CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-890

OTHER REVIEW(S)

505(b)(2) ASSESSMENT REVISED

Application Information		
NDA # 200890	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Isopto Carpine Established/Proper Name: pilocarpine hydrochloride ophthalmic solution Dosage Form: ophthalmic solution 1%, 2% and 4% Strengths: 1%, 2% and 4%		
Applicant: Alcon		
Date of Receipt: December 22, 2009		
PDUFA Goal Date: June 22, 2010	Action Goal Date (if different): June 22, 2010	
Proposed Indication(s): ISOPTO Carpine is a muscarinic cholinergic agonist indicated for • open-angle glaucoma or ocular hypertension • acute angle-closure glaucoma • prevention of (b) (4) postoperative elevated IOP • induction of miosis		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO x

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Pilocarpine is pre-38 drug that has been marketed for many years. Currently the product is on the FDA compliance list of Medically Necessary Unapproved Marketed Drugs. The Applicant has referenced numerous literature articles for each of the clinical indications attached separately to the end of this document.

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

BA/BE studies not conducted…bridging to published studies considered adequate.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES x NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO x

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO x

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO x

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) <u>and</u> there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" <u>or</u> if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES x NO

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES x NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES x NO

*If "**YES**" <u>and</u> there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "**NO**" <u>or</u> if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed x *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply <u>and</u> identify the patents to which each type of certification was made, as appropriate.)*

x No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification*

was submitted, proceed to question #15.

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

Appears This Way On Original

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200890	ORIG-1	ALCON INC	PILOCARPINE HYDROCHLORIDE OPHTHALMIC SOLUTION, 1%, 2% AND 4%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LORI M GORSKI
06/25/2010
Revised 505(b)(2) assessment

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: Tuesday, June 18, 2010

TO: William Boyd, MD, Cross Discipline Team Leader
Division of Anti-Infective and Ophthalmology Products

FROM: Kassa Ayalew, M.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA or BLA: NDA 200890

APPLICANT: Alcon Research Ltd
6201 South Freeway
Fort Worth, Texas 76134-2099
Contact: Michael C. Son, Ph.D., RAC
Senior Manager, Regulatory Affairs
Michael.Son@AlconLabs.com
Phone : (817) 551-8120

DRUG: ISOPTO® Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2% and 4%

NME: No

THERAPEUTIC CLASSIFICATION: Priority

INDICATIONS: For the reduction of IOP in patients with open angle glaucoma or ocular hypertension; (b) (4) for acute angle-closure glaucoma; for the prevention of (b) (4) postoperative

elevated IOP associated with (b) (4) laser surgery; and for the induction of miosis.

CONSULTATION REQUEST DATE: August 18, 2009

PDUFA DATE: June 22, 2010

I. BACKGROUND:

The sponsor, Alcon Research, Ltd, submitted a New Drug Application (NDA) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ISOPTO® Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2% and 4% on a letter dated December 22, 2009 to support a labeling claim indicated for the reduction of elevated intraocular pressure (IOP) in subjects with open-angle glaucoma or ocular hypertension, (b) (4) (b) (4) for acute angle-closure glaucoma, for the prevention of (b) (4) postoperative elevated IOP associated with (b) (4) laser surgery, and (b) (4) (b) (4) as a potent miotic.

This drug is Pre-38 and currently the product is on the FDA compliance list of Medically Necessary Unapproved Marketed Drugs. The NDA was submitted at the prompting of FDA; however, DSI notes that the clinical studies included in this NDA were conducted in the early 1990s in support of another marketing application that was previously approved.

Alcon requested priority (6 month) review for this NDA because the sponsor believes ISOPTO® Carpine fulfills the unmet medical need for a safe and effective short-acting therapy for the induction of miosis and thinning of the iris prior to gonioscopic and surgical procedures involving the peripheral iris or trabecular meshwork. ISOPTO® Carpine is one of few medications used to reduce elevated IOP in subjects with acute angle-closure glaucoma. ISOPTO® Carpine is a direct acting cholinergic parasympathomimetic agent which acts through direct stimulation of muscarinic receptors and smooth muscle such as the iris and secretory glands. It contracts the ciliary muscle, causing increased tension on the scleral spur and opening of the trabecular meshwork spaces to facilitate outflow of aqueous humor. Outflow resistance is thereby reduced, lowering IOP. Pilocarpine also produces miosis through contraction of the iris sphincter muscle. Miosis relieves appositional angle narrowing and closure, which lowers IOP in certain types of angle-closure glaucoma. The product has been in the market in the United States since 1974.

To support the approval, the Applicant has provided data from 4 randomized, masked, controlled clinical trials that included an ISOPTO Carpine (pilocarpine hydrochloride ophthalmic solution) 2% treatment group.

The protocols inspected were similar in design:

Protocol C-91-47:
The C-91-47 was a 3-month study conducted to evaluate the safety and efficacy of a fixed combination of pilocarpine 1.75% and betaxolol 0.25% relative to either betaxolol 0.25% or pilocarpine 2% used alone. All three test articles were dosed TID for 90 days. Subjects diagnosed with primary open-angle glaucoma or ocular hypertension were eligible for enrollment if after a 3-week run-in period on betaxolol 0.25% (BID) their IOP at 8 AM was between 23 and 34 mmHg (inclusive). Qualified subjects were randomized equally to each of the three treatment groups at 8 centers.

Protocol C-91-54:
Protocol C-91-54 was a 3-month study conducted to evaluate the safety and efficacy of a fixed combination of pilocarpine 1.75% and betaxolol 0.25% relative to either betaxolol 0.25% or pilocarpine 2% used alone. All three test articles were dosed TID for 90 days. Subjects diagnosed with primary open-angle glaucoma or ocular hypertension were eligible for enrollment if after a 3-week run-in period on betaxolol 0.25% (BID) their IOP at 8 AM was between 23 and 34 mmHg (inclusive). Qualified subjects were randomized equally to each of the three treatment groups at 6 centers.

The primary endpoint for study C-91-47 and C-91-54 was mean change from baseline in IOP.

Two sites were selected for inspection due to high enrollment.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	**Protocol #: and # of Subjects:**	**Inspection Date**	**Final Classification**
Stephen M. Drance, MD University of British Columbia 2211, Westbrook Mall, Vancouver, BC V6T 1Z3	Protocol C90-105 Site # 1 69 Subjects	May 17, 2010	Pending Preliminary: VAI
***Robert Ritch, M.D.** 310 East 14th Street New York, New York 10003	Protocol C90-47 Investigator # 543 69 Subjects	November 13 and 20, 1996,	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary, letter has not yet issued to the CI.

****Robert Ritch, M.D: the inspection was not conducted in this cycle. Study C-91-47 in which Dr Ritch participated in support of NDA 200-890 were conducted 20 years ago under the IND for betaxolol hydrochloride ophthalmic solution (IND (b) (4)). Because the raw data from most of the clinical sites in support of NDA 200-890 were not present and maintained, DSI reviewed the inspection results from the prior NDA for the same study (Study C-91-47) in which Dr Ritch participated.***

1. Dr. Stephen M. Drance

University of British Columbia
2211, Westbrook Mall, Vancouver, BC V6T 1Z3
Ph: (604)-822-7451
Fax: (604)-822-7970
E-mail: smd@interchg.ubc.ca

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811, May 17, 2010. A total of 69 subjects were enrolled into the study and 17 medical records were reviewed.

The inspection evaluated informed consent and included review of source documents. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequate adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

Safety data in CRFs was compared to data listings for approximately 20% of the subjects and no significant discrepancies were noted. Efficacy test results were compared to data listings for approximately 50% of the subjects.

b. General observations/commentary:

The inspection of Dr. Drance's site revealed some protocol deviations.
A limited number of discrepancies (generally less than a total of 10 data points) were observed for temporal contrast sensitivity, motion detection and blue-cone perimetry when compared to data listings and were generally minor. A slightly higher number of discrepancies were observed for the Octopus 123 perimetry. The subjects with medical records had efficacy test result printouts in both their medical records and included in the CRFs.

The test results in the medical records and CRFs were identical for most subjects except for Subject 111 where the baseline test results for the temporal contrast, motion detection and blue-cone perimetry results in the medical records were notably different than those in the CRFs. The investigator had no explanation.

Some protocol deviations were observed. Examples of these deviations include consent forms not signed prior to or at the time of the screening, intraocular pressure not being done before the efficacy tests on subjects taking pilocarpine, stereophotographs not being done and approximately two subjects meeting an exclusion criterion (premenopausal critera and retinal disease) were included in the study with the approval of the investigator.

The observations made by the FDA inspector that are related to instances of isolated discrepancies between source document and CRF in temporal contrast, motion detection and blue-cone perimetry results, discrepancies (generally less than a total of 10 data points) for temporal contrast sensitivity, motion detection and blue-cone perimetry and Octopus 123 perimetry, failure to measure intraocular pressure and sterophotographs before the efficacy tests and inclusion of two subjects who did not meet inclusion criterion (premenopausal criteria and retinal disease) are unlikely to affect data integrity.

c. Assessment of data integrity:

Although regulatory violations were noted, these are considered isolated in nature and unlikely to importantly impact data integrity. Based on the preliminary inspectional findings, efficacy and safety data obtained from this site can be considered reliable.

Note: The observations noted above are based on communications with the DSI field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Robert Ritch, M.D.
310 East 14th Street
New York, New York 10003

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811 between November 13 and 20, 1996.

The studies in support of NDA 200-890 were conducted 20 years ago under the IND for betaxolol hydrochloride ophthalmic solution (IND (b) (4). Those studies were conducted to support approval of different product, for which the application was approved. The review division specifically requested that the sponsor submits an application to support the approval of pilocarpine because it is an "unapproved drug product" and consulted DSI to conduct inspections for NDA 200-890. However, during DSI's pre-assignment evaluation for NDA 200-890, it was realized that raw data from most of the clinical sites were not present as many of the CIs have destroyed their records on the basis of to the clinical sites internal record retention SOPs and in compliance with the ICH guidelines. Because the raw data from most of the clinical sites were not present and maintained, DSI reviewed the inspection results from the prior NDA for the same study that is submitted to support NDA 200-890 (Study C-91-47 in which Dr Ritch participated).

A total of 11 subjects were enrolled and randomized in the study. A record review was made in 5 of the 11 subjects.

The inspection included review of records for 5 subjects who were randomized. There were no Serious Adverse Events (SAEs) or Deaths during the study. The following items were reviewed for verification: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequacy of adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. General observations/commentary:

The inspection of Dr. Ritch's site revealed that the study was not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator. The following regulatory violations were observed during the inspection:

c. Assessment of data integrity:

Although regulatory violations were noted above, it is unlikely based on the nature of the violations that they significantly affect overall reliability of safety and efficacy data from the site, as they appear to be isolated findings. Based on the provided EIR for this site and Dr. Ritch's responses regarding the regulatory violations during the inspection, which were documented in the EIR, data derived from Dr. Ritch's site are considered reliable.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigators were inspected in support of the application. In general, the studies appear to have been conducted adequately and the data in support of the NDA appear reliable.

Note: Final headquarters classifications for Dr. Drance's inspection is pending at this time as the EIR has not been received. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIR.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200890	ORIG-1	ALCON INC	PILOCARPINE HYDROCHLORIDE OPHTHALMIC SOLUTION, 1%, 2% AND 4%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KASSA AYALEW
06/21/2010

TEJASHRI S PUROHIT-SHETH
06/21/2010

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	May 7, 2010
To:	Wiley Chambers, MD, Acting Director Division of Anti-Infective and Ophthalmology Products
Through:	Carlos Mena-Grillasca, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis
From:	Judy Park, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Labels and Labeling Review
Drug Name(s):	Isopto Carpine (Pilocarpine Hydrochloride Ophthalmic Solution) 1%, 2% and 4%
Application Type/Number:	NDA 200890
Applicant:	Alcon
OSE RCM #:	2010-85

This document contains proprietary data from the Institute for Safe Medication Practices (ISMP) and Quantros which cannot be shared outside of the FDA. Users wanting this information must contact Matthew Grissinger, RPh, FISMP, FASCP, Director, Error Reporting Programs at (215) 947-7797.

CONTENTS

1 INTRODUCTION

This review is written in response to a request from the Division of Anti-Infective and Ophthalmology Products for the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate container labels, carton and insert labeling for areas that could lead to medication errors.

1.1 REGULATORY HISTORY

Isopto Carpine (Pilocarpine Hydrochloride ophthalmic solution) is a currently marketed "Grandfathered" pre-38 drug and is currently on FDA's list of "Medically Necessary Unapproved Marketed Drugs". The Review Division requested the Applicant submit an NDA for this product. DMEPA found the name, Isopto Carpine, acceptable in OSE Review #2010-84 dated March 22, 2010.

2 METHODS AND RESULTS

2.1 LABELS AND LABELING

DMEPA used Failure Mode and Effects Analysis (FMEA)[1] in our evaluation of the container labels, carton labeling and insert labeling submitted on December 21, 2009 (see Appendices A and B).

All container labels and carton labeling are green and look identical except for the difference in strength.

2.2 MEDICATION ERROR RISK ASSESSMENT

Since Isopto Carpine is already marketed in the U.S., DMEPA searched the FDA Adverse Event Reporting System (AERS) and Institute of Safe Medication Practices (ISMP)* databases for post-marketing safety reports concerning medication errors involving the labels and labeling of the product.

2.2.1 AERS Search

The search was conducted on April 12, 2010 using the verbatim term "Isopto Carp%" and MedDRA Higher Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues."

The search did not result in any medication error cases associated with the use of Isopto Carpine in the FDA AERS database.

2.2.2 ISMP Databases*

DMEPA requested a search of the ISMP's databases for medication error cases involving Isopto Carpine. The cases from one of the databases captures errors reported between September 2008 and February 2010 and another database captures errors reported between February 2009 and February 2010.

---

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

* This document contains proprietary data from the Institute for Safe Medication Practices (ISMP) and Quantros which cannot be shared outside of the FDA. Users wanting this information must contact Matthew Grissinger, RPh, FISMP, FASCP, Director, Error Reporting Programs at (215) 947-7797.

The search resulted in eight medication errors with Pilocarpine of incorrect strengths due to "data errors, not filling errors." No further information was provided regarding the cases nor did they specify which brand of Pilocarpine products was associated with the errors.

2.2.2.1 Quantros* Database

The cases from Quantros database captures errors reported with Pilocarpine and Pilocarpine Hydrochloride between January 01, 2004 to January 25, 2010.

The search for medication error cases associated with "Pilocarpine" resulted in 45 cases all of which involved the branded product, Salagen, therefore these cases were not further analyzed.

The search for medication error cases associated with "Pilocarpine Hydrochloride" resulted in 85 cases. Forty of the 85 cases involved the branded products, Pilocar or Pilopine HS, therefore, these cases were not further analyzed. The remaining 45 cases did not specify which branded Pilocarpine Hydrochloride product was involved. The 45 cases are categorized as the following:

- Prescribing error (missing strength, dose or direction on prescriptions): n=20
- Wrong strength (dispensed or typed): n=7
- Wrong drug: n=7
- Wrong dosage form: n=3
- Computer entry error (refill entered wrong): n=2
- Wrong directions during dispensing: n=1
- Wrong quantity/size dispensed: n=2
- Others (used abbreviations, incorrect stop date, non-formulary drug): n=3

Of the 45 cases, the seven wrong strength cases were deemed as medication errors involving the labels and labeling of the product and were analyzed further. The 7 cases involved dispensing errors (n=5) where a different strength was dispensed than what was prescribed, stocking error where strengths were mixed up in the same storage bin (n=1), or entry error where wrong strength was entered (n=1).

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and carton labeling can be improved to minimize medication errors. Section 3.1 *Comments to the Division*, contains our recommendations for the insert labeling. Section 3.2 *Comments to the Applicant*, contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Brantley Dorch, OSE Project Manager, at 301-796-0150.

3.1 COMMENTS TO THE DIVISION

We have the following recommendations for the insert labeling:

A. General Comment

1. Do not use tall-man lettering in the proprietary name. The tall-man lettering is inappropriately used and we request that the name be revised so that 'ISOPTO' is presented in lower case letters to avoid the appearance of tall-man letters. Tall-man lettering is reserved for distinguishing specific portions of established names that are similar in order to differentiate known look-alike names that have been confused and resulted in medication errors.
2. Delete abbreviations (e.g. IOP, MROHD, LDPE) throughout the labeling. FDA launched a national campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols. As part of this campaign, FDA agreed not to approve such abbreviations in the approved labeling.

B. Dosage Forms and Strengths – Highlights and Full Prescribing Information

1. Present the strength as percent strength and concentration [e.g. 1 % (10 mg/mL), 2% (20 mg/mL), 4% (40 mg/mL)].

3.2 COMMENTS TO THE APPLICANT

We have the following recommendations for the container label and carton labeling:

A. General Comments – Container Labels and Carton Labeling

1. The container labels and carton labeling for all strengths look identical except for the difference in strength. Revise the labels and labeling so that all strengths are well differentiated from one another to prevent selection errors which have been reported in postmarketing with Pilocarpine ophthalmic products.
2. Relocate the route of administration and "Rx Only" statement to the principal display panel.
3. Decrease the prominence of the company name and graphic (tear drop with horizontal lines) so that it does not compete with the most important information on the labels and labeling such as drug name and strength. As currently presented, the company name and graphic are as prominent as the proprietary name.

B. Container Labels

1. The dark green font against the green background makes the information difficult to read. Revise the font color or contrast to increase readability.

4 page(s) of Draft Carton and Container Labels have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200890	ORIG-1	ALCON INC	PILOCARPINE HYDROCHLORIDE OPHTHALMIC SOLUTION, 1%, 2% AND 4%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUDY J PARK
05/07/2010

CARLOS M MENA-GRILLASCA
05/07/2010

DENISE P TOYER
05/07/2010

505(b)(2) ASSESSMENT

Application Information		
NDA # 200890	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Isopto Carpine Established/Proper Name: pilocarpine hydrochloride ophthalmic solution Dosage Form: ophthalmic solution 1%, 2% and 4% Strengths: 1%, 2% and 4%		
Applicant: Alcon		
Date of Receipt: December 22, 2009		
PDUFA Goal Date: June 22, 2010	Action Goal Date (if different): June 22, 2010	
Proposed Indication(s): ISOPTO Carpine is a muscarinic cholinergic agonist indicated for • open-angle glaucoma or ocular hypertension • acute angle-closure glaucoma • prevention of (b) (4) postoperative elevated IOP • induction of miosis		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO x

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Pilocarpine is pre-38 drug that has been marketed for many years. Currently the product is on the FDA compliance list of Medically Necessary Unapproved Marketed Drugs. The Applicant has referenced numerous literature articles for each of the clinical indications attached separately to the end of this document.

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES x NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO x

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO x

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO x

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) <u>and</u> there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" <u>or</u> if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO x

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" <u>and</u> there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "**NO**" <u>or</u> if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed x *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply <u>and</u> identify the patents to which each type of certification was made, as appropriate.)*

x No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

Table 2.7.3.1–1 Completed Safety/Efficacy Studies for ISOPTO Carpine (pilocarpine hydrochloride ophthalmic solution) 2%

Protocol Type (No.)	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing Duration	Total No. Randomized: Total No. Exposed to ISOPTO Carpine 2%
Safety/Efficacy C-90-42	Randomized, double-masked, parallel group	Adults, primary open-angle glaucoma or ocular hypertension	ISOPTO Carpine 2% Betaxolol Susp. 0.25% Betaxolol Susp. 0.25% /Pilocarpine 1% Betaxolol Susp. 0.25% /Pilocarpine 2%	1 drop BID 1 drop BID 1 drop BID 1 drop BID	90 days	76[a] total: 18 ISOPTO Carpine 2%
Safety/Efficacy C-90-105	Randomized, double-masked, parallel group	Adults, primary open-angle glaucoma	ISOPTO Carpine 2% Betaxolol Sol. 0.5% Timolol Sol. 0.5%	1 drop QID 1 drop BID 1 drop BID	24 months	69 total: 14 ISOPTO Carpine 2%
Safety/Efficacy C-91-47	Randomized, double-masked, parallel group	Adults, primary open-angle glaucoma or ocular hypertension	ISOPTO Carpine 2% Betaxolol Susp. 0.25% Betaxolol Susp. 0.25% /Pilocarpine 1.75%	1 drop TID 1 drop TID 1 drop TID	90 days	182 total: 61 ISOPTO Carpine 2%
Safety/Efficacy C-91-54	Randomized, double-masked, parallel group	Adults, primary open-angle glaucoma or ocular hypertension	ISOPTO Carpine 2% Betaxolol Susp. 0.25% Betaxolol Susp. 0.25% /Pilocarpine 1.75%	1 drop TID 1 drop TID 1 drop TID	90 days	186 total 64 ISOPTO Carpine 2%
					Total Subject/Patient Exposure	**513 total:** **157 ISOPTO Carpine**

[a]77 subjects were randomized but 1 never received the study medication.
ISOPTO Carpine 2% = ISOPTO Carpine (pilocarpine hydrochloride ophthalmic solution) 2%
Betaxolol Susp. 0.25% = Betaxolol Hydrochloride Ophthalmic Suspension, 0.25%
Betaxolol Sol. 0.5% = Betaxolol Hydrochloride Ophthalmic Solution, 0.5%
Timolol Sol 0.5% = Timolol Maleate Ophthalmic Solution, 0.5%
BID = twice daily TID = three times daily QID = four times daily

Table 2.7.3.1–2 Description of Completed Clinical Safety/Efficacy Studies for ISOPTO Carpine (pilocarpine hydrochloride ophthalmic solution) 2%

Study Number	No. of Study Centers Location	Study Start Status Total Enrollment/ Enrollment Goal	Design Control Type	Study Objective	Treatment Groups Dose, route[a] and regimen	No. of subjects/ patients by arm entered/ completed	Duration	Gender M/F Mean Age (range) for ITT Data Set	Diagnosis and Inclusion Criteria (IOP in mmHg)	Primary Endpoint
C-90-42	6 USA	January 1991 Completed 77[b] enrolled 72[c] planned	Randomized, double-masked, parallel group	Safety and Efficacy	PILO: 1 drop BID BET 0.25%: 1 drop BID Bet/Pilo 1%: 1 drop BID Bet/Pilo 2%: 1 drop BID	18/15 19/15 21/21 18/13	90 days	31 M 41 F 63.1 yrs (34-88 yrs)	POAG or OHT IOP: 23-30 at 8AM (OU) ≤ 5 difference between eyes	Mean IOP change from baseline
C-90-105	1 CAN	July 1991 Completed 69 enrolled 45 planned	Randomized, double-masked[d], parallel group	Safety and Efficacy	PILO: 1 drop QID Betaxolol 0.5%: 1 drop BID Timolol 0.5%: 1 drop BID	14/11 28/24 27/20	24 months	41 M 28 F 62.8 yrs (29-87 yrs)	POAG IOP: Not Applicable	Visual Function changes from baseline

Table 2.7.3.1–2 Description of Completed Clinical Safety/Efficacy Studies for ISOPTO Carpine (pilocarpine hydrochloride ophthalmic solution) 2% (Continued)

Study Number	No. of Study Centers Location	Study Start Status Total Enrollment/ Enrollment Goal	Design Control Type	Study Objective	Treatment Groups Dose, route[a] and regimen	No. of subjects/ patients by arm entered/ completed	Duration	Gender M/F Mean Age (range) for ITT Data Set	Diagnosis and Inclusion Criteria (IOP in mmHg)	Primary Endpoint
C-91-47	8 USA	July 1991 Completed 182 enrolled 180 planned	Randomized, double-masked, parallel group	Safety and Efficacy	PILO: 1 drop TID BET 0.25%: 1 drop TID Bet/Pilo 1.75%: 1 drop TID	61/41 61/51 60/48	90 days	63 M 98 F 59.1 yrs (31-77 yrs)	POAG or OHT IOP[e]: 23-30 at 8AM (OU) ≤ 5 difference between eyes	Mean IOP change from baseline at 8AM
C-91-54	6 USA	August 1991 Completed 186 enrolled 180 planned	Randomized, double-masked, parallel group	Safety and Efficacy	PILO: 1 drop TID BET 0.25%: 1 drop TID Bet/Pilo 1.75%: 1 drop TID	64/44 61/60 61/49	90 days	67 M 101 F 62.7 yrs (27-85 yrs)	POAG or OHT IOP[e]: 23-34 at 8AM (OU) ≤ 5 difference between eyes	Mean IOP changes from baseline

[a] Route of administration = topical ocular for all treatment groups for all studies. [b] one patient did not receive test article. [c] originally planned for 72 patients, subsequently amended to allow 120 patients however amendment was not implemented. [d]double-masked for betaxolol 0.5% and timolol 0.5% groups only, open-label for pilocarpine 2% group. [e]baseline IOP following minimum 3 week run-in period on betaxolol ophthalmic suspension, 0.25% BID. [f]non-dominant eye only; CAN = Canada; USA = United States of America; M = Males; F = Females; POAG = primary open-angle glaucoma; OHT = ocular hypertension; IOP = intraocular pressure; BID = twice daily; TID = three times daily; QID = four times daily; ITT = intent-to-treat

PILO = ISOPTO Carpine (pilocarpine HCl ophthalmic solution) 2%

BET 0.25% = Betaxolol HCl Ophthalmic Suspension, 0.25%

Bet/Pilo 1%, 2%, or 1.75% = Betaxolol HCl Ophthalmic Suspension 0.25%/Pilocarpine HCl Ophthalmic Solution, 1%, 2%, or 1.75%, respectively

Betaxolol 0.5% = Betaxolol HCl Ophthalmic Solution, 0.5%

Timolol 0.5% = Timolol Maleate Ophthalmic Solution, 0.5%

Table 2.7.3.1–3 Publications Supporting Safety/Efficacy of ISOPTO Carpine for Treatment of Open-Angle Glaucoma and Ocular Hypertension

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Pilo Conc.	Dose / Frequency	Duration of Follow-Up	Objective	Key Endpoints	Key Result / Conclusion
Diestelhorst 2000 Germany	prospective, randomized, open-label, comparator controlled, multicenter	POAG or OHT with IOP inadequately controlled by monotherapy with timolol 0.5% BID	242 latanoprost 0.005%: 121 pilocarpine 2%: 121	2%	latanoprost 0.005%: 1 gtt QD pilocarpine 2%: 1 gtt TID	6 months	compare additive effect of latanoprost and pilocarpine to timolol	IOP	similar adjunctive efficacy for latanoprost and pilocarpine when used with timolol
Geyer et al. 1997 Israel	prospective, nonrandomized, open-label, three-arm crossover, single center	untreated OHT	14	4%	Single dose of pilocarpine 4%, timolol 0.5%, and both on three separate visits	6 h post-dosing	evaluate additive effects of pilocarpine and timolol	IOP	similar efficacy between timolol and combined treatment
Laibovitz et al. 1996 USA	prospective, randomized, open-label, two-arm crossover, single center	POAG or OHT using timolol 0.5% BID	75	2%	pilocarpine 2%: 1 gtt QID for 2 weeks dorzolamide 2%: 1 gtt TID for 2 weeks	4 weeks	compare daily life impact of dorzolamide and pilocarpine	IOP, visual field, QoL survey (COMTol)	similar IOP-lowering efficacy but pilocarpine associated with more side effects and greater daily life interference
Konstas et al. 2001 Greece	prospective, randomized, two-arm crossover, single center	exfoliative glaucoma inadequately controlled with timolol 0.5% and dorzolamide 2%	30	4%	pilocarpine 4%: 1 gtt QID for 8 weeks latanoprost 0.005%: 1 gtt QD for 8 weeks	16 weeks	compare IOP-lowering efficacy of pilocarpine to latanoprost as third-line therapy	diurnal IOP	similar overall efficacy for pilocarpine and latanoprost

Table 2.7.3.1–3 Publications Supporting Safety/Efficacy of ISOPTO Carpine for Treatment of Open-Angle Glaucoma and Ocular Hypertension (continued)

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Pilo Conc.	Dose / Frequency	Duration of Follow-Up	Objective	Key Endpoints	Key Result / Conclusion
Thygesen 1990 Denmark	prospective, randomized, double-masked, single center	OAG or OHT and IOP > 21 mmHg after 3 weeks therapy with pilocarpine 4%	15 pilocarpine 4%: 5 pilocarpine 4% + timolol 0.5% BID (TP2): 5 pilocarpine 4% + timolol 0.5% QID (TP4): 5	4%	pilocarpine 4%: 1 gtt QID for 21 days TP2: 1 gtt BID for 21 days TP4: 1 gtt QID for 21 days	42 days	compare IOP-lowering efficacy of pilocarpine to a combined pilocarpine + timolol formulation	IOP	combination provided significantly greater IOP-lowering efficacy
Zadok et al. 1994 Israel	prospective, randomized, open-label, three-arm crossover, single center	OAG or OHT and IOP > 24 mmHg without therapy	43	4%	pilocarpine 4%: 1 gtt QID for 4 weeks timolol 0.5%: 1 gtt BID for 4 weeks combination: 1 gtt BID for 4 weeks	105 days	compare IOP-lowering efficacy of pilocarpine and timolol to a combined formulation	mean IOP reduction from baseline	combination provided greatest IOP-lowering efficacy
Sihota et al. 1996 India	prospective, randomized, double-masked, three-arm crossover, single center	OAG or OHT	10	1%	single dose of pilocarpine 1%, clonidine 0.125% and combination; 72 h washout between doses	12 hours per treatment	evaluate single dose response to pilocarpine 1%, clonidine 0.125% and combination	mean IOP reduction from baseline	combination provided greatest IOP-lowering efficacy

Table 2.7.3.1–3 Publications Supporting Safety/Efficacy of ISOPTO Carpine for Treatment of Open-Angle Glaucoma and Ocular Hypertension (continued)

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Pilo Conc.	Dose / Frequency	Duration of Follow-Up	Objective	Key Endpoints	Key Result / Conclusion
Drance 1998 Canada	prospective, randomized, double-masked (pilo open-label), single center	OAG with IOP ≥ 24 mmHg and evidence of optic disc and visual field abnormalities	68	2%	pilocarpine 2%: 1 gtt QID betaxolol 0.5%: 1 gtt BID timolol 0.5%: 1 gtt BID	24 months	compare effects of pilocarpine, betaxolol and timolol on visual function	visual field, contrast sensitivity and motion detection	similar visual function outcomes for all treatments
Vogel et al. 1992 USA	prospective, randomized, observer-masked, multicenter	POAG with IOP ≥ 22 mmHg	189	2% or 4%	pilocarpine 2%: 1 gtt QID (increased to 4% if IOP > 22 mmHg after 2 weeks) timolol 0.25%: 1 gtt BID (increased to 0.5% if IOP > 22 mmHg after 2 weeks)	24 months	compare visual field changes with each treatment	mean visual field threshold scores, rates of visual field loss per regression analysis	greater efficacy with timolol despite similar mean IOP and diurnal range of IOP
Robin 1996 USA	prospective, randomized, double-masked, multicenter (2 identically designed studies)	POAG or OHT with 3 months duration	Trial 1: 182 Pilo: 61 Betax: 61 Combo: 60 Trial 2: 186 Pilo: 64 Betax: 61 Combo: 61	2%	Pilocarpine 2%: 1 gtt TID Betaxolol 0.25%: 1 gtt TID Pilocarpine 1.75% / Betaxolol 0.25%: 1 gtt TID	3 months	evaluate safety and efficacy of fixed combination containing betaxolol 0.25% and pilocarpine 1.75%	mean IOP reduction	greatest efficacy with fixed combination

Table 2.7.3.1–3 Publications Supporting Safety/Efficacy of ISOPTO Carpine for Treatment of Open-Angle Glaucoma and Ocular Hypertension (continued)

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Pilo Conc.	Dose / Frequency	Duration of Follow-Up	Objective	Key Endpoints	Key Result / Conclusion
Toris et al. 2001 USA	prospective, randomized, double-masked, vehicle controlled, crossover, single center	OHT with no ocular medications for 3 weeks	30	2%	Day 1-8: pilocarpine 2% QID (one eye) and vehicle QID (fellow eye) Day 8-15: pilocarpine 2% QID + latanoprost 0.005% QD (one eye) and vehicle QID + latanoprost 0.005% QD (fellow eye) Day 16-35: washout Day 36-43: latanoprost 0.005% QD (one eye) and vehicle QD Day 43-50: latanoprost 0.005% QD + Pilo 2% QID (one eye) and vehicle QD + Pilo 2% QID	50 days	evaluate additive effects of pilocarpine and latanoprost	mean IOP, outflow facility	pilocarpine does not inhibit uveoscleral outflow mediated by latanoprost

Table 2.7.3.1–3 Publications Supporting Safety/Efficacy of ISOPTO Carpine for Treatment of Open-Angle Glaucoma and Ocular Hypertension (continued)

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Pilo Conc.	Dose / Frequency	Duration of Follow-Up	Objective	Key Endpoints	Key Result / Conclusion
Sharma et al. 1997 India	prospective, randomized, unmasked, single center	POAG	38 pilocarpine 2%: 26 eyes ALT: 26 eyes	2%	pilocarpine 2%: 1 gtt TID	2 years	compare pilocarpine and argon laser trabeculoplasty as primary treatment in newly diagnosed POAG	mean IOP	similar efficacy between pilocarpine and ALT
Bergea et al 1992 Sweden	prospective, randomized, unmasked, multicenter	POAG or exfoliative glaucoma	82 pilocarpine 4%: 42 ALT: 40	4%	pilocarpine 4%: 1 gtt QID	2 years	evaluate long-term efficacy of ALT and pilocarpine as initial treatment	number of patients with disease successfully controlled; failure defined by daily IOP ≥ 26 mmHg (confirmed one week later) or visual field loss	significantly fewer patients receiving ALT compared to pilocarpine required additional therapy at 12 and 24 months
Bergea et al 1994 Sweden	prospective, randomized, unmasked, multicenter	POAG or exfoliative glaucoma	82 pilocarpine 4%: 42 ALT: 40	4%	pilocarpine 4%: 1 gtt QID	2 years	evaluate long-term efficacy of ALT and pilocarpine as initial treatment	success rate of treatment, duration of therapy, mean IOP	success rates and duration of therapy not statistically significant; greater IOP lowering with ALT

Table 2.7.3.1–3 Publications Supporting Safety/Efficacy of ISOPTO Carpine for Treatment of Open-Angle Glaucoma and Ocular Hypertension (continued)

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Pilo Conc.	Dose / Frequency	Duration of Follow-Up	Objective	Key Endpoints	Key Result / Conclusion
Bergea et al 1995a Sweden	prospective, randomized, unmasked, multicenter	POAG or exfoliative glaucoma	82 pilocarpine 4%: 42 ALT: 40	4%	pilocarpine 4%: 1 gtt QID	2 years	evaluate long-term efficacy of ALT and pilocarpine as initial treatment	visual field loss	less visual field decay with ALT
Bergea et al 1995b Sweden	prospective, randomized, unmasked, multicenter	POAG or exfoliative glaucoma	82 pilocarpine 4%: 42 ALT: 40	4%	pilocarpine 4%: 1 gtt QID	2 years	evaluate long-term efficacy of ALT and pilocarpine as initial treatment	optic nerve damage	less optic nerve damage with ALT

POAG = primary open-angle glaucoma; OHT = ocular hypertension; QD = once daily; BID = twice daily; TID = three times daily; QID = four times daily; gtt = drop; QoL = quality of life; ALT = argon laser trabeculoplasty

Table 2.7.3.1–4 Publications Supporting Safety/Efficacy of ISOPTO Carpine for Treatment of Acute Angle-Closure Glaucoma

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Pilo Conc.	Dose / Frequency	Duration of Follow-Up	Objective	Key Endpoints	Key Result / Conclusion
Kobayashi et al. 1999 Japan	prospective, nonrandomized, unmasked, comparator controlled, single center	trabecular-iris angle ≤ 25°and receiving prophylactic LI	60 angle ≤ 25°: 30 wide angle: 30	2%	pilocarpine 4%: 1 gtt pre-biomicroscopy	60 min after pilocarpine administration	measure mechanical effects of pilocarpine on trabecular-iris angle	anterior chamber depth, trabecular-iris angle, angle opneing distance	pilocarpine increases angular width
Lai et al. 2001 Hong Kong	prospective, nonrandomized, unmasked, single center	first acute PACG attack with ≤ 1 week duration and corneal edema rendering immediate peripheral LI unsafe	9	4%	pilocarpine 4%: 1 gtt pre-DLPI; 1 gtt QID post-DLPI until LI	60 min after DLPI + follow-up through LI	evaluate the safety and efficacy of DLPI	IOP, VA, symptoms, corneal clarity, cells and flare, pupil size and reaction, iris changes, surgical complications	DLPI with topical IOP-lowering meds (including pilocarpine) was safe and effective
Lai et al. 1999 Hong Kong	prospective, nonrandomized, unmasked, single center	first acute PACG attack with ≤ 48 h duration	10	4%	pilocarpine 4%: 1 gtt pre-ALPI; 1 gtt QID post-ALPI until LI	60 min after ALPI + follow-up through LI	evaluate the safety and efficacy of limited (180°) ALPI	IOP, VA, symptoms, corneal clarity, cells and flare, pupil size and reaction, iris changes, surgical complications	limited (180°) ALPI with topical IOP-lowering meds (including pilocarpine) and without systemic IOP-lowering meds was safe and effective

Table 2.7.3.1–4 Publications Supporting Safety/Efficacy of ISOPTO Carpine for Treatment of Acute Angle-Closure Glaucoma (continued)

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Pilo Conc.	Dose / Frequency	Duration of Follow-Up	Objective	Key Endpoints	Key Result / Conclusion
Lam et al. 2002a Hong Kong	prospective, nonrandomized, unmasked, single center	first acute PACG attack with IOP ≥ 50 mmHg and duration ≤ 48 h	8	4%	pilocarpine 4%: 1 gtt pre-paracentesis; 1 gtt QID post-ALPI until LI (≤ 48 h);	2 h after paracentesis + follow-up through LI	evaluate safety and efficacy of immediate anterior chamber paracentesis with topical and systemic medications	IOP, VA, symptoms, corneal clarity, pupil size and reaction, gonioscopy, surgical complications	procedure was safe and effective
Lam et al. 1998 Hong Kong	prospective, nonrandomized, unmasked, single center	first acute PACG attack with IOP ≥ 40 mmHg	10	4%	pilocarpine 4%: 1 gtt pre-ALPI; 1 gtt QID post-ALPI until LI (≤ 48 h);	60 min after ALPI + follow-up through LI	evaluate the safety and efficacy of ALPI	IOP, VA, symptoms, corneal clarity, pupil size and reaction, gonioscopy, surgical complications	ALPI with topical IOP-lowering meds (including pilocarpine) and without systemic IOP-lowering meds was safe and effective
Lam et al. 2002b Hong Kong	prospective, randomized, unmasked, comparator controlled, single center	first acute PACG attack with IOP > 40 mmHg and corneal edema rendering immediate peripheral LI unsafe	64 (73 eyes) ALPI: 32 (33 eyes) acetazolamide (oral and IV): 32 (40 eyes)	4% pre-ALPI; 1% post-ALPI	pilocarpine 4%: 1 gtt pre-ALPI; 1 gtt QID post-ALPI until LI (≤ 48 h); fellow eye dosed if occludable angle noted by gonioscopy	24 h after ALPI + follow-up through LI	evaluate the safety and efficacy of ALPI vs systemic medical therapy	IOP, VA, symptoms, corneal clarity, pupil size and reaction, gonioscopy, surgical complications	ALPI safe and more effective than systemic medications

Table 2.7.3.1–4 Publications Supporting Safety/Efficacy of ISOPTO Carpine for Treatment of Acute Angle-Closure Glaucoma (continued)

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Pilo Conc.	Dose / Frequency	Duration of Follow-Up	Objective	Key Endpoints	Key Result / Conclusion
Pavlin et al. 1999 Canada	prospective, nonrandomized, unmasked, single center	plateau iris and persistent narrow angle after patent peripheral Nd:YAG LI	10	2%	pilocarpine 4%: 1 gtt pre-biomicroscopy	30 min after pilo admin	describe angle configuration changes associated with room lighting conditions (illuminated and dark) and pilocarpine	measurements of angle opening distance, iris thickness, and trabecular meshwork-ciliary process distance	pilocarpine effectively thins the iris and opens the angle in plateau iris syndrome

LI = laser iridotomy; DLPI = diode laser peripheral iridoplasty; ALPI = argon laser peripheral iridoplasty; IV = intravenous; VA = visual acuity; Nd:YAG = neodymium yttrium aluminum garnet; gtt = drop; QID = four times daily; PACG = primary angle-closure glaucoma

Table 2.7.3.1–5 Publications Supporting Safety/Efficacy of ISOPTO Carpine for Preventing (b) (4) Postoperative Elevated IOP

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Pilo Conc.	Dose / Frequency	Duration of Follow-Up	Objective	Key Endpoints	Key Result / Conclusion
Dapling et al. 1994 United Kingdom	prospective, randomized, observer-masked, comparator controlled, single center	POAG with IOP >21mmHg undergoing ALT	75 pilocarpine 4%: 23 apraclonidine 1%: 26 Combo: 26	4%	pilocarpine 4%: 1 gtt immediately after ALT apraclonidine 1%: 1 gtt immediately after ALT combination: 1 gtt each immediately after ALT	3 h	compare efficacy of pilocarpine, apraclondine and combination during ALT	IOP, heart rate and blood pressure	combination more effective than individual agents
Elsas et al. 1991 Norway	prospective, randomized, unmasked, comparator controlled, single center	exfoliative or OAG subjects undergoing ALT	50 pilocarpine 2%: 25 no treatment 25	2%	pilocarpine 2%: 2 gtt 1 h prior to surgery	24 h	evaluate efficacy of pilocarpine treatment prior to ALT	IOP	pilocarpine decreased magnitude of post-ALT IOP spikes
Fernandez-Bahamonde et al. 1990 Puerto Rico	prospective, randomized, unmasked, comparator controlled, single center	Hispanic subjects undergoing LI	22 pilocarpine 4%: 11 apraclonidine 1% + pilocarpine 4%: 11	4%	pilocarpine 4%: 1 gtt administered 30 min and 15 min prior to surgery apraclonidine 1%: 1 gtt 1 prior to and immediately after LI	4 weeks	compare efficiacy of apraclondine + pilocarpine vs pilocarpine during LI	IOP	pilocarpine does not interfere with effectiveness of apraclonidine

Table 2.7.3.1–5 Publications Supporting Safety/Efficacy of ISOPTO Carpine for Preventing (b) (4) Postoperative Elevated IOP (continued)

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Pilo Conc.	Dose / Frequency	Duration of Follow-Up	Objective	Key Endpoints	Key Result / Conclusion
Lewis et al. 1998 USA	retrospective, unmasked, single center	NOA, OAG or CACG receiving LPI and pretreated with pilocarpine (1% to 4%) and apraclonidine (0.5% to 1%)	179 (289 eyes)	1% to 4%	1 gtt of pilocarpine and apraclonidine 1 h prior to surgery	2 h	determine incidence of IOP rise ≥ 10 mmHg after LPI in eyes treated with pilocarpine and apraclonidine	IOP	clinically significant IOP rise after LPI is very uncommon
Liu et al. 2002 Taiwan	prospective, randomized, unmasked, comparator controlled, single center	ACG receiving Nd:YAG LI	47 (one eye randomized to pilocarpine 4%; fellow eye to pilocarpine 4% + latanoprost 0.005%)	4%	pilocarpine 4%: 1 gtt administered 45 min prior to surgery pilocarpine 4% + latanoprost 0.005%): 1 gtt administered 45 min prior to surgery	2 weeks	evaluate the efficacy of latanoprost for reducing IOP after Nd:YAG LI in patients with preoperative pilocarpine treatment	IOP	late onset of effect by latanoprost limits any additive benefit to pilocarpine
Ren et al. 1999 USA	prospective, randomized, unmasked, comparator controlled, single center	phakic subjects with POAG undergoing ALT	228 apraclonidine 1%: 114 pilocarpine 4%: 114	4%	apraclonidine 1%: 1 gtt administered 15 min prior to surgery pilocarpine 4%: 1 gtt administered 15 min prior to surgery	24 h	compare efficacy of apraclonidine vs pilocarpine during ALT	IOP	pilocarpine generally more effective than apraclonidine

POAG = primary open-angle glaucoma; ALT = argon laser trabeculoplasty; LI = laser iridotomy; gtt = drop; CACG = chronic angle-closure glaucoma; NOA = narrow open-angle; Nd:YAG = neodymium yttrium aluminum garnet; LPI = laser peripheral iridotomy

Table 2.7.3.1–6 Publications Supporting Use of ISOPTO Carpine for Management of Intraocular Pressure in Pediatric Glaucoma

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Duration of Follow-Up	Objective	Key Result / Conclusion*
Asrani 1995 USA	retrospective, single center	aphakic glaucoma	34 (64 eyes)	6-141 months (Avg = 57.7 months)	Determine interval between cataract surgery and onset of glaucoma, effect of age at time of cataract surgery	Medications alone (including pilocarpine) were able to control IOP in 21 of 33 (63.6%) eyes with no surgical intervention
Awad 1999 Saudi Arabia	retrospective, single center	Sturge-Weber	18 (22 eyes)	12-148 months (Avg = 62 months)	Describe patterns of clinical practice	4 of 22 eyes (2 patients, ages 2 years and 20 years) were treated with pilocarpine + betaxolol. None of these 4 eyes required surgical intervention.
Barsoum-Homsy 1986 Canada	retrospective, single center	pediatric glaucoma	63 (95 eyes)	2 months -10 years (Avg = 4.4 years)	Evaluate the incidence of 3 major groups of pediatric glaucoma; describe and compare treatment modalities; establish the prognosis for each group	Medical treatment (includes pilocarpine) alone sufficient for 10 of 23 eyes. 11 of 13 patients treated surgically also required medication
		secondary glaucoma (includes aphakic)	20 (24 eyes)			Medical treatment (includes pilocarpine) alone sufficient for 17 of 47 eyes. 19 of 22 eyes treated surgically also required medication
		glaucoma associated with congenital anomalies	29 (47 eyes)			23 of 24 eyes required surgical treatment. 4 of 23 eyes treated surgically also required medication (includes pilocarpine)
		primary congenital glaucoma	14 (24 eyes)			

Table 2.7.3.1–6 Publications Supporting Use of ISOPTO Carpine for Management of Intraocular Pressure in Pediatric Glaucoma (Continued)

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Duration of Follow-Up	Objective	Key Result / Conclusion*
Boger 1981 USA	prospective, unmasked, single center	pediatric glaucoma with uncontrolled IOP	34	Up to 21 months	Evaluate the IOP-lowering efficacy of timolol when asdded to maximum tolerated medical therapy	Pilocarpine was a component of the treatment for 7 of 34 (21%) patients age 11 – 24 years)
Bussières 2009 Canada	retrospective, single center	Pediatric glaucoma < 18 years of age	163 (254 eyes)	0.3 – 18.5 years	Describe a cohort of pediatric glaucoma patients in Quebec	Medical treatment alone was sufficient for 50 of 161 patients (31%). Pilocarpine was the 2nd most frequently prescribed medication between 1980 and 2000 (627 of 2885 presriptions, 21.7%) In the last year of study (2000), pilocarpine accounted for approximately 18% of prescriptions.
Enyedi 1999	prospective, unmasked, single center	Pediatric glaucoma patients prescribed latanoprost	31 (37 eyes)	1-19 months (Avg = 7 months)	Evaluate the safety and efficacy of latanoprost for children with glaucoma when added to current IOP-lowering treatment	Pilocarpine a component of medical therapy for 2 of 31 patients (1 year of age with aphakic glaucoma and 4 years of age with Sturge Weber).

Table 2.7.3.1–6 Publications Supporting Use of ISOPTO Carpine for Management of Intraocular Pressure in Pediatric Glaucoma (Continued)

Citation / Location	Study Design	Diagnosis / Inclusion	# Subjects	Duration of Follow-Up	Objective	Key Result / Conclusion*
Papadopoulos 2007 UK	prospective, multi center	Newly diagnosed pediatric glaucoma patients < 17 years of age	99 (133 eyes)	12 months	Examine the incidence, detection patterns, current management and IOP control in children newly diagnosed with glaucoma in the UK	Pilocarpine was the most commonly prescribed medication prior to surgery for primary congenital glaucoma patients
Plager 2009 USA	prospective, randomized, masked, comparator controlled, multi center	glaucoma or OHT; pediatric patients < 6 years of age	105	3 months	Study designed to evaluate the efficacy of betaxolol and timolol for reducing IOP in pediatric patients	Pilocarpine used for 2 of 45 (4.4%) patients controlled by monotherapy, and 8 of 25 (32%) patients on multiple IOP-lowering medications prior to study entry
Whitson 2008 USA	prospective, randomized, masked, comparator controlled, multi center	glaucoma or OHT; pediatric patients < 6 years of age	78	3 months	Study designed to evaluate the efficacy of brinzolamide and levobetaxolol for reducing IOP in pediatric patients	Pilocarpine used for four of 20 patients (20%) on multiple IOP-lowering medications prior to study entry

*Key result relevant to pilocarpine

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200890	ORIG-1	ALCON INC	PILOCARPINE HYDROCHLORIDE OPHTHALMIC SOLUTION, 1%, 2% AND 4%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LORI M GORSKI
04/22/2010
505b2 assessment

RPM FILING REVIEW

Application Information		
NDA # 200890	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Isopto Carpine Established/Proper Name: pilocarpine hydrochloride Dosage Form: ophthalmic solution Strengths: 1%, 2% and 4%		
Applicant: Alcon		
Date of Application: December 22, 2009 Date of Receipt: December 22, 2009		
PDUFA Goal Date: June 22, 2010	Action Goal Date : May 31, 2010	
Filing Date: February 19, 2010	Date of Filing Meeting: January 25, 2010	
Chemical Classification: 3		
Proposed indications: the reduction of IOP in patients with open angle glaucoma or ocular hypertension, (b) (4) for acute angle-closure glaucoma, for the prevention of (b) (4) postoperative elevated IOP associated with (b) (4) laser surgery and induction of miosis.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***		☐ 505(b)(1) X 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☐ Standard X Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other: **Drug is Pre-38 and is currently the product is on the FDA compliance list of Medically Necessary Unapproved Marketed Drugs.**		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):				
List referenced IND Number(s): none				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: X Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: X Not in arrears ☐ In arrears
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*	

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		x		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		x		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		x		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		x		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		x		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			x	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		x		No exclusivity requested

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?			x	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			x	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**x**			
Index: Does the submission contain an accurate comprehensive index?	**x**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: x legible x English (or translated into English) x pagination x navigable hyperlinks (electronic submissions only) **If no**, explain.	**x**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*			x	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			x	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	x			
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	x			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	x			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	x			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	x			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	x			

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	x			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				The sponsor has requested a full waiver but has been asked to provide literature to reflect known usage in children
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			x	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***			x	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		x		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	x			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	x Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) x Carton labels x Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	x			
Is the PI submitted in PLR format?	x			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			x	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	**x**			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			x	
REMS consulted to OSE/DRISK?			x	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	x			
OTC Labeling	**x Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***			x	

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			x	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			x	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			x	
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***			x	

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			x	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			x	
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***			x	

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

TEAM MEETING AGENDA
January 25, 2010

NDA	200890
Drug	Isopto Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2% and 4%
Indication	The reduction of IOP in patients with open angle glaucoma or ocular hypertension, [redacted] for acute angle-closure glaucoma, for the prevention of [redacted] postoperative elevated IOP associated with [redacted] laser surgery and Induction of miosis.
Sponsor	Alcon
Received	December 22, 2009
Day 60:	February 19, 2010
Day 74:	March 5, 2010
First Reviews	May 7, 2010
User Fee Date	June 22, 2010

	Primary Reviewer Team Leader	**Filable**	**First Review Date**
Project Manager	Lori Gorski Maureen Dillon Parker	pre-38 Medically Necessary Unapproved Marketed Drug	505b2
Micro	Denise Miller Jim Mc Vey	No filing issues	
Stats	Rima Izem Yan Wang	No filing issues	
Pharm/Tox	Conrad Chen Wendy Schmidt	No filing issues	
CMC	Rao Kambhampati Steve Miller	No filing issues	
Clin Pharm	Eric Zhang Chuck Bonapace	No filing issues	
Clinical	Bill Boyd	No filing issues	
OSE	Brantley Dorch Judy Park	Proprietary name under review	
DSI	Jean Mulinde Kassa Ayalew	Consult to be sent	

From: Gorski, Lori M
Sent: Friday, January 29, 2010 8:24 AM
To: Chambers, Wiley A; Boyd, William M; Harris, Jennifer; Nevitt, Martin; Wadhwa, Sonal; Lloyd, Rhea; Lim, Lucious; Schmidt, Wendelyn J; Ng, Linda L; Bonapace, Charles; Wang, Yan; McVey, James; Puglisi, Michael; Miller, Stephen; Chen, Conrad H; Izem, Rima; Zhang, Yongheng; Miller, Denise; Izadi, Fariba; Kambhampati, Rao V; Loewke, Sally A; Dorch, Brantley; Mulinde, Jean; Park, Judy; Ayalew, Kassa; Samanta, Susmita
Subject: NDA 200890 pilocarpine Recap of filing meeting on January 25, 2010

Hi All

Just a recap of Mondays filing meeting for Alcon's pilocarpine literature NDA. This is a Priority review.

1. If you have any issues or requests to convey to Alcon please email them to me as soon as possible.

2. There were no filing issues. See reviewers filing reviews for specific information.

3. First review target date is May 7th and everyone agreed they could meet that date or sooner.

4. Rima and Bill will provide Lori with a request for additional literature to support the proposed indications.

5. Alcon has been advised they should change their pediatric section from 'complete waiver' of studies to 'completed' and provide available literature for labeling children.
   This application will go to PERC on March 24, 2009.

6. Lori will follow up with a consult to DSI and with DDMAC once the label has been drafted by the division.

If I've missed anything please let me know!

Thanks everyone.

Lori Gorski
Project Manager
Division of Anti-Infective & Ophthalmology Products
Phone 301-796-0722
Fax 301-796-9881
E-mail lori.gorski@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200890	ORIG-1	ALCON INC	PILOCARPINE HYDROCHLORIDE OPHTHALMIC SOLUTION, 1%, 2% AND 4%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LORI M GORSKI
01/29/2010
RPM filing review original NDA

DSI CONSULT: Request for Clinical Inspections

Date: February 1, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Jean Mulinde, Medical Officer, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: William Boyd, MD, Clinical Team Leader, 301-796-0686
Division of Anti-Infective and Ophthalmology Products

From: Lori Gorski, Regulatory Health Project Manager, 301-796-0722
Division of Anti-Infective and Ophthalmology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-200890
Applicant/ Applicant contact information:
Michael C. Son, Ph.D., RAC
Senior Manager, Regulatory Affairs
Alcon Laboratories, Inc.
Michael.Son@AlconLabs.com
(817) 551-8120

Drug Proprietary Name: Isopto Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2% and 4%
NME: No
Review Priority: Priority

Study Population includes < 17 years of age: Yes
Is this for Pediatric Exclusivity: No

Proposed Indications:
For the reduction of IOP in patients with open angle glaucoma or ocular hypertension; (b) (4) for acute angle-closure glaucoma; for the prevention of (b) (4) postoperative elevated IOP associated with (b) (4) laser surgery; and for the induction of miosis.

PDUFA: June 22, 2010
Action Goal Date: May 31, 2010
Inspection Summary Goal Date: May 7, 2010

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
DSI Choice	C-90-42	76	reduction of IOP in patients with open angle glaucoma or ocular hypertension
DSI Choice	C-90-105	69	reduction of IOP in patients with open angle glaucoma or ocular hypertension
DSI Choice	C-91-47	182	reduction of IOP in patients with open angle glaucoma or ocular hypertension
DSI Choice	C-91-54	186	reduction of IOP in patients with open angle glaucoma or ocular hypertension

An inspection is requested for at least one site for each of these clinical trials only as your resources permit. See rationale below

III. Site Selection/Rationale

The clinical portion of the application has been preliminarily reviewed, and no issues have been identified to date to suggest a problem with data integrity.

This is a 505(b)(2) application primarily based on literature but which includes submission of clinical study reports. All of the clinical trials submitted in NDA 200890 for Isopto Carpine were conducted under Alcon's IND for betaxolol hydrochloride ophthalmic solution, IND (b) (4) These clinical trials were completed approximately 15-20 years ago.

Studies C-91-47 and C-91-54 were previously reviewed by clinical in NDA 20-619 for BetopticPilo which was approved 4/17/97 but never marketed.

An inspection is requested for at least one site for each of these clinical trials only as your resources permit.

Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
__X__ Other (specify): Routine Inspections

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Goal Date for Completion:
If routine inspections are completed the Inspection Summary Results should be provided by May 7, 2010**.** We intend to issue an action letter on this application by May 31, 2010. The PDUFA due date for this application is **June 22, 1010.**

Should you require any additional information, please contact Lori Gorski at 301-796-0722 or William Boyd, MD at 301-796-0686.

Additional Information:

This is an electronic NDA. The clinical portion of the application has been preliminarily reviewed and no issues have been identified to date to suggest a problem with data integrity.

C-90-42 Investigators

LIST OF INVESTIGATORS

Inv. No.	Name/Address	Dates of Participation
1277	Fred Blum, M.D. Madison Eye Associates Suite 400 One South Park St. Madison, WI 53715	3/7/91 - 8/8/91
1008	Barry Horwitz, M.D. 8945 Long Point RD. Houston, TX 77055	3/18/91 - 8/22/91
1157	Jerrold Levin, M.D. Eye Care Center Of Cincinnati 5300 Cornwall Rd. Cincinnati, OH 45242	3/5/91 - 9/3/91
331	Alan Mandell, M.D. O'Ryan Medical Building 6005 Park St. Memphis, TN 38138	2/23/91 - 9/4/91
1118	Alfred Roberts, M.D. Denver Eye Surgery Center 13772 Denver West Park Parkway Building 55, Suite 100 Golden, CO 80401	1/30/91 - 9/25/91
415	Stuart Terry, M.D. 215 E. Quincy Suite 200 San Antonio, TX 78215	3/8/91 - 9/6/91

C-90-105 Investigator

Investigator Name/Number	**Address**	**Dates of Participation**	**Number of Subjects Enrolled**
Stephen M Drance, MD Investigator No. 102	University of British Columbia Health Sciences Mall Vancouver, BC V6T 1Z3	July 28, 1991 to June 13, 1996	69

C-91-47 Investigators

LIST OF INVESTIGATORS

Inv. No.	Name/Address	Dates of Participation
1402	Margaret Digaetano, M.D. Halifax Medical Center 311 N. Clyde Morris Ave. Suite 520 Daytona Beach, FL 32114	9/17/91 - 4/16/92
970	Robert Lehmann, M.D. Lehmann Eye Center 4848 N.E. Stallings Suite 102 Nacogdoches, TX 75961	12/16/91 - 6/5/92
331	Alan Mandell, M.D. St. Frances Professional Building Suite 926-B 6005 Park Ave. Memphis, TN 38138	8/5/91 - 2/3/92
1473	Thomas Mundorf, M.D. 1718 E. Fourth St. Suite 902 Charlotte, NC 28204	12/5/91 - 5/21/92
1394	Stephen Perlmutter; M.D. Hope Eye Center 3150 N. 7th St. Phoenix, AZ 85014	8/22/91 - 11/11/91

Inv. No.	Name/Address	Dates of Participation
543	Robert Ritch, M.D. New York Eye and Ear Infirmary 310 E. 14th St. New York, NY 10003	12/24/91 - 6/3/92
1390	Julia Sargent, M.D. Barton Research, Inc. 4029 S. Capitol of Texas Highway Suite 125 Austin, TX 78704	11/22/91 - 6/6/92
1212	Michael Stiles, M.D. Hunkler Eye Clinic 4321 Washington Suite 6000 Kansas City, MO 64111	Did Not Enroll Any Patients
1401	Ernest Wilkinson, M.D. Rocky Mountain Eye Center 4400 S. 700 E. Salt Lake City, UT 84107	8/12/91 - 3/2/92

C-91-54 Investigators

LIST OF INVESTIGATORS

Inv. No.	Name/Address	Dates of Participation
470	Donald Brotherman, M.D. Professional Plaza 3 10 Medical Parkway Dallas, TX 75234	8/6/91 - 4/21/92
1229	Luther Crabb, M.D. Eye Tech 5406 Knight Arnold Memphis, TN 38116	12/5/91 - 5/21/92
1200	Kenneth Fox, M.D. 110 Cambridge St. Fredricksburg, VA 22405	9/17/91 - 5/06/92
1403	Jeffrey Morris, M.D. 477 N. el Camino Real Suite A-210 Encinitas, CA 92024	08/06/91 - 3/23/92
471	Gerald Meltzer, M.D. Barton Research, Inc. 4999 E. Kentucky Ave. Suite 202 Denver, CO 80222	No Patients Enrolled
1393	Michael Rotberg, M.D. Doctors Clinic 2300 5th Ave. Vero Beach, FL 32960	8/20/91 - 4/17/92
271	Robert Stewart, M.D. Houston Eye Associates 2855 Gramercy Houston, TX 77025	8/28/91 - 6/19/92

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200890	ORIG-1	ALCON INC	PILOCARPINE HYDROCHLORIDE OPHTHALMIC SOLUTION, 1%, 2% AND 4%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LORI M GORSKI
02/02/2010
DSI consult for clinical sites