Drug	Patients on Vehicle	Total
Inadequate CAC response at day 1	1	5	6
General non-compliance with drops	1		1
Inadequate washout of antihistamine		1	1
Pre-existing psoriasis	1		1
Pre-existing rosacea		1	1

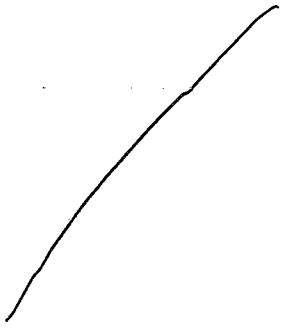
There were numerous individual visits where patients were not amenable to evaluation, for varied reasons (p1215/1328). However, the number of subjects not completing a particular visit was never more than 6 per treatment arm.

Efficacy Endpoint Outcomes

The primary efficacy endpoints were the frequency of ocular itching and ocular redness during the 3 days prior to each study visit as reported by the subjects. Pollen counts varied by site over the 12 weeks, but most resembled a bell shaped curve with a peak centered on weeks 5-6 (p.108/1328). Results from the intent-to-treat and per protocol analyses were similar, as were results from different geographic regions.



Redness Frequency (mean, ITT)



Reviewer comments: *Efficacy is not demonstrated in the — f itching over the 12 weeks, regardless of pollen count or geographic location.*

Conclusions Regarding Efficacy Data in Study C-01-10

Reviewer comments: *Results do not support a once-daily claim for .* —

Overview of Efficacy for Itching—All Trials

The 2 CAC studies with "by-eye" designs were relied upon to assess drug efficacy. To examine the distribution of scores, results at the 16-hour visit are depicted below. In the charts, each tick represents a subject's study eye. The D-D group represents subjects who received drug in both eyes, the P-P group represents subjects who received placebo in both eyes, and the D-P groups represent subjects who received drug/placebo in contralateral eyes.

Study C-01-18: Itching Scores at 16-hour Visit (10 minutes after CAC)

4			II			II
3.5						
3				I		I
2.5	II	I	I	II	III	III
2	IIII		I	II	IIII	III
1.5	I			III	I	III
1	IIIII	I	IIIIIIII		IIIIII	IIIIIIII
0.5	II	I	II		III	II
0	IIIIII	IIIIIIII	III	IIII	IIIIIIIIIIIII	IIIIII
	D-D	D-P	P-P	D-P	DRUG EYE	PLACEBO EYE
	DRUG EYE		PLACEBO EYE		TOTALS	

Study C-01-100: Itching Scores at 16-hour Visit (7 minutes after CAC)

4			II			II
3.5	I	I		II	II	II
3	II		II	IIIII	II	IIIIIII
2.5		II	IIIIIIIII	IIIII	II	IIIIIIIIIIIIII
2	IIII	I	IIIIII	IIIIIIII	IIII	IIIIIIIIIIIII
1.5	IIIIII	IIIIII	IIIIIIIII	IIIII	IIIIIIIIII	IIIIIIIIIIII
1	IIII	III	IIIIII	IIIII	IIIIIII	IIIIIIIIII
0.5	IIIIIII	IIIIIIIII	I	IIIII	IIIIIIIIIIIIII	IIIII
0	IIIIIIIIIII	IIIIIIIIIIIII	IIII	IIII	IIIIIIIIIIIIIIIIIIIIIIIIIIIII	IIIIIII
	D-D	D-P	P-P	D-P	DRUG EYE	PLACEBO EYE
	DRUG EYE		PLACEBO EYE		TOTALS	

Reviewer comments: *In both trials, subjects who received the drug experienced lower itching scores than those on placebo, but the effect was substantially more convincing in C-01-100. In C-01-18, almost all scores were ≤ 1 on both drug and placebo, though several more subjects on drug experienced complete relief of itching.*

The difference in results between the two trials might have been due to different study sample sizes or due to the different post-CAC time points (10 minutes vs. 7 minutes).

6.4. Efficacy Conclusions

Of the 4 trials designed to test efficacy (3 CAC studies and one environmental study), the study drug demonstrated a clinically significant ability to prevent ocular itching in patients with allergic conjunctivitis at its "onset of action" in all 3 CAC studies and after 16 hours in 2 of the 3 CAC studies.

Of these 2 CAC studies that demonstrated efficacy at 16 hours, one used the preferred "by-eye" design, but the other was flawed due to shortcomings intrinsic to a contralateral design. Thus, there is only one reliably designed, adequate and well-controlled study that demonstrated clinically significant efficacy at the 16-hour time point. The other "by-eye" study, which did show a trend toward efficacy, coupled with the flawed study together may be used as supportive evidence for efficacy at 16 hours.

CAC Study Design Analysis

Protocol	Study Design	Strength of Design	Strength of Results	Contribution
C-00-36	Contralateral	Flawed	Efficacy shown	Supportive
C-01-18	By-eye	Reliable	Trend to efficacy	Supportive
C-01-100	By-eye	Reliable	Efficacy shown	Significant

The environmental study did not demonstrate efficacy in any measured endpoint related to allergic conjunctivitis.

7. Integrated Review of Safety

7.1. Brief Statement of Findings

Olopatadine 0.2% administered once daily is safe and well-tolerated in pediatric and adult subjects with seasonal allergic conjunctivitis, based on a review of adverse events and an assessment of ocular parameters. Adverse events in the overall treatment population were mostly non-serious and mild to moderate, generally resolved without treatment, and usually did not interrupt subject continuation in the studies.

7.2. Materials Utilized in the Review

The overall experience using olopatadine 0.2% ophthalmic solution was evaluated in 5 clinical trials. In addition, one clinical trial using an oral formulation of olopatadine contributed to the safety data set. The 3 CAC studies provided short-term data, the environmental and topical safety study provided long-term data, and the oral study provided oral systemic data.
The topical safety (C-01-77) and oral safety (C-00-23) studies are described briefly (below).

Study C-01-77, Topical Safety
This study was a double-masked, placebo-controlled, randomized, parallel group, multi-center (6) trial in subjects 3 years of age or older with asymptomatic eyes to demonstrate that the drug is safe and well-tolerated when administered once daily in both eyes for up to six weeks (the length of a typical allergy season). Subjects were forbidden from using any

other topical ocular drops (including artificial tears) during the study. Contact lens wearers were permitted. Of 351 subjects enrolled, 236 were randomized to drug and 115 to placebo.

Safety assessments were based on multiple factors: physician-queried and subject-volunteered adverse events, the extent of exposure to study drug, visual acuity scores, slit-lamp biomicroscopy evaluations, dilated fundus examinations, IOP measurements, and pulse and blood pressure readings.

Principal Investigators

Name	Location	Number of Patients	
		Olopatadine	Vehicle
Thomas Chandler, MD	Radiant Research 12221 N. MoPac Expwy Austin, TX 78758	43	21
Harvey DuBiner, MD	Clayton Eye Center 1000 Corporate Center Dr. Suite 100 Morrow, GA 30260	43	21
Thomas Henderson, MD	Metatrials, Inc 1012 MoPac Circ. Ste 110 Austin, TX 78746	43	22
Steven Lichtenstein, MD	Louisville Children's Eye Metro United Way Bldg 334 East Broadway, Ste 325 Louiville, KY 40202	35	17
Jay Rubin, MD	Eye Clinics of South Texas 999 E. Basse Rd, Ste 128-B San Antonio, TX 78209	28	13
David Wirta, MD	1501 Superior Ave, Ste 303 Newport Beach, CA 92663	44	21

Study Plan

Parameters	Eligibility Visit Day 1	Office Visits Weeks 1, 3	Tel. Contacts Weeks 2, 4, 5	Exit Visit Week 6
Informed Consent	X			
Medical Hx/ Demogr.	X			
Pulse, Blood pressure	X			X
Pregnancy Test[a]	X			X
Visual Acuity	X	X		X
Slit Lamp Exam	X	X		X
IOP	X			X
Fundus Exam (dilated)	X			X
Give and/or collect study medication	X	X		
Record Adverse Event	X[b]	X	X	X
Update Med. Hx and Record other meds		X	X	X
Record missed doses		X	X	X
Collect study med.				X
Exit form				X

[a]Pregnancy test was performed at Day 1 and at the Exit Visit for all women of childbearing potential.
[b]Any adverse events which occurred after instillation of study medication were recorded.

Adverse event results from C-01-77 are listed in the subsequent composite tables.

Study C-00-23, Oral Safety

The other safety study was conducted with an oral formulation of olopatadine. This was a double-masked, randomized, placebo-controlled, multiple-dose, two-period, two-sequence crossover study. The primary safety objective of this study was to assess the effect on the QTc interval of a 5 mg oral olopatadine solution administered twice daily (q12 hour) for 2.5 days compared to an oral placebo solution also administered twice daily (q12 hour) for 2.5 days. This study included a population of healthy male and female volunteers ages 18 to 75 years. A secondary objective of the study was to assess the olopatadine plasma pharmacokinetics and the relationship, if any, between QTc interval and plasma olopatadine concentrations.

To examine the effects of olopatadine on the QTc interval, serial 12-lead electrocardiograms (ECGs) were obtained at 15 and 30 minutes, and 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the first dose (single-dose) and last dose (steady-state) in each of the two study periods. In addition, Holter monitoring was done at steady state beginning at Hour 12 of Day 2 (Period 1) and Day 9 (Period 2), and ending at Hour 12 on Day 3 (Period 1) and Day 10 (Period 2).

Plasma samples for the determination of olopatadine concentrations were obtained prior to each morning and evening dose, 1 hour and 12 hours after the first dose, and at the same time points as the ECG recordings after the last dose. Pulse and blood pressure measurements were performed at screening, the beginning of each period, prior to each dose, and at numerous points after each dose. Additionally, clinical laboratory sample collection was performed at screening, Day 3, and prior to study exit (Day 10, Period 2). Physical examinations were performed at screening, Day 7, and prior to study exit (Day 10, Period 2).

The study enrolled 117 patients at least 18 years old, randomized to either olopatadine then placebo or vice-versa. Similar numbers of male and female patients, and predominantly Caucasian and Hispanic patients were enrolled. Seven subjects discontinued the study due to adverse events (listed in subsequent section).

Olopatadine (5mg, q12 hours) was not associated with any effect on QTc interval that was not seen with placebo. Six subjects experienced a single-dose increase in QTcB interval >60msec, five (5/102; 4.9%) with placebo and one (1/102; 1.0%) with olopatadine. One subject experienced a steady-state increase in QTcB interval >60 msec with placebo, and none with olopatadine treatment (below).

Incidence of Single-Dose and Steady State E_{max} Values

	Drug N=102	Placebo N=102	Uncorrected p-value	Hochberg-corrected p-value
Single-dose QTcB E_{max}				
<30 msec	74 (72.5%)	71 (69.6%)	0.728	1.000
≥30 to ≤60 msec	27 (26.5%)	26 (25.5%)	1.000	1.000
>60 msec	1 (1.0%)	5 (4.9%)	0.219	0.875
Steady state QTcB E_{max}				
<30 msec	78 (76.5%)	68 (66.7%)	0.121	0.729
≥30 to ≤60 msec	24 (23.5%)	33 (32.4%)	0.175	0.875
>60 msec	0	1 (1.0%)	1.000	1.000

Peak plasma concentrations of olopatadine (up to 125 ng/ml) were up to 250 times greater than those previously observed following topical ophthalmic administration. No relationship was observed between the QTc interval and peak plasma olopatadine concentrations.

7.3. Description of Patient Exposure

Of the 5 topical studies, only in C-01-10 (environmental study) and C-01-77 (safety study) did the subjects receive prolonged duration of exposure (12 weeks and 6 weeks, respectively)—for a total of 355 subjects enrolled. In contrast, drug was administered multiple days apart for the CAC studies, and subjects received at the most 3 drops during the course of the those trials.

Long-term Patient Exposure to Drug

	Study C-01-10	Study C-01-77	Combined
Exposure	10 ≤ weeks ≤ 12+	5 ≤ weeks ≤ 6+	Minimum 5 weeks
Age 3-11 yrs.	3[a]	61[a]	64
Age 12-17 yrs.	4	26	30
Age ≥18 yrs.	108	137	245
Total Patients	115	230	**345**

[a] Minimum age for C-01-10 was 10 years, while minimum age for C-01-77 was 3 years.

7.4. Safety Findings from Clinical Studies

Overall, ocular adverse events were similar regardless of contact lens use, iris color, race/ethnicity or gender.

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Most Frequent Adverse Events—Long-term Studies

Protocol	C-01-10 (up to 12 weeks)				C-01-77 (up to 6 weeks)				
	Drug N=119		Placebo N=121		Drug N=236		Placebo N=115		Totals N=591
Adverse Events	N	%	N	%	N	%	N	%	
Ocular									
Dry eye	2	1.7							**2**
Lid disease	1	0.8	3	2.5					**4**
Discomfort eye			2	1.7	2	0.8	1	0.9	**5**
Lid margin crusting	1	0.8	2	1.7	3	1.3			**6**
Hyperemia eye	1	0.8			3	1.3	1	0.8	**5**
Conjunctivitis	1	0.8	2	1.7	3	1.3	2	1.7	**8**
Tearing					2	0.8	2	1.7	**4**
Non Ocular									
Body as a whole									
Cold syndrome	13	10.9	10	8.4					**23**
Infection	4	3.4	2	1.7	7	3.0	5	4.3	**18**
Headache	5	4.2	5	4.1	5	2.1	2	1.7	**17**
Respiratory system									
Pharyngitis	8	6.7	3	2.5	3	1.3	2	1.7	**16**
Rhinitis	3	2.5	1	0.8	3	1.3			**7**
Cough increased	1	0.8			4	1.7	3	2.6	**8**
Sinusitis	5	4.2	2	1.7					**7**
Digestive system									
Dry mouth	3	2.5							**3**
Special senses									
Taste perversion	6	5.0							**6**
Otitis media			3	2.5	4	1.7	2	1.7	**9**

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All Topical Clinical Trials: Cumulative Adverse Events Occurring at ≥ 1.0% per Trial (2.7.4.7 Appx., p.26; C-00-36, C-01-10, C-01-18, C-01-77, C-01-100)

	Drug-Drug N=390		Drug-Placebo N=103		Placebo-Placebo N=271	
Adverse Events (in descending order)	N	%	N	%	N	%
OCULAR						
Conjunctivitis	4	1.0			4	1.5
Lid Margin Crusting	4	1.0	2		2	0.7
Discomfort eye	2	0.5			5	1.8
Hyperemia eye	4	1.0			1	0.4
Tearing	2	0.5	1	1.0	2	0.7
Discharge eye NOS	1	0.3	1	1.0	2	0.7
Lid Disease	1	0.3			3	1.1
Pruritis Eye	1	0.3	1	1.0	1	0.4
Subconjunctival hem.			1	1.0	1	0.4
NON-OCULAR						
Body as whole						
Cold Syndrome	13	3.3	2	1.9	10	3.7
Infection	11	2.8			7	2.6
Headache	10	2.6	1	1.0	7	2.6
Injury Accidental	1	0.3	2	1.9		
Neck Rigid			2	1.9	1	0.4
Pain Abdominal	1	0.3	1	1.0		
Cardiovascular						
Tachycardia	1	0.3				
Digestive						
Abscess periodontal			1	1.0		
Gastritis			1	1.0		
Musculoskeletal						
Bone fracture, spontan.	1	0.3	1	1.0		
Respiratory						
Pharyngitis	11	2.8	1	1.0	5	1.8
Rhinitis	8	2.1	2	1.9	1	0.4
Cough increased	5	1.3			3	1.1
Sinusitis	5	1.3			3	1.1
Skin, Appendages						
Herpes Simplex	1	0.3	1	1.0		
Special Senses						
Otitis Media	4	1.0			5	
Taste Perversion	6	1.5				
Urogenital						
Menopause			1	1.0		

Adverse events in pediatric populations:
In the environmental study (C-01-10), 2 adverse events were reported in the pediatric population (pharyngitis and sinusitis); both subjects were 14 years old and randomized to the olopatadine 0.2% group, and both cases were mild in intensity and resolved without treatment.

In the 6-week safety study (C-01-77), all adverse events in subjects 3-5 years of age were non-serious, of mild-moderate severity, and did not interrupt continuation in the study. Further, they were similar in type to those typically observed in the overall pediatric population. Of the subjects who received study drug, 9 were 3 years old, 8 were 4 years old, and 9 were 5 years old.

All Adverse Events in Subjects 3-5 Years of Age

Adverse Event	Drug N=26	Placebo N=11
OCULAR		
Discomfort eye	1	
Conjunctivitis (viral)	1	1
Staining corneal	1	
Injury accidental		1
NON-OCULAR		
Body as a whole		
Infection (URI)	1	1
Digestive System		
Vomit		1
Respiratory System		
Cough increased	2	
Special Senses		
Otitis media	2	1

Composite subject discontinuations (all trials):
There were no subject discontinuations due to adverse events in the 3 CAC studies; the 18 subject discontinuations in studies C-01-10, C-01-77, and C-00-23 are listed in the table below:

Subjects Who Discontinued Due to Adverse Events—All Trials (2.7.4.7 Appx p.97)

Study	Drug or Placebo	Age	Sex	Adverse Event	Onset Day	Intensity	Duration	Outcome
Environ	Drug	47	M	Tachycardia	1	Mild	15 min.	Resolved w/o tx
Environ	Drug	45	F	Dry Eye	66	Mild	Intermit.	Continuing w/tx
Environ	Drug	56	F	1) Retinal tear 2) Vitreous dis[a]	70	Moderate	1 day	Resolved w/tx
Environ	Drug	37	M	Surgical proc.[b]	51	Severe	1 day	Resolved w/tx
Environ	Placebo	38	F	Otitis media	1	Moderate	5 days	Resolved w/tx
Environ	Placebo	35	F	Sinusitis	37	Severe	1 days	Continuing w/tx
Environ	Placebo	44	F	Otitis media	36	Mild	11 days	Resolved w/tx
Safety	Drug	13	F	Dermatitis[c]	15	Moderate	Contin.	Continuing w/tx
Safety	Drug	22	F	Conjunctivitis	3	Moderate	3 days	Resolved w/tx
Safety	Drug	34	F	1) Ocular pain 2) Headache 3) Tachycardia	5	Mild	15 days	Resolved w/o tx (all)
Safety	Placebo	31	M	Conjunctivitis	4	Mild	4 days	Resolved w/tx
Oral	Drug	56	M	AV block compl.	Period 1	Mild	1 min.	Resolved
Oral	Drug	22	M	Acne	Period 1	Mild	n/a	Ongoing
Oral	Drug	47	M	Tachycardia vent	Period 1	Mild	1 min.	Resolved
Oral	Drug	57	F	Tachycardia vent	Period 1	Mild	1 min.	Resolved
Oral	Placebo	48	M	Tachycardia vent	Period 1	Mild	1 min.	Resolved
Oral	Drug	35	F	Syncope	Period 1	Severe	8 min.	Resolved
Oral	Placebo	29	F	Hepatitis	Period 1	Moderate	18 days	Resolved

[a]New floater
[b]Creation of a LASIK flap
[c]Poison ivy rash

No subjects on study drug experienced a clinically relevant change from baseline in visual acuity, intraocular pressure, ocular signs, fundus examination, laboratory findings or cardiovascular parameters. One potentially relevant exception reported was the difference in mean triglyceride change from baseline in subjects enrolled in (oral) study C-00-23. A mean increase of 92.2 mg/dL (range of change: -65 to 429) was noted in the study drug group with a mean increase of 54.7 mg/dL (range of change: -78 to 294) in the placebo group.
No deaths were reported in any of the submitted clinical studies.

7.5. Literature Review for Safety
No additional relevant information.

7.6. Postmarketing Surveillance
Discussed in a previous section.

7.7. Safety Update
See Safety Update Review.

7.8. Drug Withdrawal, Abuse, and Overdose Experience

No reports of overdose, drug abuse, or withdrawal/rebound phenomena were submitted. There is no foreseen potential for abuse and dependence.

7.9. Adequacy of Safety Testing

Overall, the safety data generated by the clinical studies was adequate. The drug was dosed in over 300 patients for at least 6 weeks—the length of a typical allergy season. It included an adequate number of children and an even representation of most demographic groups, with the exception of Caucasians representing 76% of subjects with long term exposure to the study drug. Ocular and systemic testing parameters were appropriately chosen and relevant.

7.10. Labeling Safety Issues and Postmarketing Commitments

Safety signals that need to be highlighted in the drug's labeling are consistent with those found in the olopatadine 0.1% label.

8. Dosing, Regimen, and Administration Issues

Reviewed in previous section.

9. Use in Special Populations

9.1. Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity

Based on a review of adverse events by age in the subjects with long term exposure to the drug, there are no apparent trends or safety concerns. Similarly, an analysis of adverse events by gender, race/ethnicity, and eye color revealed no notable, clinically relevant differences.

9.2. Pediatric Program (e.g., pediatric waivers, deferrals, written requests)

The Sponsor requests a waiver of information regarding the use of Olopatadine HCl Ophthalmic Solution (0.2% as base) in pediatric patients under the age of 3 years.

9.3. Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy

The drug product has negligible systemic absorption.

10. Conclusions, Recommendations, and Labeling

10.1. Conclusions Regarding Safety and Efficacy

In the 3 CAC studies, the drug demonstrated relative efficacy in reducing itching symptoms at onset and 16 hours after administration. This effect was moderate in magnitude, less evident at 16 hours, and relatively uniform within each study; however, the effect was variable between studies.

The environmental study did not demonstrate drug efficacy for any endpoint.

None of the studies demonstrated a clinically meaningful reduction of any evaluated signs and symptoms other than itching, and there were no studies directly comparing the drug to other treatments.

Overall, the clinical study designs met the Division's recommendations for replication and clinical significance, and the relative shortcomings in strength of efficacy results are offset by the minimal risk likely attributed to taking the drug.

The 3 CAC studies provide limited supportive safety data because subjects were exposed to no more than 3 drops of the drug, each separated by multiple days. Conversely, the environmental study randomized 119 patients to 12 weeks of daily drug exposure and the safety study randomized 236 patients to 6 weeks of daily drug exposure, totaling 355 patients that included 64 children ranging from 3 to 11 years of age. Safety data from these 2 relatively long-term studies are generally amenable to extrapolation.

Overall, adverse events were relatively few in number, mild, resolved without treatment, and rarely resulted in discontinuation of participation in a trial. There were no significant adverse events that warrant special monitoring.

One safety study tested a 5 mg oral form of the drug versus placebo in 102 patients. As expected, this dose resulted in higher plasma concentrations than those expected with topical administration. There was no evidence of drug effect on cardiac repolarization, and no clinically relevant treatment-related changes in laboratory parameters or vital signs relative to placebo.

In sum, the clinical trials met the Division's safety recommendations for minimum number of exposures, duration, and patient monitoring. It is likely that the similarity of adverse events reported in trials for the two olopatadine concentrations is predictive of those anticipated in a post-marketing patient population using olopatadine 0.2%.

10.2. Recommendations on Approvability

From a clinical perspective, NDA 21-545 is recommended for approval of once-daily dosing in the — ocular itching due to allergic conjunctivitis with the labeling revisions listed in this review.

10.3. Labeling

Claims in the Sponsor's proposed label include th —

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Wiley Chambers
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MEDICAL OFFICER

Medical Officer's Review of NDA 21-545
Label Review

Submission Date:	April 30, 2003
Received Date:	May 1, 2003
Review Completed:	May 1, 2003
Proposed Trademark:	Pending
Generic Name:	Olopatadine HCl ophthalmic solution 0.2%
Chemical Name:	11-[(Z)-3-(Dimethylamino) propylidene]-6-11-dihydrodibenz[b,e] oxepin-2-acetic acid, hydrochloride
Molecular Formula:	$C_{21}H_{23}NO_3 \bullet HCl$
Molecular Weight:	373.88
Sponsor:	Alcon, Inc. P.O. Box 62 Bosch 69 CH-6331 Hunenberg Switzerland Alcon Research, Ltd. 6201 S. Freeway Fort Worth, TX 76134-2099 (817) 551-4933
Pharmacologic Category:	Antihistamine and mast cell stabilizer
Proposed Indication:	—
Dosage Form:	Ophthalmic solution
Route of Administration:	Topical ocular
NDA Drug Classification:	3S
Related IND:	IND 60,991
Related NDA:	NDA 20-688 (Patanol®)

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_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical-_____

Reviewer's comments: *Label acceptable, pending submission of proposed Trademark.*

Reviewer's recommendation: *Please submit proposed Trademark.*

Matthew Feinsod, M.D.
Medical Officer

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Wiley Chambers
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MEDICAL OFFICER

Medical Officer's Review of NDA 21-545
Amendment

NDA 21-545
Amendment 1

Submission: 12/13/02
Review completed: 3/15/03

Drug name: Olopatadine hydrochloride ophthalmic solution 0.2%

Chemical name: 11-[(Z)-3-(Dimethylamino)propylidene]-6-11-dihydrobenz[b,e]-oxepine-2-acetic acid hydrochloride

Sponsor: Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76115
(817) 568-6116

Pharmacologic Category: Selective H1-receptor antagonist and mast cell stabilizer

Proposed Indication(s): Treatment of —

Dosage Form(s) and Route of Administration: Topical ophthalmic solution

Submitted: Additional studies to assess the clinical safety and efficacy of olopatadine hydrochloride ophthalmic solution 0.2%.

Reviewer's Comments: *Studies #1-6 were reviewed as part of the original NDA submission.*

Table of Contents:

Study #7: Protocol C-01-90

Title: A comparative study of olopatadine QD versus vehicle in patients with seasonal allergic conjunctivitis or rhinoconjunctivitis

Design:
Prospective, multicenter (8 sites), double-masked, parallel-group, placebo-controlled environmental study designed to compare the efficacy of Olopatadine 0.2% versus placebo. Target enrollment to support the statistical power of the study was 110 patients per treatment arm. Patients enrolled in the study were adults at least 10 years of age, of any race and either sex, with a history of seasonal allergic conjunctivitis or rhinoconjunctivitis, a positive response to grass in the conjunctival antigen challenge (CAC) model and a positive skin prick test with grass antigen within the past 24 months. Eligible patients were randomized to one of two treatments, Olopatadine 0.2% or placebo once-daily for a treatment period of at least 12 weeks.

Office visits: Baseline, week 1, 2, 4, 6, 8, 10, (exit visit week 12).

Investigators:

Number	Investigator	Address	Olopatadine Group	Vehicle Group
2346	Doug Dehning, MD	Discover Vision Center 4741 S. Cochise Dr Independence, MO 64055 (816) 350-4550	15	15
1927	Harvey DuBiner, MD	Clayton Eye Center 1000 Corporate Center Dr Suite 100 Morrow, GA 30260 (770) 960-2473	21	21
3504	Mark Gross, MD	Kentucky Center for Vision 120 N. Eagle Creek Dr, Suite 431 Lexington, KY 40509 (859)263-4631	11	12
3281	Suzanne Li, MD	Eye Physicians and Surgeons 2100 Webster St, Suite 209 San Francisco, CA 94115 (415) 923-3030	26	26
3434	Joseph Markoff, MD	Philadelphia Eye Associates 1113 Hospital Dr, Suite 302 Willingboro, NJ 08046 (609) 871-1112	13	13
3435	Jonathan Seidenberg, MD	Seidenberg-Protzko Eye Assoc 930 Revolution Street Havre de Grace, MD 21078 (410) 939-6477	14	15
3436	Ronald D. Plotnick, MD	University of Rochester 601 Elmwood Ave, Box 659 Rochester, NY 14642 (585) 275-6182	11	11
3505	Gail Torkildsen, MD	17 Village Square Chelmsford, MA 01824 (978) 250-8001	8	8

Subject Disposition:

	Number of Patients	
	Olopatadine 0.2%	Placebo
Enrolled	119	121
Discontinued		
Adverse Events*	1	4
Lost to follow-up	3	6
Patient decision	2	1
Noncompliance	0	1
Treatment failure	1	1
Other	2	5
TOTAL	9	18

* Subjects Discontinued due to Adverse Events

Subject	Treatment	Age	Adverse Event	Outcome
2346.711	Olopatadine 0.2%	29	Pharyngitis	Resolved w/tx
			Lung Disorder	Resolved w/tx
3504.415	Placebo	47	Dry eye	Continuing tx
			Edema lid	Resolved w/o tx
3281.341	Placebo	53	Rhinitis	Resolved w/tx
			Urticaria	Resolved w/tx
3436.513	Placebo	26	Corneal abrasion	Resolved w/tx
3435.903	Placebo	50	Asthenia	Continuing w/o tx
			Menopause	Continuing w/o tx

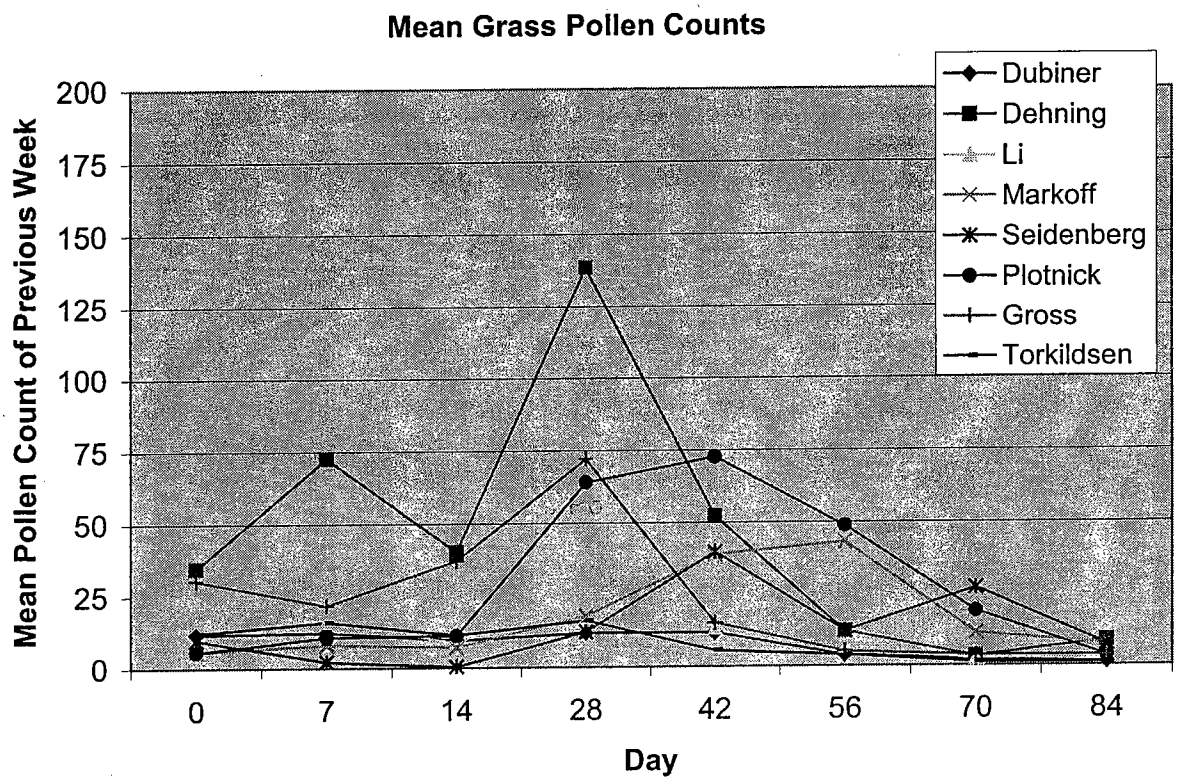
Patients excluded from Per-protocol analysis:

Patient Number	Treatment Group	Reason
207	Olopatadine 0.2%	Lost to f/u after Day 0 (also excluded from ITT)
237	Olopatadine 0.2%	Inclusion criteria (inadequate washout)
510	Olopatadine 0.2%	Exclusion criteria (meibomianitis)
611	Vehicle	Inclusion criteria (baseline CAC itching not avail)

Demographics for Intent-to-Treat Patients

		Placebo	Drug	P-value
Age	MEAN	36.9	38.0	0.5664**
	STD	14.9	14.9	
	N	121	118	
	MIN	10	10	
	MAX	73	73	
	10-11 y.o.	1	2	
	12-17 y.o.	13	7	
Gender				
Male	N	45	49	0.4927*
Female	N	76	69	
Race				
Caucasian	N	75	80	0.1959*
Black	N	20	14	
Asian	N	6	12	
Japanese	N	10	9	
Hispanic	N	6	1	
Other	N	4	2	
Iris color				
Brown	N	64	57	0.6860*
Hazel	N	21	18	
Green	N	11	9	
Blue	N	23	32	
Gray	N	2	2	

* = p value based on chi-square or Fisher's exact test
** = p value based on two-sample t-test



Reviewer's Comments: *Pollen counts varied considerably between sites. Pollen counts were highest at most sites between days 28 and 42.*

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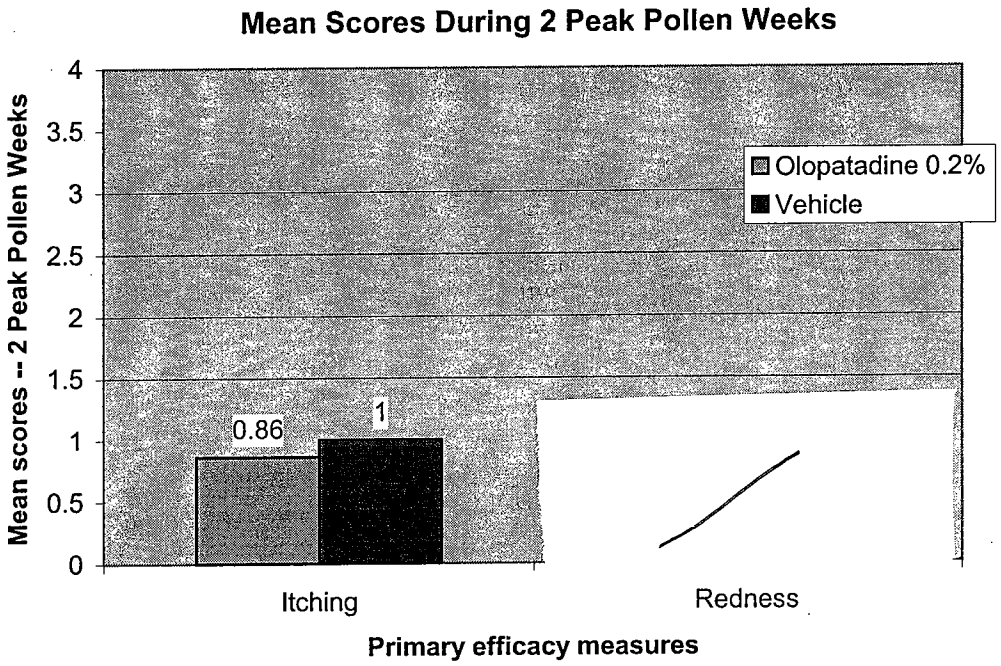
Efficacy

The primary efficacy variables were severity scores for ocular itching and redness. Subjects evaluated their worst ocular itching and redness during the day using a scale that ranged from 0 (none) to 4 (severe). The primary efficacy analysis was based on the average of scores reported over a 2-week peak pollen period. The peak pollen period was determined for each subject as the two non-overlapping 7-day periods with the highest average pollen counts. The two periods were not necessarily consecutive. The two treatment groups were compared using a 2-sample t-test for the average scores of worst daily itching and redness over the 2-week peak pollen period.

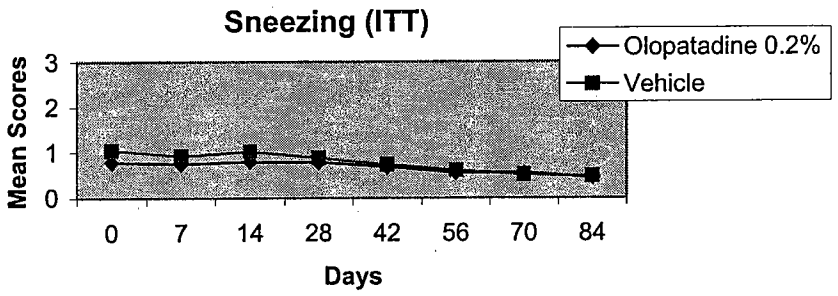


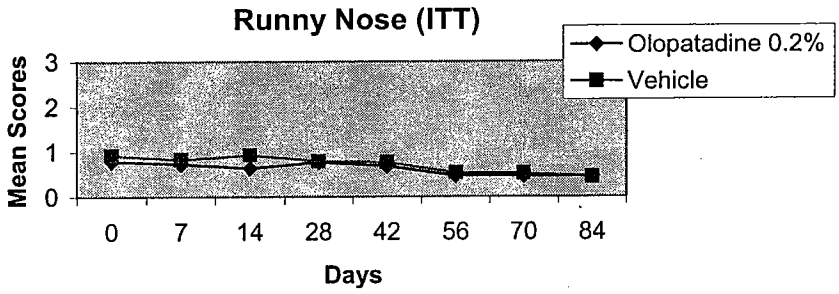
P=0.2214 for Itching by 2-sample t-test
P=0.5561 for Redness by 2-sample t-test

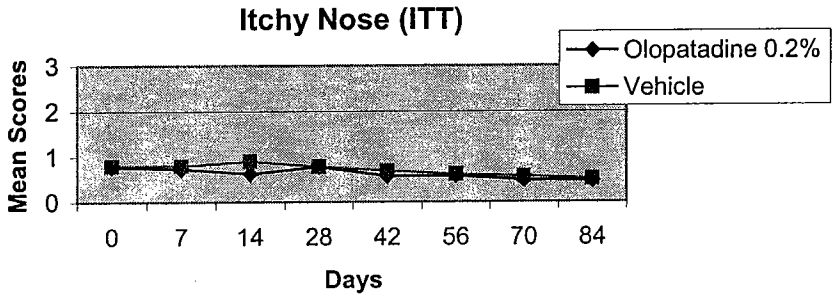
Reviewer's Comments: *For both itching and redness, there was no clinically meaningful difference between the olopatadine and vehicle groups.*

Nasal Symptoms

Secondary efficacy analyses included severity scores for sneezing, runny nose, and itchy nose, ranging from 0 (none) to 3 (severe) in whole-unit intervals.







Reviewer's Comments: *There are no significant differences between drug and vehicle.*

Visual Acuity (logMAR) Change from Baseline to Final Visit

Treatment		Lines of Visual Acuity Change (0.1 = 1 Line)											
		>2 lines Improve.		1 line Improve.		No Change		1 Line Decrease		2 Lines Decrease		>2 Lines Decrease	
	N	N	%	N	%	N	%	N	%	N	%	N	%
Olopatadine 0.2%	117[a]	3	2.6	12	10.3	83	70.9	13	11.1	3	2.6	3	2.6
Placebo	120[b]	2	1.6	11	9.2	87	72.5	15	12.5	4	3.3	1	0.8

[a] Subjects 207 and 237 had only baseline visual acuity data.

[b] Subject 405 had only baseline visual acuity data.

Intraocular Pressure

Mean IOP		
	Baseline	Exit
Olopatadine 0.2%	14.9	15.0
Vehicle	14.9	14.9

Reviewer's Comments: *There are no clinically significant differences.*

Adverse Experiences (>1 event in either group)

Adverse Events	Drug N=119		Placebo N=121	
	N	%	N	%
OCULAR				
Conjunctivitis			2	1.7
Discomfort eye			2	1.7
Dry eye			3	2.4
Visual acuity dec.	2	1.7	4	3.3
Chalazion	1	0.8	2	1.7
Meibomitis	3	2.5		
Vision blurred	1	0.8	2	1.7
NON-OCULAR				
Body as whole				
Cold Syndrome	3	2.5	4	3.3
Infection	3	2.5	1	0.8
Flu Syndrome	4	3.4	1	0.8
Pain	2	1.7	3	2.5
Pain Back	2	1.7		
Endocrine				
Diabetes Mell	2	1.7		
Metabolic /Nutritional				
Hypercholesterem	2	1.7		
Musculoskeletal				
Bone fracture, spontan				
Myalgia	1	0.8	2	1.7
Respiratory				
Epistaxis	3	2.5		

Conclusions: Efficacy has not been demonstrated in the relief of itching in this study.

Overall, most of the safety data observed are similar to the safety data originally filed in the NDA. A few additional adverse events have been noted (e.g., vision blurred, meibomitis, flu syndrome), and the label will be adjusted accordingly.

Recommendations: Amendment 1 of NDA 21-545 is not supportive of the efficacy.

Matt Feinsod, MD

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