CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-890

MEDICAL REVIEW(S)

CLINICAL REVIEW for NDA 200-890

Application Type	NDA
Application Number(s)	200-890
Priority or Standard	Priority
Submit Date(s)	December 22, 2009
Received Date(s)	December 22, 2009
PDUFA Goal Date	June 22, 2010
Division / Office	DAIOP/OAP
Reviewer Name(s)	William M. Boyd, M.D.
Review Completion Date	May 7, 2010
Established Name	pilocarpine ophthalmic solution 1, 2, 4%
(Proposed) Trade Name	Isopto Carpine
Therapeutic Class	cholinergic agonist
Applicant	Alcon Research, Ltd.
Formulation(s)	topical ophthalmic solution
Dosing Regimen	one drop in the eye(s) up to four times daily
Proposed Indication(s)	1) Open-angle glaucoma or ocular hypertension 2) Acute angle-closure glaucoma 3) Prevention of (b) (4) postoperative elevated IOP 4) Induction of miosis
Intended Population(s)	Pediatric and adult patients

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 200890, Isopto Carpine (pilocarpine ophthalmic solution) 1, 2, and 4%, is recommended for approval for:

1) the reduction of elevated intraocular pressure in patients with ocular hypertension or open angle glaucoma
2) the management of acute angle closure glaucoma
3) the prevention of postoperative elevated IOP associated with (b) (4) laser surgery
4) the induction of miosis

with the labeling submitted by Alcon on 6/16/2010 and found in this Medical Officer Review (see Appendix 1).

1.2 Risk Benefit Assessment

The benefits of Isopto Carpine (pilocarpine ophthalmic solution) 1, 2, and 4% for the recommended indications outweigh the associated risks.

This is a 505(b)(2) application primarily based on literature but which includes submission of clinical study reports. The submitted Clinical Study reports were reviewed and summarized in this review. These studies were completed 15-20 years ago.

Support for the proposed indications are also provided by a literature review conducted by the applicant and by an additional literature review conducted by the Medical Officer.

The most frequently reported adverse reactions occurring in ≥5 % of patients in the controlled studies were: headache, blurred vision, eye irritation, visual impairment (dim, dark, or “jumping” vision), and eye pain.

Overall, the majority of the most common adverse events (ocular or nonocular) reported in patients treated with pilocarpine, began with the onset of study medication use, were transient in nature, and resolved without treatment with the exception of headaches which in many cases required concomitant therapy to resolve.

A five-year Periodic Safety Update Report on pilocarpine hydrochloride (2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml, 60 mg/ml and 40 mg/g) for ophthalmic use was compiled for the regulatory authorities in the European Union. It summarizes

the safety data received from world-wide sources by Alcon's Department of Medical Safety from 01 August 2004 to 31 July 2009. Approximately (b) (4) units of Alcon products containing different concentrations of pilocarpine hydrochloride for ophthalmic use were distributed during the period covered by this safety report.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

1.4 Recommendations for Post-market Requirements and Commitments

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

2 Introduction and Regulatory Background

Pilocarpine hydrochloride ophthalmic solution (1%, 2%, and 4%) has been used as a miotic for the clinical therapy of primary open-angle glaucoma and other forms of chronic glaucoma since 1876. Pilocarpine is a direct acting cholinergic agonist. It is believed that pilocarpine produces contraction of the ciliary muscle resulting in opening of the trabecular meshwork spaces to facilitate outflow of the aqueous humor, thus lowering intraocular pressure (IOP).

The support for the fourth indication (induction of miosis) is therefore supported and derived from the other three indications.

2.1 Product Information

Isopto Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2% or 4% is a sterile, preserved ophthalmic solution containing 1%, 2% or 4% of pilocarpine hydrochloride. Isopto Carpine was developed by Alcon Laboratories more than 50 years ago as a topical therapy for the reduction of elevated intraocular pressure (IOP).

Pilocarpine is an alkaloid obtained from jaborandi leaves (*Pilocarpus microphyllus*) with chlorinergic actions.

Since Isopto Carpine is a sterile aqueous solution presented in a multiple-dose container, benzalkonium chloride (0.01%) is added (b) (4) .

Isopto Carpine is packaged in a plastic bottle with a plastic dispensing plug and plastic closure. The bottle is made of natural low density polyethylene (LDPE), the dispensing plug is made of green LDPE and the closure is made of green polypropylene (PP). Tamper evidence is provided by a (b) (4) shrink band, which when heated shrinks to conform around the neck and closure area of the bottle.

Table 3.2.P.1–1 Composition of ISOPTO Carpine 1%, 2% and 4%

Component	Concentration (%w/v)			Function	Compendial Status
	Isopto Carpine 1%[a]	Isopto Carpine 2%[b]	Isopto Carpine 4%[c]		
Pilocarpine hydrochloride	1.0	2.0[d]	4.0[d]	Active Ingredient	USP
Boric acid	(b) (4)			(b) (4)	NF
Sodium chloride					USP
Sodium citrate, dihydrate					USP
Benzalkonium chloride	0.01	0.01	0.01		NF
Hypromellose 2910 (HPMC)	(b) (4)				USP
Hydrochloric Acid and/or Sodium Hydroxide				pH Adjustment	NF NF
Purified Water				(b) (4)	USP

[a] Formulation ID No. 10026; [b] Formulation ID No. 11631; [c] Formulation ID No. 99222;
[d] Up to (b) overage may be added (b) (4)

Table 3.2.P.5.1–1 Regulatory Acceptance Specifications for ISOPTO Carpine

Test	Regulatory Acceptance Specification
Pilocarpine Hydrochloride Identity[a] (HPLC)	Positive
Pilocarpine Hydrochloride Identity[a] (TLC)	Positive
Pilocarpine Hydrochloride Assay	(b) (4)% of Label
Pilocarpine Hydrochloride Impurities[b]: (b) (4) Any Single Unspecified Impurity Total Impurities	 NMT (b) (4) NMT NMT NMT NMT NMT
Benzalkonium Chloride Identity [a]	Positive
Benzalkonium Chloride Assay	(b) (4)% of Label
pH	3.5 to 5.5
Osmolality	(b) (4)
Color	Colorless (≤ Ph Eur Ref Solution B9)
Clarity	Practically clear (NMT (b) (4)
Viscosity	(b) (4)
Particulate Matter	NMT (b) (4) NMT NMT
Bacterial Endotoxins[a]	NMT (b) (4) mL
Sterility	Meets USP Requirements

[a] Release test only
[b] Includes all impurities other than drug substance process impurities.

2.2 Tables of Currently Available Treatments for Proposed Indications

INDUCTION OF MIOSIS

There are no currently approved topical ophthalmic products for the induction of miosis. Miostat (carbachol intraocular solution) is indicated for obtaining miosis during surgery.

POSTOPERATIVE IOP ELEVATION

Iopidine (apraclonidine hydrochloride ophthalmic solution) is indicated to control or prevent postsurgical elevations in intraocular pressure that occur in patients after argon laser trabeculoplasty, argon laser iridotomy or Nd:YAG posterior capsulotomy.

ACUTE ANGLE CLOSURE

Diamox (acetazolamide tablets) 125mg and 250 mg and Diamox (acetazolamide for Injection) are approved preoperatively in acute angle-closure glaucoma where delay of surgery is desired in order to lower intraocular pressure.

Methazolamide is currently marketed to decrease IOP in patients with chronic open-angle glaucoma, secondary glaucoma and preoperatively in acute angle-closure glaucoma prior to surgery.

Osmoglyn (glycerin), Osmitrol (mannitol injection), and Ismotic (isosorbide) are hyperosmotic agents used to treat the markedly elevated eye pressure seen in acute angle closure. Osmoglyn, a 50% glycerin oral agent, is marketed without a New Drug Application. Osmitrol is marketed under a New Drug Application with one of its indications being for the reduction of elevated intraocular pressure when the pressure cannot be lowered by other means.

OPEN ANGLE GLAUCOMA OR OCULAR HYPERTENSION ELEVATED IOP

There are numerous topical products currently available for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. These products include topical beta-blockers, topical carbonic anhydrase inhibitors, topical alpha-2 agonists, and topical prostaglandin analogues.

Drug Products with Approved NDAs

Pharmacologic Class/Applicant	Tradename	Established Name
Alpha-2 agonists		
Alcon	Iopidine	Apraclonidine
Allergan, Inc.	Alphagan/ Alphagan P	brimonidine tartrate
Beta-adrenergic antagonists		
Alcon	Betoptic/ Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	metipranolol
Vistakon	Betimol	timolol hemihydrate
Aton Pharma	Timoptic	timolol maleate
Ista	Istalol	timolol maleate
Aton Pharma	Timoptic XE	timolol maleate gel forming solution
Carbonic Anhydrase Inhibitors		
Duramed Pharamaceuticals	Diamox	acetazolamide
Sandoz, Inc.	N/A	methazolamide
Topical Carbonic Anhydrase Inhibitors		
Alcon	Azopt	brinzolamide
Merck	Trusopt	dorzolamide hydrochloride

Pharmacologic Class/Applicant	Tradename	Established Name
Cholinergic agonist		
Alcon	Pilopine HS	pilocarpine hydrochloride gel
Prostaglandin Analogues		
Allergan	Lumigan	bimatoprost
Pharmacia	Xalatan	latanoprost
Alcon	Travatan	travoprost
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl
Sympathomimetics		
Allergan	Propine	dipivefrin hydrochloride
Combination Products		
Merck	Cosopt	dorzolamide hydrochloride/timolol maleate
Allergan	Combigan	brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	betaxolol hydrochloride/ pilocarpine hydrochloride
Osmotics		
Baxter Healthcare Corp	Osmitrol	mannitol injection
Alcon	Ismotic	isosorbide

2.3 Availability of Proposed Active Ingredient in the United States

Salagen Tablets (pilocarpine hydrochloride tablets) are approved in the United States under NDA 20-237 for the treatment of symptoms of dry mouth from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck and for the treatment of symptoms of dry mouth in patients with Sjogren's Syndrome. Pilopine HS (pilocarpine hydrochloride ophthalmic gel) 4% is a sterile topical ophthalmic aqueous gel approved in the United States under Alcon's NDA 18-796 to control intraocular pressure.

NDA 20-619 for BetopticPilo was approved 4/17/97, but the drug product has never been marketed.

2.4 Important Safety Issues with Consideration to Related Drugs

Salagen Tablets (pilocarpine hydrochloride tablets) are approved in the United States under NDA 20-237 for the treatment of symptoms of dry mouth from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck and for the treatment of symptoms of dry mouth in patients with Sjogren's syndrome. In head and

neck cancer patients, the most frequent adverse events[1] seen in controlled clinical trials were:

Adverse Event	Pilocarpine HCl		Placebo
	10 mg t.i.d. (30mg/day) N=121	5 mg t.i.d. (15mg/day) N=141	(t.i.d.) N=152
Sweating	68%	29%	9%
Nausea	15	6	4
Rhinitis	14	5	7
Diarrhea	7	4	5
Chills	15	3	<1
Flushing	13	8	3
Urinary Frequency	12	9	7
Dizziness	12	5	4
Asthenia	12	6	3

In Sjogren's syndrome patients, the most frequent adverse events[1] seen in controlled clinical trials were:

Adverse Event	Pilocarpine HCl 5 mg q.i.d. (20 mg/day) N=255	Placebo (q.i.d.) N=253
Sweating	40%	7%
Urinary Frequency	10	4
Nausea	9	9
Flushing	9	2
Rhinitis	7	8
Diarrhea	6	7
Chills	4	2
Increased Salivation	3	0
Asthenia	2	2

Fatal overdosage with pilocarpine has been reported in the scientific literature at doses presumed to be greater than 100 mg in two hospitalized patients. 100 mg of pilocarpine is considered potentially fatal.[1]

Pilopine HS (pilocarpine hydrochloride ophthalmic gel) 4% is a sterile topical ophthalmic aqueous gel approved in the United States under Alcon's NDA 18-796 to control intraocular pressure.

1 Salagen Tablets Prescribing Information, 2003.

From the approved labeling for Pilopine HS[2]: The following adverse experiences associated with pilocarpine therapy have been reported: lacrimation, burning or discomfort, temporal or periorbital headache, ciliary spasm, conjunctival vascular congestion, superficial keratitis and induced myopia. Systemic reactions following topical administration are extremely rare, but occasional patients are peculiarly sensitive to develop sweating and gastrointestinal overactivity following suggested dosage and administration. Ocular reactions usually occur during initiation of therapy and often will not persist with continued therapy. Reduced visual acuity in poor illumination is frequently experienced in older individuals and in those with lens opacity. A subtle corneal granularity was observed in about 10% of patients treated with Pilopine HS. Cases of retinal detachment have been reported during treatment with miotic agents; especially in young myopic patients. Lens opacity may occur with prolonged use of pilocarpine.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Alcon holds no IND for pilocarpine ophthalmic solution. There was no formal presubmission regulatory activity related to this submission, i.e., no End-of-Phase 2 meeting or Pre-NDA meeting.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This is a 505(b)(2) application primarily based on literature but which includes submission of clinical study reports.

The clinical trials with pilocarpine hydrochloride ophthalmic solution (C-90-42, C-90-105, C-91-47, C-91-54, C-95-17 and C-92-56) were conducted by Alcon between 1990 and 1995 under the IND for betaxolol hydrochloride ophthalmic solution (IND (b) (4)), prior to the requirement to obtain financial disclosure information from clinical investigators. These clinical trials were completed approximately 15-20 years ago.

Four of the 6 clinical trials were performed in the United States (C-90-42, C-91-47, C-91-54 and C-92-56). The other 2 studies were performed in Canada (C-90-105) and France (C-95-17).

2 Pilopine HS Annual Report, NDA 18-796, 11/2009

Reference literature reports, surveys, and articles cited in this review are representative of the published literature. There is no evidence that these references refer to trials not conducted in accordance with acceptable clinical ethical standards.

3.2 Compliance with Good Clinical Practices

This is a 505(b)(2) application primarily based on literature but which includes submission of clinical study reports.

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

There is no evidence to suggest that the clinical trials conducted by Alcon were not conducted in compliance with good clinical practices.

Reference literature reports, surveys, and articles cited in this review are representative of the published literature. There is no evidence that these references refer to trials not conducted in accordance with acceptable clinical ethical standards.

3.3 Financial Disclosures

The clinical trials with pilocarpine hydrochloride ophthalmic solution (C-90-42, C-90-105, C-91-47, C-91-54, C-95-17 and C-92-56) were conducted by Alcon between 1990 and 1995 under the IND for betaxolol hydrochloride ophthalmic solution (IND (b) (4)), prior to the requirement to obtain financial disclosure information from clinical investigators. These clinical trials were completed approximately 15-20 years ago.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Section 2.1.

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

Pregnancy
Animal reproduction studies have not been conducted with pilocarpine hydrochloride ophthalmic solution. It is also not known whether pilocarpine hydrochloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Isopto Carpine should be given to a pregnant woman only if clearly needed.

Carcinogenesis, Mutagenesis, Impairment of Fertility
As reported by Schmahl D; and Habs M in "Life-Span Investigations for Carcinogenicity of some Immune-Stimulating, Immunodepressive and Neurotropic Substances in Sprague-Dawley Rats" published in Zeitschrift Fur Krebsforschung Und Klinische Onkolo, 1976 May 3; 86 (1) : 77 – 84, pilocarpine is not carcinogenic. Atropine, pilocarpine, nicotine, and phenyl-ethyl-barbituric acid (phenobarbital) which are known to have neurotropic effects were tested. Pilocarpine was given intraparitoneally at a dose of 30 mg/kg/week. Nicotine and phenobarbital were found to diminish the mean survival times. None of these neurotropic substances was found to be carcinogenic.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Pilocarpine is a direct acting cholinergic parasympathomimetic agent acting through direct stimulation of muscarinic receptors and smooth muscle such as 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, therefore reducing IOP. It also produces miosis through contracting of the iris sphincter muscle.

4.4.2 Pharmacodynamics

Neither dose-response nor concentration-response studies were performed by Alcon. Isopto Carpine is available in three strengths: 1%, 2% and 4%, allowing for dose titration based on the indication and patient response.

The effect of the commonly known intrinsic factors including race, gender, and age on the PK of pilocarpine following topical administration of Isopto Carpine 4% has not been thoroughly studied. Given the low systemic exposure following topical administration, dose adjustment is not warranted in patients based on the commonly known intrinsic factors.

4.4.3 Pharmacokinetics

Systemic exposure to pilocarpine was evaluated in 14 healthy subjects administered 2 drops of Isopto Carpine (pilocarpine hydrochloride ophthalmic solution) 4% to both eyes four times daily for eight days. A comparison of Cmax values on Days 5 and 8 indicated that pilocarpine concentrations in plasma reached steady-state following topical administration of Isopto Carpine 4%. The mean (SD) Cmax and AUC0-last values on Day 8 were 3.7 (3.2) ng/mL and 7.7 (8.4) ng×hour/mL, respectively. The Tmax values on Day 8 ranged from 0.5 to 1 hour.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This is a 505(b)(2) application primarily based on literature but which includes submission of clinical study reports.

The clinical trials with pilocarpine hydrochloride ophthalmic solution (C-90-42, C-90-105, C-91-47, C-91-54, C-95-17 and C-92-56) were conducted by Alcon between 1990 and 1995 under the IND for betaxolol hydrochloride ophthalmic solution (IND (b) (4)), prior to the requirement to obtain financial disclosure information from clinical investigators. 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.

The following tables are:

- The applicant's listing of the completed clinical efficacy and safety trials for Isopto Carpine (Table 2.5.1-3). This Table excludes a description of Alcon Study C-92-56, topical ocular pharmacokinetic (PK) study that assessed the steady-state plasma concentration/time profile of pilocarpine 4% and the fixed combination of betaxolol 0.25% /pilocarpine 1.75% in 14 healthy subjects.

- The applicant's submitted literature support for the reduction of elevated IOP with open angle glaucoma/ocular hypertension indication (Table 2.5.1-4).

- The applicant's submitted literature support for the acute angle glaucoma indication (Table 2.5.1-5).

- The applicant's submitted literature support for the prevention of (b) (4) postoperative elevated IOP indication (Table 2.5.1-6).

- The applicant's submitted literature support for the management of IOP in Pediatric Glaucoma (Table 2.5.1-7).

Table 2.5.1–3 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 BET 0.5%: 1 drop BID TIM 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
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]: 23-34 at 8AM (OU) ≤ 5 difference between eyes	Mean IOP change from baseline at 8AM

Table 2.5.1–3 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-91-54	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
C-95-17	1 FR	June 1995 Completed 79 enrolled 90 planned	Randomized, double-masked, parallel group	Comfort	PILO: 1 drop BID[f] BET 0.25%: 1 drop BID[f] Bet/Pilo 1.75%: 1 drop BID[f]	26/26 26/26 27/27	7 days	40 M 39 F 25.4 yrs (18-54 yrs)	Normal Healthy Volunteers IOP: < 10 in either eye	Ocular comfort/ acceptability

[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; FR = France; 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
PILO = ISOPTO Carpine (pilocarpine hydrochloride ophthalmic solution) 2%
BET 0.25% = Betaxolol Hydrochloride Ophthalmic Suspension, 0.25%
Bet/Pilo 1%, 2%, or 1.75% = Betaxolol Hydrochloride Ophthalmic Suspension, 0.25%/Pilocarpine Hydrochloride Ophthalmic Solution, 1%, 2%, or 1.75%, respectively
BET 0.5% = Betaxolol Hydrochloride Ophthalmic Solution, 0.5%
TIM 0.5% = Timolol Maleate Ophthalmic Solution, 0.5%

Table 2.5.1–4 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 2.5.1–4 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 2.5.1–4 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 2.5.1–4 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 2.5.1–4 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 2.5.1–4 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 2.5.1–5 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 2.5.1–5 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 2.5.1–5 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 pilocarpine dose	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 2.5.1–6 Publications Supporting Safety/Efficacy of ISOPTO Carpine for Prevention of (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 2.5.1–6 Publications Supporting Safety/Efficacy of ISOPTO Carpine for Prevention of (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 2.5.1–7 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 secondary glaucoma (includes aphakic) glaucoma associated with congenital anomalies primary congenital glaucoma	63 (95 eyes) 20 (24 eyes) 29 (47 eyes) 14 (24 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 Medical treatment (includes pilocarpine) alone sufficient for 17 of 47 eyes. 19 of 22 eyes treated surgically also required medication 23 of 24 eyes required surgical treatment. 4 of 23 eyes treated surgically also required medication (includes pilocarpine)

Table 2.5.1–7 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 2.5.1–7 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

5.2 Review Strategy

This is a 505(b)(2) application primarily based on literature but which includes submission of clinical study reports.

The submitted Clinical Study reports were reviewed and summarized in this review. These studies were completed 15-20 years ago.

Support for the proposed indications are also provided by a literature review conducted by the applicant and by an additional literature review conducted by the Medical Officer.

5.3 Discussion of Individual Studies/Clinical Trials

This is a 505(b)(2) application primarily based on literature but which includes submission of clinical study reports. See Section 5.1.

6 Review of Efficacy

Efficacy Summary

This is a 505(b)(2) application primarily based on literature but which includes submission of clinical study reports.

The clinical trials with pilocarpine hydrochloride ophthalmic solution (C-90-42, C-90-105, C-91-47, C-91-54, C-95-17 and C-92-56) were conducted by Alcon between 1990 and 1995 under the IND for betaxolol hydrochloride ophthalmic solution (IND (b) (4). The submitted Clinical Study reports were reviewed and are summarized in this review with the exception of C-95-17 (comfort) and C-92-56 (pK). Support for the proposed indications are provided by literature review conducted by the applicant and by additional literature review conducted by the Medical Officer.

There is adequate support from the clinical study reports and from the literature to support the following indications for pilocarpine ophthalmic solution 1%, 2% and 4%:

1) the reduction of elevated intraocular pressure in patients with ocular hypertension or open angle glaucoma
2) the management of acute angle closure glaucoma
3) the prevention of (b) (4) postoperative elevated IOP associated with (b) (4) laser surgery
4) the induction of miosis.

Pilocarpine is a direct acting cholinergic agonist. It is believed that pilocarpine produces contraction of the ciliary muscle resulting in opening of the trabecular meshwork spaces

to facilitate outflow of the aqueous humor, thus lowering intraocular pressure (IOP). The support for the fourth indication (induction of miosis) is therefore supported and derived from the other three indications. Alcon's C-91-47 and C-91-54 contain pupil size evaluations as part of their analyses.

6.1 Indication: The reduction of elevated intraocular pressure in patients with ocular hypertension or open angle glaucoma

6.1.1 Methods – Alcon Studies

6.1.1. A C-90-42

Intraocular Pressure Reduction by 0.25% Betaxolol Suspension/1.0% and 2.0% Pilocarpine Combinations Compared to 0.25% Betaxolol Suspension and 2.0% Pilocarpine

METHODS
Two combination Betaxolol/Pilocarpine HCl products (Betaxolol Suspension 0.25%/Pilocarpine HCl 1 % and Betaxolol Suspension 0.25%/Pilocarpine HCl 2%; Combination 1 % and Combination 2%, respectively) were compared to Betaxolol Suspension 0.25% and Pilocarpine HCl 2% in the treatment of patients with ocular hypertension or primary open-angle glaucoma. This trial was considered a pilot because pilocarpine was not administered TID or QID – it was administered BID to maintain masking.

This multicenter study (6 sites) was a double-masked, active-controlled, parallel trial in which data obtained from 72 patients were included in the efficacy analysis and data from 76 patients were included in the safety analysis. The study design included an initial three (3) week Betaxolol Suspension 0.25% BID run-in phase, followed by a maximal one (1) week eligibility phase when baseline IOP values were obtained. Treatment with masked test medications was BID for 90 days. Efficacy data were obtained from measurement of IOP while safety data were generated from adverse experiences, visual acuity, visual fields, color vision and dilated ophthalmoscopy.

DISPOSITION
Six investigators enrolled a total of 77 patients into this prospective, multicenter, double-masked, clinical trial. Five patients did not have follow-up IOP data and were excluded from all efficacy analyses. One of these five patients never received test medication and was also not evaluated for safety. Therefore, of the 77 patients enrolled, 72 patients were evaluated for efficacy and 76 patients were evaluated for safety. Of the 76 patients who received test medication, 12 discontinued and 64 completed all 90 days of masked therapy.

DEMOGRAPHICS

Table 6

Demographic Characteristics of All Patients Included in the Efficacy Analyses

Variable	Randomized Treatment Group[1]				P Value[2]
	Combination 1% (N=21)	Combination 2% (N = 16)	Betaxolol (N = 19)	Pilocarpine (N = 16)	
Age (yrs)					
Mean	61.3	63.4	64.0	62.7	0.91
STD	12.3	10.6	13.7	12.5	
Sex					
Male	11	10	8	2	0.03
Female	10	6	11	14	
Race					
Caucasian	14	9	14	12	0.84
Black	6	6	5	3	
Other	1	1	0	1	
Iris Color					
Brown	11	9	6	10	0.27
Other	10	7	13	6	
Diagnosis					
POAG	16	11	9	12	0.24
Ocular HTN	5	5	10	4	

Abbreviations used include the following: POAG (Primary Open-Angle Glaucoma); HTN (Hypertension); STD (Standard Deviation).

1 Treatment groups included the following: Combination 1% (Betaxolol 0.25%/Pilocarpine HCl 1%); Combination 2% (Betaxolol 0.25%/Pilocarpine HCl 2%); Betaxolol 0.25%; and Pilocarpine HCl 2.0%).

2 P values reflect the test of any differences between treatment groups (Fisher's Exact Test used for all except age in which one-way ANOVA was used).

Table 3

List of Patients Discontinued From the Double-Masked Study

Investigator No.	Patient No.	Treatment Group[1]	Reason[2]
331	1516	Combination 2%	Lost to follow-up
331	1519	Combination 2%	Protocol violation (severe visual field loss)
331	1533*	Combination 2%	Drug related AE
1008	1102*	Combination 2%	Drug related AE
1118	1409	Combination 2%	Drug related AE
331	1524	Betaxolol	Protocol violation (history of retinal tear)
1008	1103	Betaxolol	Inadequate IOP control
1008	1108	Betaxolol	Lost to follow-up
1118	1411	Betaxolol	Inadequate IOP control
331	1517	Pilocarpine	Patient decision to withdraw
1118	1408*	Pilocarpine	Drug related AE
1157	1205*	Pilocarpine	Drug related AE

Abbreviations used include the following: AE (Adverse Event); IOP (Intraocular Pressure).

[1] Treatment groups included the following: Combination 1% (Betaxolol 0.25%/Pilocarpine HCl 1%); Combination 2% (Betaxolol 0.25%/Pilocarpine HCl 2%); Betaxolol 0.25%; and Pilocarpine HCl 2.0%.

[2] Descriptions of the individual patients discontinued due to an adverse experience are included in Table 17.

* These patients were excluded from the efficacy analyses and are listed in Table 2.

Table 17

Patients Discontinued Due to Adverse Events

Inv. No.	Pt. No.	Age	Sex	Treatment	Reason for Discontinuation	Study Day	Intensity	Duration of Event	Outcome of Event	Serious	Causality Assessment
1008	1102	81	M	Combination 2%	Vision Blurred, Browache	5	Moderate	2 Hrs	Resolved	No	Related
1118	1409	74	M	Combination 2%*	Retinal Tear	NA	Mild	NA	Resolved	Yes	Related
331	1533	71	F	Combination 2%	Hypertension	7	Moderate	1 Day	Resolved	No	Related
1157	1205	75	M	Pilocarpine	Vision Blurred	1	Moderate	2 Hrs	Resolved	No	Related
					Discomfort Eye	1	Moderate	10 Secs	Resolved	No	Related
1118	1408	44	M	Pilocarpine	Vision Blurred	2*	Moderate	2 Hrs	Resolved	No	Related

Related = Possibly, Probably or Definitely Related
*Event Occurred with Each Instillation
*Retinal Tear Related to the Pilocarpine Component of Combination 2%

PRIMARY ENDPOINT/ANALYSIS

The primary efficacy variable was the mean reduction in IOP from baseline. A total of

72 patients (16 Combination 2%, 21 Combination 1 %, 19 Betaxolol and 16 Pilocarpine) from six (6) different study sites were included in the analysis of efficacy.

The primary efficacy analysis was the repeated measures analysis of variance in which IOP measurements from the combination Betaxolol and Pilocarpine groups were compared using the changes from baseline at each treatment time (8:00 a.m., 10:00 a.m., 12 N and 2:00 p.m.).

Mean Changes in Intraocular Pressure From Baseline at Each Treatment Visit (mmHg)

Treatment Group[1]	Day 14				Day 45	Day 90			
	8 a.m.	10 a.m.	12 N	2 p.m.	8 a.m.	8 a.m.	10 a.m.	12 N	2 p.m.
Combination 2%									
IOP change (mmHg)	-2.9	-5.0	-5.8	-5.7	-3.2	-2.0*	-4.3	-5.5	-5.6
% Change	-11.3	-20.0	-23.3	-22.9	-12.6	-7.4	-16.8	-21.6	-22.2
N Value	16	16	16	16	16	12	13	13	13
Combination 1%									
IOP change (mmHg)	-1.8	-5.9	-6.2	-5.9	-3.5	-2.5	-4.3	-5.6	-5.4
% Change	-6.8	-22.2	-23.4	-22.1	-13.3	-9.7	-16.2	-21.3	-20.2
N Value	21	21	21	21	21	21	21	21	21
Betaxolol									
IOP change (mmHg)	-1.8	-3.0	-4.7	-4.3	-2.0	-1.9	-3.5	-4.2	-4.4
% Change	-6.8	-12.2	-18.4	-16.6	-8.1	-7.8	-14.3	-16.5	-17.3
N Value	19	19	19	19	16	15	15	15	15
Pilocarpine									
IOP change (mmHg)	-0.4*	-4.1	-4.5	-5.3	-2.1	-1.4*	-2.9	-4.0	-4.5
% Change	-1.8	-16.4	-18.1	-20.8	-8.2	-5.4	-11.7	-15.7	-17.9
N Value	16	16	16	16	16	15	15	15	15

* Not significantly different from baseline ($p > 0.05$; one sample t-test)

Both Combination formulations reduced IOP from baseline more than either Betaxolol or Pilocarpine at all times (8:00 a.m., 10:00 a.m., Noon and 2:00 p.m.). However, these differences were not statistically significant at most treatment times in this pilot efficacy trial. Pilocarpine 2% administered BID did not lower IOP by a statistically significant amount from baseline at Day 14 or Day 90; this administration differs from the clinical use of pilocarpine TID or QID.

This type of trial design would not be currently acceptable. Dosing of control agent (i.e. pilocarpine) would be expected at more clinically relevant dosing intervals. Additional IOP measurements would be expected at week 6 (peak and trough).

6.1.1. B C-91-47

Intraocular Pressure Reduction by 0. 25% Betaxolol Suspension/1.75% Pilocarpine Combination Compared to 0 .25% Betaxolol Suspension and 2.0% Pilocarpine

METHODS
This was a prospective, randomized, double-masked, multicenter trial to determine the additive IOP-lowering effect of combining 1.75% Pilocarpine Hydrochloride with 0.25% Betaxolol Suspension in a single formulation as compared to 0.25% Betaxolol Suspension or 2.0% Pilocarpine Hydrochloride Solution used alone.

Data was obtained from 156 and 182 patients were included in the efficacy and safety analyses, respectively. The study design included an initial three (3) week open-label Betaxolol Suspension 0.25% BID run-in phase, followed by a maximal one (1) week eligibility phase when baseline IOP values were obtained. Treatment with masked test medications was TID for 90 days. Efficacy data were obtained from measurement of IOP, while safety data were generated from adverse events, pupil size, pulse, visual acuity, visual fields, cup/disk ratio, color vision and ocular signs.

One hundred eighty-two (182) patients were randomized to treatment, received at least one dose of test medication, and were included in the safety analyses (Combination 60; Betaxolol 61; Pilocarpine 61). Two separate patient groups were analyzed for efficacy which included both intent-to-treat and primary patients. The intent-to-treat group consisted of 161 patients because 21 of the 182 randomized patients were excluded from these analyses due to the absence of any follow-up IOP data. The primary group consisted of 156 patients because 5 of the 161 intent-to-treat patients were ruled non-evaluable by the Medical Monitor. Thus, the primary efficacy group to be discussed with this report contained 156 patients which included 52, 58, and 46 patients, respectively, in the Combination, Betaxolol and Pilocarpine groups.

DEMOGRAPHICS

Table 5

Demographic Characteristics of All Patients Included in the Primary Efficacy Analyses

Variable	Randomized Treatment Group[1] Combination (N = 52)	Betaxolol (N = 58)	Pilocarpine (N = 46)	P Value[2]
Age (yrs)				
Mean	59.6	58.8	58.3	0.84
STD	11.3	11.3	11.0	
Sex				
Male	19	20	22	0.34
Female	33	38	24	
Race				
Caucasian	38	47	37	0.84
Black	9	7	5	
Other	5	4	4	
Iris Color				
Brown	30	26	25	0.32
Blue	16	16	13	
Hazel	5	14	5	
Green	1	2	3	
Diagnosis				
POAG	30	32	25	0.78
Ocular HTN	20	25	21	
Pseudoex. Glaucoma	1	1	0	
Pigment. Glaucoma	1	0	0	

Abbreviations used include the following: POAG (Primary Open-Angle Glaucoma); HTN (Hypertension); Pseudoex. (Pseudoexfoliative); and Pigment. (Pigmentary).

[1] Treatment groups included the following: Combination (Betaxolol 0.25%/Pilocarpine HCl 1.75%); Betaxolol 0.25%; and Pilocarpine HCl 2.0%).

[2] P values reflect the test of any differences between treatment groups (Chi-square test used for all except age in which one-way ANOVA was used).

DISPOSITION

A total of 42 subjects discontinued the study.

Table 4

Distribution by Reason and Treatment Group of Patients Discontinued From the Double-Masked Study

	Randomized Treatment Group			
Reason	**Combination**	**Betaxolol**	**Pilocarpine**	**Total**
Drug related AE	8	2	12	22
Inadequate IOP Control	2	3	3	8
AE (non-drug related)	0	3	1	4
Protocol violation	1	1	1	3
Patient decision	0	0	3	3
Noncompliance	0	1	0	1
Lost to follow-up	1	0	0	1
TOTALS	**12**	**10**	**20**	**42**

Table 17

Patients Discontinued Due to Adverse Events

Inv. No.	Pt. No.	Age	Sex	Treatment	Reason for Discontinuation	Study Day	Intensity	Duration of Event	Outcome of Event	Serious	Causality Assessment
331	7234	67	F	Combination	Vision Blurred	1	Moderate	2 Hrs	Resolved	No	Related
					Vision Abnormal	1	Moderate	3 Hrs	Resolved	No	Related
331	7241	25	M	Combination	Vision Blurred, Headache	1	Moderate	1 Day	Resolved	No	Related
1390	7501	40	F	Combination	Vision Blurred, Vision Abnormal	1	Severe	3 Hrs	Resolved	No	Related
					Headache	1	Severe	1 Hr	Resolved	No	Related
					Nausea	1	Mild	30 Mins	Resolved	No	Related
					Dizziness	1	Moderate	30 Mins	Resolved	No	Related
1390	7559	72	M	Combination	Vision Blurred, Headache	1[b]	Moderate	45 Mins	Resolved	No	Related
1401	7603	51	M	Combination	Vision Blurred, Vision Dim, Headache	1	Severe	8 Hrs	Resolved	No	Related
970	7718	35	M	Combination	Vision Blurred	1	Moderate	14 Days	Resolved	No	Related
					Browache, Headache, Nausea	1	Moderate	1 Hr	Resolved	No	Related
					Dreams Abnormal	1	Mild	NA	Resolved	No	Related
					Hyperglycaemia	1	Mild	14 Days	Resolved	No	Not Related

Related = Possibly, Probably or Definitely Related.
[b] Event Occurred with Each Instillation.
Not Related = Unlikely or Definitely Unrelated.

Table 17 (continued)

Patients Discontinued Due to Adverse Events

Inv. No.	Pt. No.	Age	Sex	Treatment	Reason for Discontinuation	Study Day	Intensity	Duration of Event	Outcome of Event	Serious	Causality Assessment
331	7227	59	F	Combination	Headache, Nausea	13	Severe	2 Days	Resolved	No	Related
970	7714	67	F	Combination	Headache	1	Mild	3 Hrs	Resolved	No	Related
1402	7001	74	F	Betaxolol	Vision Blurred, Pain Eye, Headache	1	Moderate	2 Hrs	Resolved	No	Related
1473	7901	58	F	Betaxolol	Tachycardia, Anxiety	49	Moderate	5 Days	Resolved	No	Related
1390	7551	71	F	Betaxolol	Scotoma, Occlusion Retinal Artery	59	Moderate	NA	Continuing	Yes	Not Related
1390	7531	70	M	Betaxolol	Flu Syndrome	3	Moderate	NA	LFU	No	Not Related
543	7406	70	F	Betaxolol	Surgical/Medical Procedure	32	Severe	NA	Resolved	Yes	Not Related
543	7401	84	F	Pilocarpine	Vision Blurred	1	Severe	30 Hrs	Resolved	No	Related
1390	7510	58	M	Pilocarpine	Vision Blurred	1	Moderate	3 Hrs	Resolved	No	Related
					Headache	1	Severe	3 Hrs	Resolved	No	Related
					Nausea	1	Mild	45 Mins	Resolved	No	Related

Related = Possibly, Probably or Definitely Related.
Not Related = Unlikely or Definitely Unrelated.
NA = Not Available.
LFU = Lost to Follow-up.

Table 17 (continued)

Patients Discontinued Due to Adverse Events

Inv. No.	Pt. No.	Age	Sex	Treatment	Reason for Discontinuation	Study Day	Intensity	Duration of Event	Outcome of Event	Serious	Causality Assessment
331	7223	57	F	Pilocarpine	Foreign Body Sensation	1	Moderate	1 Hr	Resolved	No	Related
1402	7002	66	M	Pilocarpine	Retinal Tear	12	Mild	3 Days	Resolved	Yes	Related
970	7701	69	F	Pilocarpine	Infarction Myocardial	88	Severe	NA	Fatal	Yes	Not Related

Related = Possibly, Probably or Definitely Related
NA = Not Available.
Not Related = Unlikely or Definitely Unrelated.

PRIMARY ENDPOINT/ANALYSIS

The primary efficacy variable was the mean reduction in IOP from the 8:00 a.m. Betaxolol Suspension 0.25% BID baseline to the 8:00 a.m. IOPs on Days 14, 45, and 90. The secondary efficacy variables were mean IOP changes from the 8:00 a.m. Betaxolol Suspension 0.25% BID baseline to the IOPs at 12 N and 4:00 p.m. on Days 14 and 90.

Mean Changes in Intraocular Pressure From the Betaxolol Suspension 0.25% BID Baseline at Each Treatment Visit

Treatment Group	Day 14			Day 45	Day 90		
	8 A.M.	12 N	4 P.M.	8 A.M.	8 A.M.	12 N	4 P.M.
Combination							
Change from Baseline (mmHg)	-3.6*	-6.1*†	-6.4*†	-3.1*†	-2.3*†	-5.0*†	-5.2*†
% Change from Baseline	-13.6	-23.3	-24.5	-12.2	-9.0	-18.6	-19.9
N Value	50	49	49	46	44	44	43
Betaxolol							
Change from Baseline (mmHg)	-1.0	-3.6	-4.0	-1.6	-0.6#	-3.2	-3.7
% Change from Baseline	-3.9	-13.8	-15.2	-5.8	-2.3	-12.0	-14.2
N Value	56	58	53	55	47	48	48
Pilocarpine							
Change from Baseline (mmHg)	-2.9	-5.0	-5.3	-2.0	-0.9#	-2.5	-2.9
% Change from Baseline	-11.1	-18.9	-19.7	-7.6	-3.4	-9.2	-11.3
N Value	46	45	44	43	38	40	40

* Significantly greater than Betaxolol ($p \leq 0.02$; repeated measures analysis of variance)
† Significantly greater than Pilocarpine ($p < 0.05$; repeated measures analysis of variance)
# Not significantly different from baseline ($p > 0.05$; one sample t-test)

The mean IOP reductions from baseline were significantly greater at all visit times (8:00 a.m., 12 N and 4:00 p.m.) in the Combination group (3.1, 5.7 and 5.7 mmHg, respectively) compared to Betaxolol ($p < 0.001$) (0.9, 3.4 and 3.7 mmHg, respectively). These IOP reductions were maintained throughout the day in all treatment groups evidenced by the 12 N and 4:00 p.m. IOP measurements obtained both 4 hours (12 N measurement) and 8 hours (4:00 p.m. measurement) following 8:00 a.m. dosing. This reflects the additive contribution of the pilocarpine.

Mean Changes in Pupil Diameter From the Betaxolol Suspension 0.25% BID Baseline at Each Treatment Visit

Treatment Group	Visit Time		
	Day 14	Day 45	Day 90
	8 A.M.	8 A.M.	8 A.M.
Combination			
Mean Pupil Diameter	2.6 ± 0.9	2.3 ± 0.7	2.4 ± 0.9
N Value	50	46	44
Change from Baseline	-0.8	-1.0	-0.9
Betaxolol			
Mean Pupil Diameter	3.7 ± 0.8	3.7 ± 0.8	4.0 ± 0.8
N Value	55	54	47
Change from Baseline	+0.2	+0.2	+0.4
Pilocarpine			
Mean Pupil Diameter	2.6 ± 0.8	2.5 ± 0.7	2.6 ± 0.7
N Value	46	43	37
Change from Baseline	-0.7	-0.8	-0.7

There were statistically significant ($p < 0.01$) decreases in pupil diameter from baseline following treatment with both the Combination product and Pilocarpine at the 8:00 a.m. visits on Day 14 (Combination, 0.8 mm decrease; Pilocarpine, 0.7 mm decrease), Day 45 (Combination, 1.0 mm decrease; Pilocarpine, 0.8 mm decrease), and Day 90 (Combination, 0.9 mm decrease; Pilocarpine, 0. 7 mm decrease).

6.1.1. C C-91-54

Intraocular Pressure Reduction by 0.25% Betaxolol Suspension /1.75% Pilocarpine Combination Compared to 0.25 % Betaxolol Suspension and 2.0 % Pilocarpine

METHODS
This multicenter study (6 sites) was a double-masked, active-controlled, parallel trial Determine the additive IOP-lowering effect of combining 1.75% Pilocarpine Hydrochloride with 0.25% Betaxolol Suspension in a single formulation as compared to 0.25% Betaxolol Suspension or 2.0 % Pilocarpine Hydrochloride Solution used alone.

The study design included an initial three (3) week open-label Betaxolol Suspension 0. 25 % BID run-in phase, followed by a maximal one (1) week, eligibility phase at which time baseline IOP values were obtained. Treatment with masked test medications was TID for 90 days. Efficacy data were obtained from measurement of IOP, while safety

data were generated from adverse events, pulse, pupil size, visual acuity, dilated fundus, visual fields, color vision, and ocular signs.

One hundred eighty (186) patients were randomized to treatment, received at least one dose of test medication, and were included in the safety analyses (Combination 61; Betaxolol 61; Pilocarpine 64). Two separate patient groups were analyzed which included both intent-to-treat and primary patients. The intent-to-treat group consisted of 168 patients because 18 of the 186 randomized patients were excluded from these analyses due to the absence of any follow-up IOP data. The primary group consisted of 160 patients because 8 of the 168 intent-to-treat patients were ruled non-evaluable by the Medical Monitor. Thus, the primary efficacy group to be discussed within this report contained 160 patients which included 50, 59, and 51 patients, respectively, in the Combination, Betaxolol and Pilocarpine groups.

DEMOGRAPHICS

Table 5

Demographic Characteristics of All Patients Included in the Primary Efficacy Analyses

Variable	Randomized Treatment Group[1] Combination (N = 50)	Betaxolol (N = 59)	Pilocarpine (N = 51)	P Value[2]
Age (yrs)				
Mean	61.7	64.0	61.7	0.42
STD	11.2	10.4	10.9	
Sex				
Male	21	25	18	0.71
Female	29	34	33	
Race				
Caucasian	39	44	34	0.04
Black	8	15	17	
Other	3	0	0	
Iris Color				
Brown	25	31	26	0.65
Blue	19	19	12	
Hazel	4	7	10	
Green	2	1	2	
Grey	0	1	1	
Diagnosis				
POAG	46	58	49	0.52
Ocular HTN	3	1	1	
Pigment. Glaucoma	1	0	1	

Abbreviations used include the following: POAG (Primary Open-Angle Glaucoma); HTN (Hypertension); and Pigment. (Pigmentary).

[1] Treatment groups included the following: Combination (Betaxolol 0.25%/Pilocarpine HCl 1.75%); Betaxolol 0.25%; and Pilocarpine HCl 2.0%).

[2] P values reflect the test of any differences between treatment groups (Chi-square test used for all except age in which one-way ANOVA was used).

DISPOSITION

A total of 31 subjects discontinued the study.

Table 4

Distribution by Reason and Treatment Group of Patients Discontinued From the Double-Masked Study

	Randomized Treatment Group			
Reason	**Combination**	**Betaxolol**	**Pilocarpine**	**Total**
Drug related AE	10	0	13	23
AE (non-drug related)	0	0	2	2
Protocol violation	0	1	4	5
Patient decision	0	0	1	1
TOTALS	**10**	**1**	**20**	**31**

Table 17

Patients Discontinued Due to Adverse Events

Inv. No.	Pt. No.	Age	Sex	Treatment	Reason for Discontinuation	Study Day	Intensity	Duration of Event	Outcome of Event	Serious	Causality Assessment
470	4016	63	F	Combination	Vision Blurred, Nausea	1	Moderate	2 Hours	Resolved	No	Related
					Headache	1	Mild	30 Mins	Resolved	No	Related
1200	4227	41	F	Combination	Vision Blurred, Headache	1	Moderate	3 Hours	Resolved	No	Related
1403	4335	71	M	Combination	Vision Blurred	28	Moderate	3 Hours	Resolved	No	Related
					Vitreous Disorder	29	Moderate	3 Hours	Resolved	No	Related
1393	4416	66	F	Combination	Vision Blurred, Vision Abnormal	1	Moderate	90 Minutes	Resolved	No	Related
					Headache	1	Severe	20 Minutes	Resolved	No	Related
1403	4330	79	F	Combination	Vision Abnormal	1	Moderate	2 Days	Resolved	No	Related
1403	4339	62	M	Combination	Vision Abnormal	4	Moderate	2 Hours	Resolved	No	Related
1200	4209	79	M	Combination	Pain Eye	2	Mild	3 Hours	Resolved	No	Related
470	4008	54	F	Combination	Headache, Palpitation	1	Moderate	3 Hours	Resolved	No	Related
					Dizziness	1	Moderate	90 Minutes	Resolved	No	Related
					Laryngismus	1	Moderate	30 Minutes	Resolved	No	Related

Related = Possibly, Probably, or Definitely Related Not Related = Unlikely or Definitely Unrelated
* Event Occurred Intermittently
* Event Occurred with Each Installation
N/A = Not Available

Table 17 (continued)

Patients Discontinued Due to Adverse Events

Inv. No.	Pt. No.	Age	Sex	Treatment	Reason for Discontinuation	Study Day	Intensity	Duration of Event	Outcome of Event	Serious	Causality Assessment
271	4505	85	F	Combination	Blepharitis, Edema Conjunctiva, Edema Periorbital	18	Mild	32 Days	Resolved	No	Related
271	4516	59	F	Combination	Vision Dim, Pain Eye	1	Moderate	2 Hours	Resolved	No	Related
470	4029	47	F	Pilocarpine	Vision Blurred	1	Moderate	2 Hours	Resolved	No	Related
					Headache	1	Mild	6 Days	Resolved	No	Related
1200	4231	52	M	Pilocarpine	Vision Blurred	1	Moderate	2 Hours	Resolved	No	Related
1403	4307	70	M	Pilocarpine	Vision Blurred, Headache	1	Severe	3 Hours	Resolved	No	Related
1403	4331	55	M	Pilocarpine	Vision Blurred	1	Moderate	15 Minutes	Resolved	No	Related
1403	4341	67	F	Pilocarpine	Vision Blurred, Headache	1	Moderate	2 Hours	Resolved	No	Related
1393	4401	66	M	Pilocarpine	Vision Abnormal	27*	Moderate	2 Days	Resolved	No	Related
1393	4410	47	F	Pilocarpine	Vision Abnormal	1	Moderate	N/A	Resolved	No	Related
					Headache	1	Severe	2 Hours	Resolved	No	Related
271	4527	52	M	Pilocarpine	Vision Decreased	1	Mild	1 Day	Resolved	No	Related

Related = Possibly, Probably, or Definitely Related Not Related = Unlikely or Definitely Unrelated
* Event Occurred Intermittently ᵇ Event Occurred with Each Instillation
N/A = Not Available

Table 17 (continued)

Patients Discontinued Due to Adverse Events

Inv. No.	Pt. No.	Age	Sex	Treatment	Reason for Discontinuation	Study Day	Intensity	Duration of Event	Outcome of Event	Serious	Causality Assessment
271	4532	65	F	Pilocarpine	Vision Decreased	1	Moderate	2 Days	Resolved	No	Related
470	4019	72	M	Pilocarpine	Vision Dim, Headache	1	Moderate	5 Hours	Resolved	No	Related
					Hyperemia Eye	1ᵇ	Mild	1 Day	Resolved	No	Related
271	4512	68	F	Pilocarpine	Pain Eye, Headache	13	Moderate	1 Hour	Resolved	No	Related
1403	4336	68	M	Pilocarpine	Headache	2	Moderate	1 Day	Resolved	No	Related
1403	4344	49	F	Pilocarpine	Headache	12	Severe	3 Hours	Resolved	No	Related
1200	4202	70	M	Pilocarpine	Bone Fracture Spontaneous	12	Severe	N/A	Continuing	No	Not Related
1403	4333	66	F	Pilocarpine	Bone Fracture Spontaneous	1	Moderate	21 Days	Resolved	No	Not Related

Related = Possibly, Probably, or Definitely Related
Not Related = Unlikely or Definitely Unrelated
* Event Occurred Intermittently
ᵇ Event Occurred with Each Instillation
N/A = Not Available

PRIMARY ENDPOINT/ANALYSIS

The primary efficacy variable was the mean reduction in IOP from the 8:00 a.m. Betaxolol Suspension 0.25% BID baseline to the 8:00 a.m. IOPs on Days 14, 45, and 90. The secondary efficacy variables were mean IOP changes from the 8:00 a.m. Betaxolol Suspension 0.25% BID baseline to the IOPs at 12 N and 4:00 p.m. on Days 14 and 90.

Mean Changes in Intraocular Pressure From the Betaxolol Suspension 0.25% BID Baseline at Each Treatment Visit

Treatment Group	Day 14			Day 45	Day 90		
	8 A.M.	12 N	4 P.M.	8 A.M.	8 A.M.	12 N	4 P.M.
Combination							
Change from Baseline (mmHg)	-2.9*†	-5.5*†	-5.1*†	-2.8*†	-3.0*†	-5.2*†	-4.6*
% Change from Baseline	-11.5	-21.7	-19.8	-11.2	-11.9	-20.2	-18.3
N Value	48	48	50	49	45	45	45
Betaxolol							
Change from Baseline (mmHg)	-1.4	-3.2	-2.7	-1.1	-0.9	-3.4	-2.9
% Change from Baseline	-5.6	-12.7	-10.8	-4.3	-3.6	-13.4	-11.7
N Value	59	59	59	58	54	56	56
Pilocarpine							
Change from Baseline (mmHg)	-1.7	-4.1	-3.9	-1.5	-1.6	-4.1	-3.9
% Change from Baseline	-6.4	-15.3	-14.9	-5.5	-6.0	-15.2	-14.4
N Value	50	49	49	43	41	41	41

* Significantly greater than Betaxolol ($p < 0.01$; repeated measures analysis of variance)
† Significantly greater than Pilocarpine ($p < 0.04$; repeated measures analysis of variance)

The mean IOP reductions from baseline were significantly greater at all visit times (8:00 a.m., 12 N and 4:00 p.m.) in the Combination group (2.8, 5.5 and 5.0 mmHg, respectively) compared to Betaxolol ($p < 0.001$) (1.1, 3.3 and 2.8 mmHg, reductions were maintained throughout the day in all treatment groups by the 12 N and 4:00 p.m. IOP measurements obtained both 4 hours (12 N measurement) and 8 hours (4:00 p.m. measurement) following 8:00 a.m. dosing. This demonstrates the additive contribution of pilocarpine.

Mean Changes in Pupil Diameter From the Betaxolol Suspension 0.25% BID Baseline at Each Treatment Visit

Treatment Group	Visit Time		
	Day 14	Day 45	Day 90
	8 A.M.	8 A.M.	8 A.M.
Combination			
Mean Pupil Diameter	2.3 ± 0.9	2.2 ± 0.8	2.2 ± 0.8
N Value	48	49	44
Change from Baseline	-1.1	-1.1	-1.1
Betaxolol			
Mean Pupil Diameter	3.3 ± 0.7	3.3 ± 0.6	3.4 ± 0.8
N Value	58	56	54
Change from Baseline	-0.2	-0.1	-0.1
Pilocarpine			
Mean Pupil Diameter	2.5 ± 0.9	2.4 ± 0.8	2.4 ± 0.8
N Value	50	42	41
Change from Baseline	-0.8	-1.0	-1.0

There were statistically significant ($p < 0.01$) decreases in pupil diameter from baseline following treatment with both the Combination product and Pilocarpine at the 8:00 a.m. visits on Day 14 (Combination, 1.1 mm decrease; Pilocarpine, 0.8 mm decrease), Day 45 (Combination, 1.1 mm decrease; Pilocarpine, 1.0 mm decrease), and Day 90 (Combination, 1.0 mm decrease; Pilocarpine, 1.0 mm decrease).

6.1.1. D Other Alcon Studies

Summaries of C-95-17 (comfort) and C-92-56 (topical ocular pharmacokinetics) excluded from this Section on Efficacy because they do not directly contribute useful information.

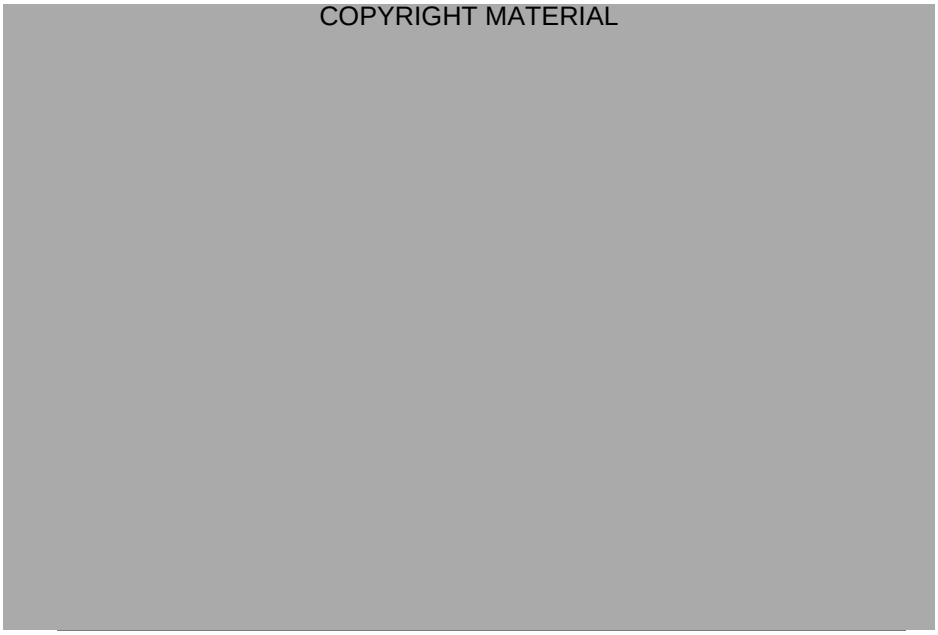
6.1.2 Methods – Literature

In addition to the Alcon studies previously summarized, the applicant has submitted eleven literature references in support of the reduction of elevated intraocular pressure in patients with ocular hypertension or open angle glaucoma. Only three of the submitted literature references will be summarized here; these three references represent the “best” trial design, duration of treatment, and patient exposure to drug product.

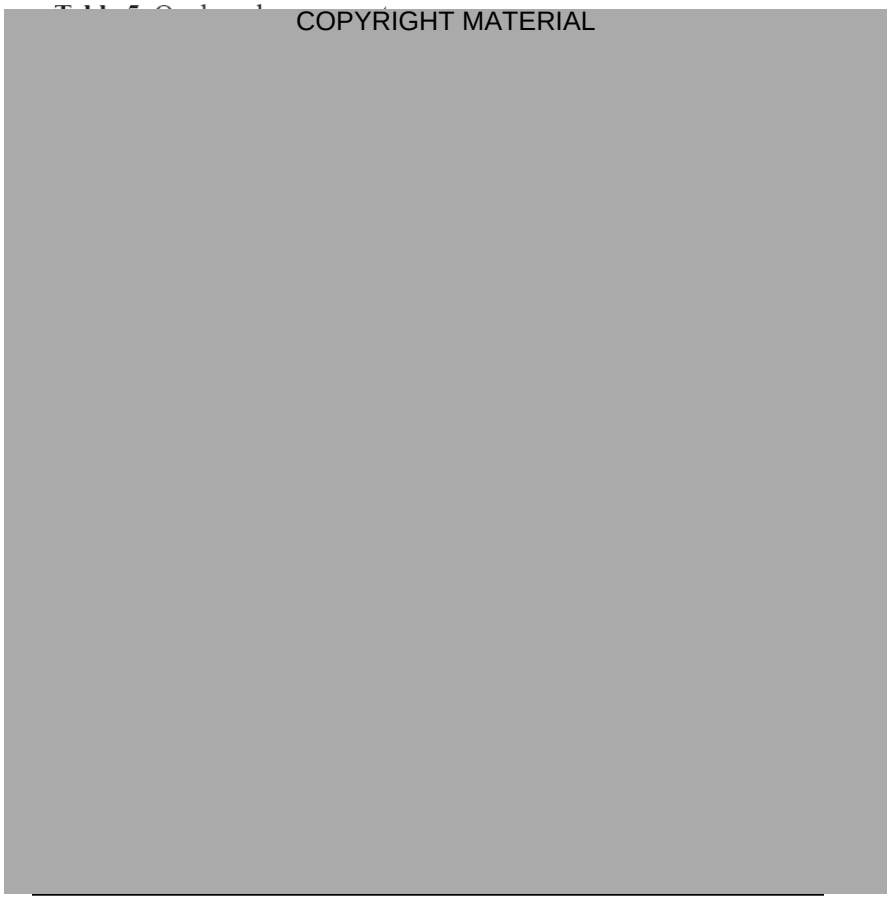
See Section 5.1 of this review for a complete literature listing.

Diestelhorst M. The additive intraocular pressure-lowering effect of latanoprost 0.005% daily once and pilocarpine 2% t.i.d. in patients with open-angle glaucoma or ocular hypertension, a 6-month, randomized, multicenter study. German Latanoprost Study Group. Graefes Arch Clin Exp Ophthalmol. 2000 May; 238(5):433-9.

In a 6-month, multicenter, randomized, open-label study 242 patients with primary open-angle glaucoma or ocular hypertension whose IOP was not controlled with timolol 0.5% b.i.d. were enrolled. Eyes had not been treated with pilocarpine and latanoprost for at least 2 years. The additional intraocular pressure-lowering effect of latanoprost 0.005% administered once daily was compared with that of pilocarpine 2% administered three times daily in patients currently on monotherapy with timolol 0.5% twice daily.



For both treatments the diurnal IOP reduction after 6 months was statistically significant. IOP was reduced from 23.3 to 17.8 (-5.6) mmHg in the latanoprost 0.005% group and from 23.0 to 18.5 (-4.8) mmHg in pilocarpine 2% t.i.d.-treated eyes.



The number of patients with adverse events in the pilocarpine 2%/timolol group was twice that of the latanoprost/timolol group (57 vs 110).

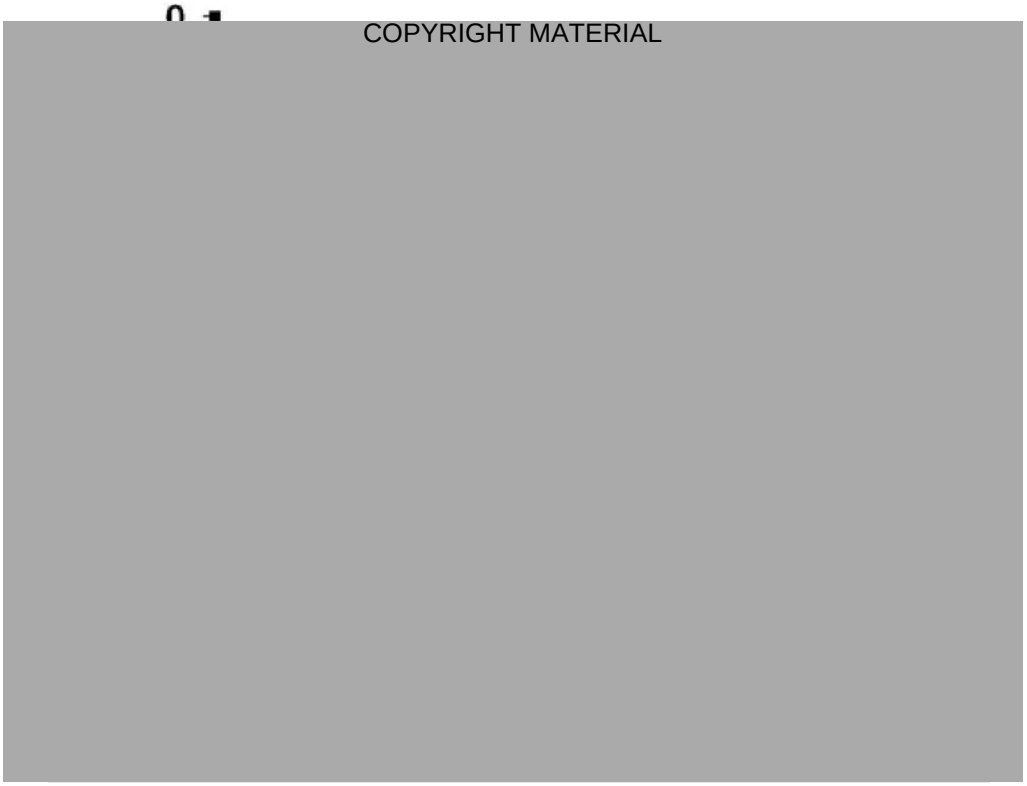
Drance SM. A comparison of the effects of betaxolol, timolol, and pilocarpine on visual function in patients with open-angle glaucoma. J Glaucoma. 1998 Aug; 7(4):247-52.

Sixty-eight patients with early glaucoma were randomly allocated to betaxolol, timolol, or pilocarpine treatment and their visual fields, motion detection, and contrast sensitivity were studied over a 24-month period. One eye of each patient was used in the analysis.

Patients with primary open-angle glaucoma were divided randomly into three groups. The first group used betaxolol 0.5% twice daily, the second group used timolol 0.5% twice daily, and the third group used 2% pilocarpine four times daily. The timolol and betaxolol were masked, whereas the pilocarpine was clearly labeled, as the author felt the pupillary effects and frequency of instillation would make masking meaningless.

All patients were seen at 3, 6, 12, 18, and 24 months. On each visit all the psychophysical tests, Snellen acuity, applanation pressure, blood pressure, pulse, and disc evaluation were carried out.

The pressure reductions on pilocarpine 2% four times daily were as good as those produced by timolol and none of the differences were statistically significant. The pilocarpine pressure reduction was statistically significantly more than the betaxolol response, but only at 3, 6, and 18 months. The timolol response was better than the betaxolol pressure response for the first 18 months of the study but only at 3 months was the difference statistically significant ($p = 0.0053$).



Per the author, the inclusion of pilocarpine showed that it remains an impressive pressure-reducing agent. It fell into clinical disrepute because of the annoying local side effects, particularly in younger patients and those with cataracts, and the necessity for more frequent administration of the drops. None of the differences in visual function between the pilocarpine group and the other two groups had statistical significance.

This literature reference describes Alcon's C-90-105 (see Section 6.1.1. B).

Vogel R, Crick RP, Mills KB, Reynolds PM, Sass W, Clineschmidt CM, Tipping R. Effect of timolol versus pilocarpine on visual field progression in patients with primary open-angle glaucoma. Ophthalmology. 1992 Oct;99(10):1505-11.

In an observer-masked study, 189 patients with primary open-angle glaucoma received either timolol or pilocarpine by random allocation. The dose of the IOP-lowering agent was increased from 0. 25% to 0.5% twice daily for timolol or from 2 % to 4 % four times daily for pilocarpine if the initial IOP response was inadequate. Patients were examined every 4 months throughout the 2-year study.

Table 5. Mean Intraocular Pressure (mmHg)

The maximum IOP permitted to continue in the study after the dose adjustment period was 25 mmHg, but all patients had at least a 5 mmHg reduction in IOP. For pilocarpine treated patients, the IOP change from baseline was approximately 6-7 mm Hg. The number of patients receiving pilocarpine who discontinued therapy because of ineffective control over the two years was double the number who discontinued timolol therapy.

Literature Summary: reduction of elevated intraocular pressure in patients with ocular hypertension or open angle glaucoma

All of the submitted literature articles support the use of pilocarpine for the reduction of elevated intraocular pressure. The overall reduction in intraocular pressure for this indication is roughly 3-7 mm Hg.

Vogel, et al, 1992, describes a prospective, two year observer-masked study with randomized 189 patients with primary open-angle glaucoma who received either timolol or pilocarpine. For pilocarpine treated patients, the IOP change from baseline was approximately 6-7 mm Hg.

6.2 Indication: The management of acute angle closure glaucoma

6.2.1 Methods – Literature

From Allingham, et al, 2005[3]:

Kobayashi H, Kobayashi K, Kiryu J, Kondo T. Pilocarpine induces an increase in the anterior chamber angular width in eyes with narrow angles. Br J Ophthalmol. 1999 May; 83(5):553-8.

The purpose of this trial was to determine the mechanical effects of pilocarpine on the trabecular-iris angle opening in eyes with narrow angles compared with its effects on healthy control subjects with wide angles.

A narrow angle was defined as 25 degrees or less of trabecular-iris angle on ultrasound biomicroscopic examination. The change in anterior chamber depth (ACD), trabecular-iris angle (TIA), angle opening distance (AOD, distance between trabecular meshwork and iris) measured at 250 micrometers and 500 micrometers from the scleral spur (AOD250 and AOD500). Iris thickness was determined by ultrasound biomicroscopy in

3 Allingham R, Damji K, Freedman S, Moroi S, Shafranov G, Shields M. Shield's Textbook of Glaucoma. Chapter 33: Cholinergic Agents. Lippencott, Williams, & Wilkins. 2005. 501-05.

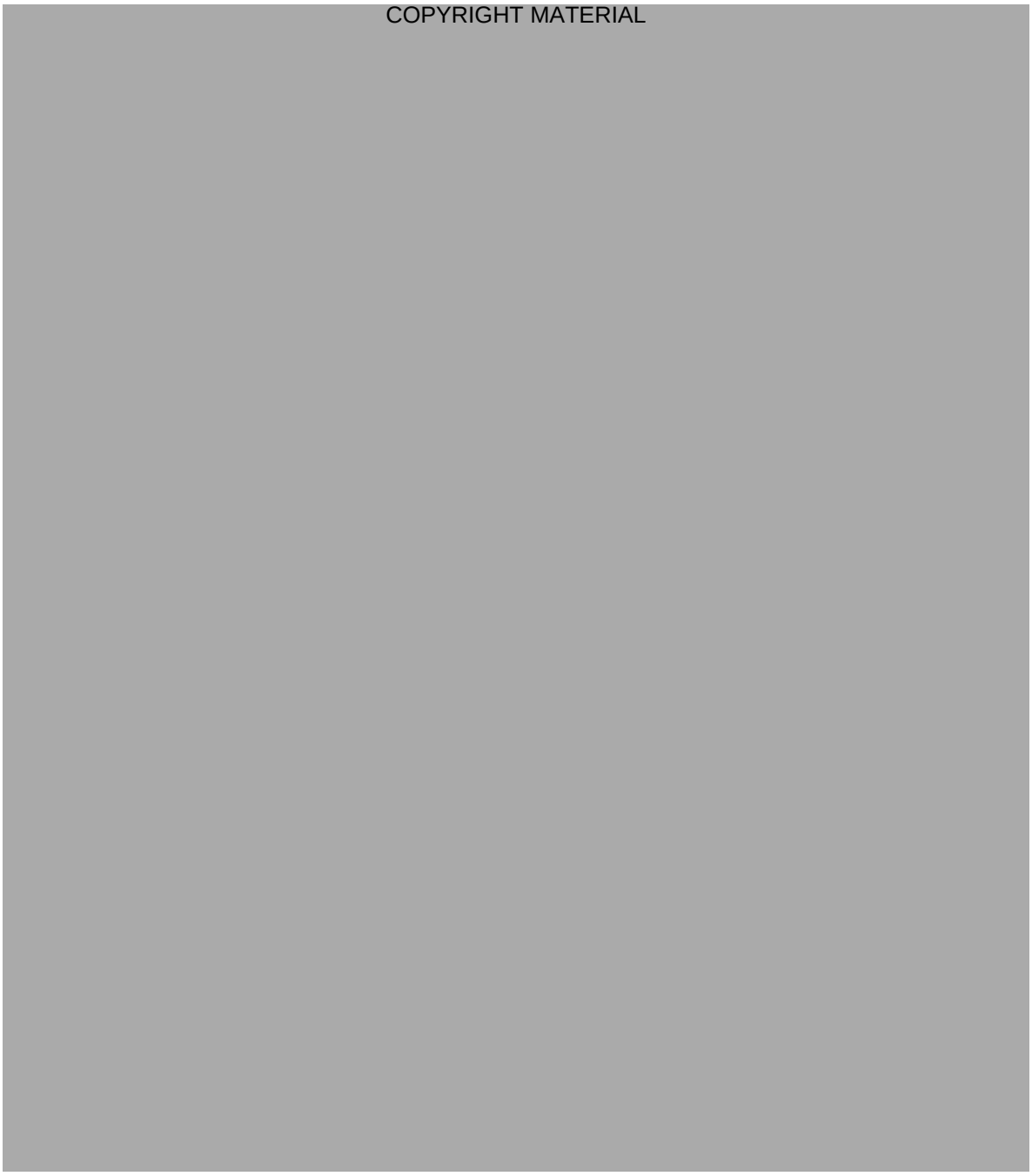
30 eyes of 30 patients (13 men and 17 women, between 63 and 82 years (mean 70.4 years) with narrow angles and in 30 sex and age matched control subjects with wide angles before and 1 hour after the instillation of 2% pilocarpine hydrochloride.

In all eyes with narrow angles, pilocarpine increased the TIA, AOD250, and AOD500; these changes increased significantly and linearly as the corresponding pretreatment values decreased ($r = 0.807$, $p = 0.0001$; $r = 0.787$, $p = 0.0001$; $r = 0.852$, $p = 0.0001$).

Of 30 eyes with wide angles, 23 eyes whose ACD was 2670 micrometers and more showed a decrease in the TIA, AOD250, and AOD500; the changes in TIA, AOD250, and AOD500 also significantly correlated with the corresponding pretreatment values ($r = 0.913$, $p = 0.0001$; $r = 0.882$, $p = 0.0001$; $r = 0.895$, $p = 0.0001$).

Pilocarpine induced a smaller decrease in ACD in eyes with narrow angles than in those with wide angles ($p = 0.0001$). There was a linear correlation between the increase in ACD change and the decrease in pretreatment ACD in eyes with narrow angles and those with wide angles ($r = 0.781$, $p = 0.0003$; $r = 0.798$, $p = 0.0001$).

IOP was not assessed in this trial; its purpose was to measure mechanical effects of pilocarpine on the trabecular-iris angle opening.



The authors reason that since pilocarpine increases angular width in patients with narrow angles, this agent is useful for treating patients with narrow angles and angle closure glaucoma.

Lai JS, Tham CC, Chua JK, Lam DS. Immediate diode laser peripheral iridoplasty as treatment of acute attack of primary angle closure glaucoma: a preliminary study. J Glaucoma. 2001 Apr;10(2):89-94.

The authors' purpose was to study the efficacy and safety of diode laser peripheral iridoplasty as a first-line treatment of acute primary angle-closure glaucoma without the use of systemic IOP-lowering agents (i.e. carbonic anhydrase inhibitors and hyperosmotic agents).

Primary angle-closure glaucoma is caused by occlusion of the drainage angle by iris apposition to the trabecular meshwork, as a result of pupillary block. An eye suffering from acute attack of primary angle-closure glaucoma is characterized by an abrupt rise in the intraocular pressure (IOP), a shallow peripheral anterior chamber, iris bombe, and corneal edema. Laser iridotomy is the definitive treatment, providing an alternative route for aqueous and thus bypassing the pupillary block. Laser iridotomy may not be possible during an acute attack because of corneal edema and a dilated pupil. The authors propose that Argon laser peripheral iridoplasty (ALPI) is effective in mechanically pulling opening an appositionally closed angle in primary angle-closure glaucoma.

Nine consecutive patients with acute primary angle-closure glaucoma were recruited into the study. Each patient received topical pilocarpine (4%), timolol (0.5%), apraclonidine (1%), and immediate diode laser peripheral iridoplasty as primary treatment. The intraocular pressures (IOPs) 15, 30, and 60 minutes after diode laser peripheral iridoplasty were documented by Goldmann applanation tonometry.

The mean IOP of this group of patients was reduced from 66.3 +/- 9.7 mm Hg, before diode laser peripheral iridoplasty, to 36.6 +/- 16.4 mm Hg at 15 minutes, 26.3 +/- 12.6 mm Hg at 30 minutes, and 18.9 +/- 8.4 mm Hg at 60 minutes after diode laser peripheral iridoplasty. In seven of the nine patients, the corneal edema cleared up 1 hour after diode laser peripheral iridoplasty. In the remaining patient, the cornea cleared up 12 hours after diode laser peripheral iridoplasty.

The authors conclude that diode laser peripheral iridoplasty, together with topical IOP-lowering medications without adjunctive systemic carbonic anhydrase inhibitors and hyperosmotic agents, appeared to be effective and safe in controlling the IOP in acute primary angle-closure glaucoma.

Lai JS, Tham CC, Lam DS. Limited argon laser peripheral iridoplasty as immediate treatment for an acute attack of primary angle closure glaucoma: a preliminary study. Eye (Lond). 1999;13 (Pt 1):26-30.

Similar to the previous reference, the authors' purpose was to study the efficacy and safety of limited (180 degrees) argon laser peripheral iridoplasty (ALPI) as a first-line treatment for acute primary angle closure glaucoma without the use of systemic IOP-lowering agents (i.e. carbonic anhydrase inhibitors and hyperosmotic agents).

Ten consecutive patients with primary angle closure glaucoma were recruited into the study. Each patient received topical pilocarpine (4%) and timolol (0.5%), and immediate limited ALPI as primary treatment. The intraocular pressures at 15, 30 and 60 min after ALPI were documented by Goldmann applanation tonometry.

The mean intraocular pressure (IOP) of this group of patients was reduced from 57.9 +/- 10.6 mmHg to 39.0 +/- 10.9 mmHg at 15 min, 28.3 +/- 9.1 mmHg at 30 min and 20.4 +/- 9.0 mmHg at 60 min after ALPI. No complications were encountered. In 8 of the 10 patients the corneal edema cleared 1 h after ALPI. In the remaining 2 patients the corneal edema cleared 2 h after ALPI. The authors conclude that immediate limited ALPI, without adjunctive systemic IOP-lowering agents, appeared to be effective and safe in controlling the IOP in treating acute primary angle closure glaucoma with a duration of attack < or = 48 h.

Although the trial designs are similar, these are 10 different patients than those presented in Lai, et al, 2001.

Lam DS, Chua JK, Tham CC, Lai JS. Efficacy and safety of immediate anterior chamber paracentesis in the treatment of acute primary angle-closure glaucoma: a pilot study. Ophthalmology. 2002 Jan; 109(1):64-70.

The authors' purpose was to study the safety and effectiveness of immediate anterior chamber paracentesis, combined with IOP-lowering medications in the intraocular pressure control and relief of symptoms of acute primary angle-closure glaucoma.

Eight consecutive patients with their first attack of acute primary angle-closure glaucoma, with intraocular pressure > or =50 mmHg, were recruited into the study. On presentation, each patient received topical pilocarpine (4%) and timolol (0.5%), immediate anterior chamber paracentesis, and systemic acetazolamide and mannitol as primary treatment. The intraocular pressures at 15 and 30 minutes, and then at 1, 2, 3, 12, and 24 hours, were documented by applanation tonometry. Symptoms, visual acuity, intraocular pressure, corneal edema, angle status on gonioscopy, and pupillary size, were recorded.

Ten eyes of eight patients seen with acute primary angle-closure glaucoma were recruited. The mean intraocular pressure was reduced from 66.6 +/- 9.1 mmHg to 15.1 +/- 3.5 mmHg immediately after paracentesis, and then to 17.1 +/- 7.0 mmHg at 15 minutes, 21.7 +/- 10.2 mmHg at 30 minutes, 22.7 +/- 11.0 mmHg at 1 hour, and 20.1 +/- 14.6 mmHg at 2 hours after paracentesis. The mean intraocular pressure was less than 21 mmHg at 2 hours and beyond. There was instant symptomatic relief for all patients. No complications from the paracentesis were reported.

The pupils were "unreactive" to "very sluggish" in all 10 eyes before paracentesis. All 10 eyes showed constrictive response to the topical pilocarpine at 2 hours after paracentesis.

Lam DS, Lai JS, Tham CC. Immediate argon laser peripheral iridoplasty as treatment for acute attack of primary angle-closure glaucoma: a preliminary study. Ophthalmology. 1998 Dec; 105(12):2231-6.

The authors aimed to examine the intraocular pressure (IOP)-lowering effects and safety of immediate argon laser peripheral iridoplasty (ALPI) as a first-line treatment for acute primary angle-closure glaucoma. This prospective cohort study enrolled ten consecutive patients with their first attack of primary angle-closure glaucoma, with an IOP of 40 mmHg or greater.

On presentation, each patient received topical pilocarpine (4%) and timolol (0.5%) and immediate ALPI as primary treatment. The IOPs at 15, 30, and 60 minutes after ALPI were documented by applanation tonometry. When the corneal edema had settled,

laser peripheral iridotomy was performed as a definitive treatment. The IOP, corneal edema, and complications from ALPI were measured.

The mean IOP of this group of patients was reduced from 59.5+/-10.4 mmHg to 28.7+/-14.9 mmHg at 15 minutes, 21.7+/-13.1 mmHg at 30 minutes, and 16.0+/-9.4 mmHg at 60 minutes after ALPI. No complications from the laser procedure were encountered during the study period. In nine of the ten patients, the corneal edema cleared up 1 hour after ALPI. In the remaining patient, the cornea cleared up 2 hours after ALPI.

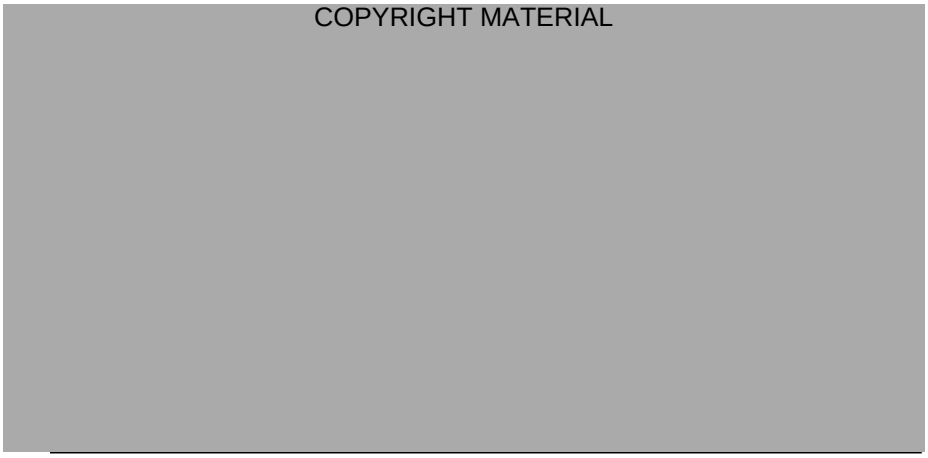
From this preliminary study, the authors conclude that immediate ALPI, along with topical IOP-lowering Timoptic and pilocarpine but without adjunctive systemic IOP-lowering agents, appeared to be effective in controlling the IOP and returning corneal clarity in acute primary angle-closure glaucoma.

Lam DS, Lai JS, Tham CC, Chua JK, Poon AS. Argon laser peripheral iridoplasty versus conventional systemic medical therapy in treatment of acute primary angle-closure glaucoma: a prospective, randomized, controlled trial. Ophthalmology. 2002 Sep; 109(9):1591-6.

The authors describe a prospective, randomized, controlled trial to study whether argon laser peripheral iridoplasty (ALPI) is as effective and safe as conventional systemic

medications in treatment of acute primary angle-closure glaucoma when immediate laser peripheral iridotomy is neither possible nor considered safe.

Seventy-three eyes of 64 consecutive patients with their first presentation of acute primary angle-closure glaucoma, with intraocular pressure (IOP) levels of 40 mmHg or more, were recruited into the study. The acute primary angle-closure glaucoma eye of each consenting patient received topical pilocarpine (4%) and topical timolol (0.5%). The patients were then randomized into one of two treatment groups. The ALPI group received immediate ALPI under topical anesthesia. The medical treatment group was given 500 mg of intravenous acetazolamide, followed by oral acetazolamide 250 mg four times daily, and an oral potassium supplement until IOP levels normalized. Intravenous mannitol also was administered to the latter group if the presenting IOP was higher than 60 mmHg. The acute primary angle-closure glaucoma eye of both groups continued to receive topical pilocarpine (1%) until peripheral iridotomy could be performed. Intraocular pressure profile, corneal clarity, symptoms, visual acuity, angle status by indentation gonioscopy, and complications of treatment were recorded.



The ALPI-treated group had lower IOP levels than the medically treated group at 15 minutes, 30 minutes, and 1 hour after the start of treatment. The differences were statistically significant. The difference in IOP levels became statistically insignificant from 2 hours onward. The duration of attack did not appear to affect the efficacy of ALPI in reducing IOP in acute angle-closure glaucoma.

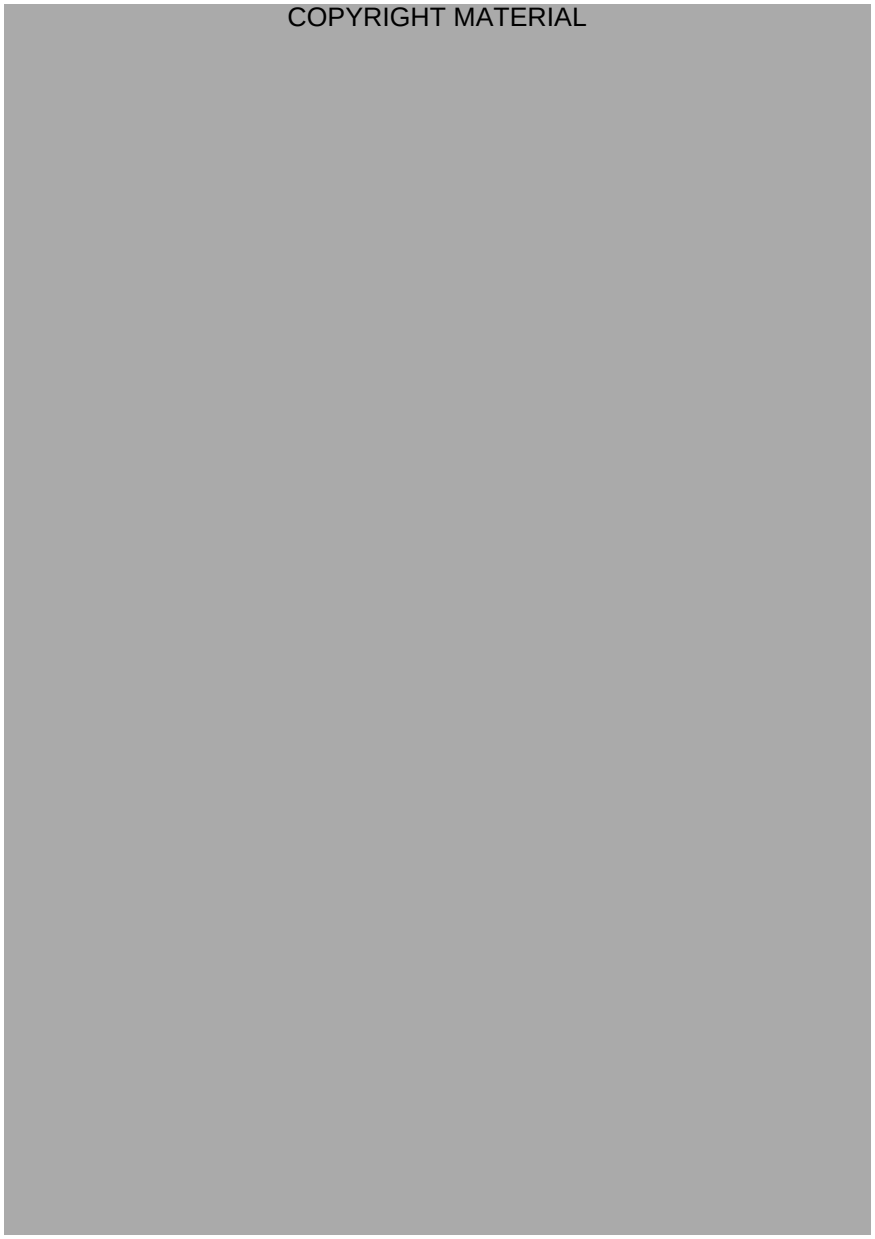
Pavlin CJ, Foster FS. Plateau iris syndrome: changes in angle opening associated with dark, light, and pilocarpine administration. Am J Ophthalmol. 1999 Sep; 128(3):288-91.

Plateau iris syndrome is characterized clinically by persistent angle narrowing in an eye with a patent iridotomy. Angle closure and increased pressure can occur spontaneously or with pupillary dilation. This condition is caused by anteriorly positioned ciliary processes that provide structural support to the peripheral iris. This structural support

prevents the peripheral iris from moving posteriorly after iridotomy, leaving the angle relatively narrow. Pupillary dilation can produce an acute increase in intraocular pressure in eyes with this syndrome. Therapy of plateau iris syndrome includes treatment with pilocarpine, which produces pupillary constriction and opens the angle

The objective of this trial was to report changes in angle configuration associated with dark, light, and pilocarpine administration in plateau iris syndrome. In 10 eyes of 10 patients with plateau iris syndrome and persistent narrow angles after patent peripheral Nd:YAG laser iridotomy, ultrasound biomicroscopy was used to image variations in angle opening, iris thickness, and trabecular-ciliary process distance. Measurements were taken in the dark, in full room light, and after administration of pilocarpine 2%.

Average angle opening distance increased in the light compared with the dark and increased further after pilocarpine administration. Average iris thickness decreased in the light compared with the dark and decreased further after pilocarpine administration. Average trabecular meshwork-ciliary process distance measurements were smaller than normal and did not change significantly in the light compared with the dark or after pilocarpine administration compared with light.



The authors conclude that changes in angle opening in dark and light are solely related to changes in iris thickness. Pilocarpine produces iris thinning and is an effective method of opening the angle. Ultrasound biomicroscopy can be used to perform a darkroom provocative test, which provides information on whether the angle anatomically closes in the dark.

Literature Summary: management of acute angle closure glaucoma

All of the submitted literature articles support the use of pilocarpine for the management of acute angle closure glaucoma.

Kobayashi, et al, 1999, describes a prospective, nonrandomized, non-masked, comparator controlled, single center trial in 60 subjects to determine the mechanical effects of pilocarpine on the trabecular-iris angle opening in eyes with narrow angles. IOP was not assessed in this trial; its purpose was to measure mechanical effects of pilocarpine on the trabecular-iris angle opening. This trial does provide support for the miotic effect of pilocarpine.

Lai, et al, 1999 and 2001, both describe the use of laser peripheral iridoplasty as treatment of acute attack of primary angle closure glaucoma in conjunction with the use of pilocarpine, timolol, and apraclonidine (2001 only) in prospective, nonrandomized, non-masked, single center trials. The authors conclude that diode laser peripheral iridoplasty, together with topical IOP-lowering medications without adjunctive systemic carbonic anhydrase inhibitors and hyperosmotic agents, appeared to be effective and safe in controlling the IOP in acute primary angle-closure glaucoma.

Lam, et al, 2002, studied the safety and effectiveness of immediate anterior chamber paracentesis, combined with topical pilocarpine and timolol in the intraocular pressure control and relief of symptoms of acute primary angle-closure glaucoma in a prospective, nonrandomized, unmasked, single center trial. There was instant symptomatic relief for all patients post paracentesis.

Lam, et al, 2002, describes a prospective, randomized, controlled trial to study argon laser peripheral iridoplasty (ALPI). All subjects received topical pilocarpine and timolol; the “medically treated” group also received systemic IOP-lowering agents versus the ALPI group. The ALPI-treated group had lower IOP levels than the medically treated group at 15 minutes, 30 minutes, and 1 hour after the start of treatment. The differences were statistically significant.

Pavlin, et al, 1999, describes changes in angle configuration associated with dark, light, and pilocarpine administration in plateau iris syndrome. Pilocarpine produced iris thinning and was an effective method of opening the angle.

6.3 Indication: The prevention postoperative elevated IOP associated with (b) (4) laser surgery

6.3.1 Methods – Literature

Dapling RB, Cunliffe IA, Longstaff S., Influence of apraclonidine and pilocarpine alone and in combination on post laser trabeculoplasty pressure rise. Br J Ophthalmol. 1994 Jan; 78(1):30-2.

In a prospective randomized study, the authors compared the ability of apraclonidine and pilocarpine alone and in combination to prevent post trabeculoplasty laser pressure spikes. Patients already receiving regular pilocarpine to either eye were excluded.

Seventy five eyes received either apraclonidine (26 eyes – Group A), pilocarpine (23 eyes – Group B), or both drugs (26 eyes – Group C). Apraclonidine 1% was instilled 1 hour before and immediately after, and pilocarpine 4% immediately after trabeculoplasty. IOP was measured before and at 1, 2, and 3 hours following trabeculoplasty. In only two (8%) eyes receiving combined treatment was a pressure rise observed. This frequency was significantly lower than that seen in eyes treated with apraclonidine alone (38%), or pilocarpine alone (39%). The mean fall in IOP at 1, 2, and 3 hours was significantly greater in those eyes receiving combined treatment than in the other two groups.

During the first three hours post-laser, 21 eyes had a rise in IOP. No rises in IOP were greater than 10 mmHg.

Note: In this case, pilocarpine was administered after laser treatment, either alone or in combination with pre-laser apraclonidine.

Elsås T, Johnsen H, Stang O. Pilocarpine to prevent acute pressure increase following primary laser trabeculoplasty. Eye (Lond). 1991; 5 (Pt 4):390-4.

The effect of pilocarpine 2% pretreatment on the transient pressure elevations immediately following primary laser trabeculoplasty was investigated in a prospective, randomized study. Fifty eyes of 50 patients, 33 with exfoliative and 17 with open-angle glaucoma were treated in 360 degrees of the trabecular meshwork. The mean maximum pressure increase was 2.4 (SD = 4.4) mm Hg with pilocarpine pretreatment and 12.8 (SD = 11.2) mm Hg without pretreatment (p less than 0.05). Except in two cases, all peak pressures appeared during the first two hours after treatment.

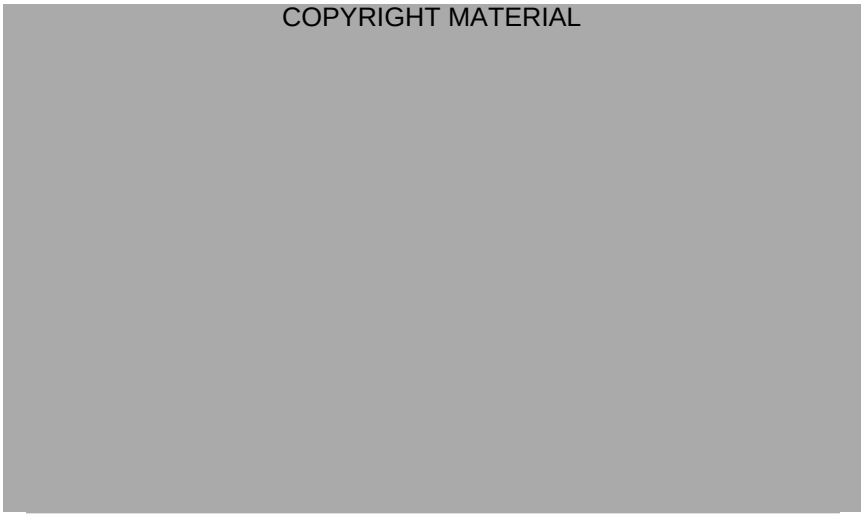
This trial was not masked because of the miotic effect of pilocarpine.

The authors postulate possible mechanisms for the IOP increase after ALT: mechanical blockage of the outflow channels by trabecular tissue damage, obstruction of the trabecular flow by entrapment of pigment and cellular debris, a prostaglandin mediated pressure increase, or a neuropeptide induced rise.

Fernandez-Bahamonde JL, Alcaraz-Michelli V. The combined use of apraclonidine and pilocarpine during laser iridotomy in a Hispanic population. Ann Ophthalmol. 1990 Dec; 22(12):446-9.

In a randomized, double-masked prospective study, the authors evaluated the efficacy of apraclonidine combined with pilocarpine versus pilocarpine alone during argon laser iridotomy in a Hispanic population. A significantly lower early postoperative IOP with less frequent severe pressure spikes occurred in the apraclonidine/pilocarpine treated patients versus pilocarpine treated subjects alone.

Twenty-two subjects were enrolled; all were Hispanic with iris colors from brown to dark brown.



Four subjects had IOP elevations greater than 10 mmHg; all had a history of chronic angle-closure glaucoma and were in the pilocarpine-only therapy group. Per the authors, the incidence of chronic angle closure glaucoma is higher in Hispanics than in other populations. Hispanics have darker and thicker irises which may lead to more frequent pressure spikes and postoperative inflammation.

The authors recommend premedication with apraclonidine, the addition of pilocarpine to stretch the iris, and meticulous postoperative IOP monitoring.

Lewis R, Perkins TW, Gangnon R, Kaufman PL, Heatley GA. The rarity of clinically significant rise in intraocular pressure after laser peripheral iridotomy with apraclonidine. Ophthalmology. 1998 Dec; 105(12):2256-9.

The authors performed a retrospective chart review to determine the incidence of intraocular pressure (IOP) rise of varying degrees after laser peripheral iridotomy (LPI) in patients with and without glaucoma treated peri-operatively with pilocarpine and apraclonidine. The difference between preoperative and postoperative IOP, absolute postoperative IOP, and the need for acute IOP-lowering treatment was noted

The charts of all patients undergoing LPI at the University of Wisconsin and one of its satellite clinics between February 1990 and December 1996 were reviewed. A total of 289 eyes in 179 patients with narrow occludable angles (N = 148), open-angle glaucoma or ocular hypertension (N = 115), or chronic-angle closure glaucoma (N = 26) were reviewed. Most iridotomies were made with a neodymium:YAG laser alone (n=278); some were made with a combination of argon and neodymium:YAG lasers (n=11).

Only 1.1% (95% confidence interval [CI], 0.03%-5.8%; 1 of 94) of patients and 0.7% (95% CI, 0.02%-3.7%; 1 of 148) of eyes with narrow occludable angles experienced a rise of more than 10 mmHg 1 to 2 hours after LPI.

Intraocular pressure in 1 of 115 eyes (0.9%, 95% CI, 0.02%-4.7%) with open angle glaucoma rose more than 10 mmHg, requiring acute treatment. None of the 26 chronic-angle closure glaucoma eyes experienced a rise of more than 10 mmHg (95% CI, 0%-13.2%).

The authors conclude that the IOP rise that requires further intervention after LPI with the perioperative use of pilocarpine and apraclonidine is very uncommon.

The authors state, however, that the limitations of the study include: limited sample size, homogeneous population, lack of information regarding race and iris color, and retrospective nature.

Liu CJ, Cheng CY, Chiang SC, Chiu AW, Chou JC, Hsu WM, Liu JH. Use of latanoprost to reduce acute intraocular pressure rise following neodymium:Yag laser iridotomy. Acta Ophthalmol Scand. 2002 Jun;80(3):282-6.

In this prospective, randomized, non-masked, comparator controlled, single center trial, the authors randomized primary angle-closure glaucoma eyes to receive premedication with latanoprost and pilocarpine or with pilocarpine alone before neodymium:Yag laser iridotomy to evaluate the efficacy of latanoprost in reducing acute intraocular pressure (IOP) elevation.

Postoperative IOP changes were compared with Wilcoxon signed-ranks test using the fellow eyes of 47 patients who had one eye in each group. Postoperative pressure spikes were significantly lower ($p = 0.010$) in the latanoprost + pilocarpine group (4.1 +/- 5.0 mmHg) than in the pilocarpine group (6.7 +/- 7.0 mmHg). Mean elevation of IOP

was less in the latanoprost + pilocarpine group than in the pilocarpine group at 1 hour (2.5 +/- 4.8 versus 4.1 +/- 4.7 mmHg, p = 0.013) and 2 hours (0.8 +/- 5.6 versus 4.4 +/- 8.1 mmHg, p = 0.003) postoperatively. Eleven eyes in the latanoprost + pilocarpine group (23.4%) and 20 eyes in the pilocarpine group (42.6%) developed a rise in IOP > or = 6 mmHg (p = 0.048).

Because the study design utilized the fellow eye as a control, some incongruity within the literature reference occurs when the authors switch between “eyes” and “subjects” with IOP elevations greater than or equal to 6 mm Hg.

A patent iridotomy was obtained in all eyes. Per the authors, pilocarpine is usually administered prior to laser iridotomy to keep the iris under tension and make the procedure easier to perform.

Ren J, Shin DH, Chung HS, Birt CM, Glover BK, Juzych MS, Hughes BA, Kim C. Efficacy of apraclonidine 1% versus pilocarpine 4% for prophylaxis of intraocular pressure spike after argon laser trabeculoplasty. Ophthalmology. 1999 Jun; 106(6):1135-9.

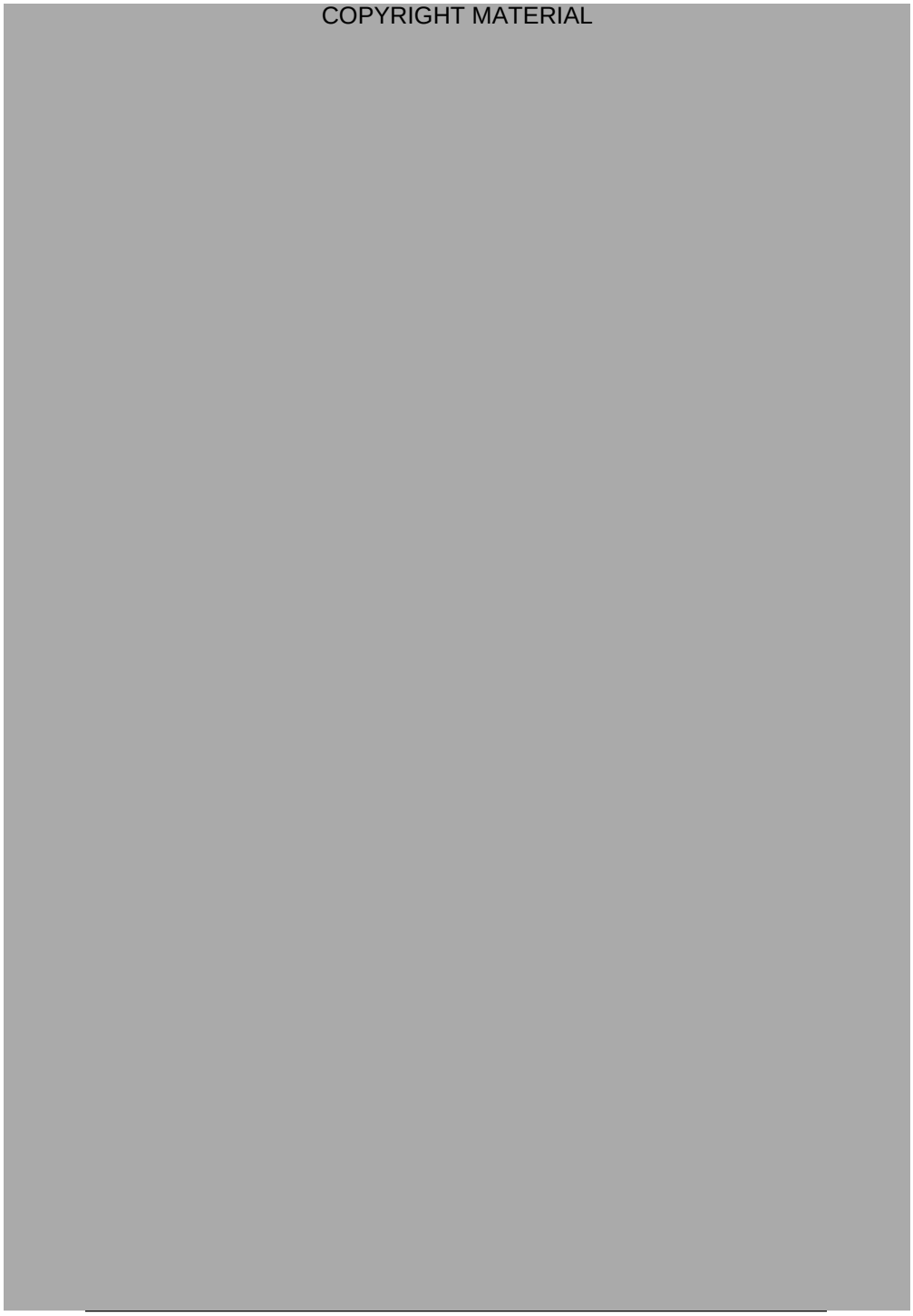
In a prospective, randomized clinical trial, the authors compared the efficacy of apraclonidine 1% versus pilocarpine 4% prophylaxis of post-argon laser trabeculoplasty (ALT) intraocular pressure (IOP) spike.

The authors utilized the term “Peri-ALT” to represent “Pre-ALT.” Here Pre-ALT is utilized for clarity and specificity.

Two hundred twenty-eight eyes of 228 patients with primary open-angle glaucoma undergoing ALT were studied. Patients were given 1 drop of either apraclonidine 1% (n = 114) or pilocarpine 4% (n = 114) 15 minutes before ALT. Pre-operative ALT IOPs and incidences of post-ALT IOP spikes at 5 minutes, 1 hour, and 24 hours were compared between the two groups. The two groups were similar in age, race, and medical history.

Post-ALT mean IOPs at 5 minutes, 1 hour, and 24 hours were significantly lower than pre-ALT mean IOPs in both apraclonidine ($P < 0.001$) and pilocarpine ($P < 0.001$) groups. Incidences of IOP spikes greater than 1, 3, and 5 mmHg at 1 hour post-ALT were 21.1%, 14.9%, and 8.8% for the apraclonidine group and 12.3%, 5.3%, and 4.4% for the pilocarpine group ($P = 0.076$, 0.015, and 0.18 chi-square test). In the apraclonidine prophylaxis group, patients on long-term apraclonidine showed significantly higher incidence of post-ALT IOP spike than the patients without such long-term apraclonidine use (35.7%, 15 of 42 eyes, vs. 12.5%, 9 of 72 eyes; $P = 0.003$). In addition, pre-ALT pilocarpine prophylaxis tended to be less effective in patients undergoing long-term pilocarpine therapy but without statistical significance (17.4%, 8 of 46 eyes, vs. 9.4%, 6 of 64 eyes; $P = 0.17$).

Per the authors, pre-ALT pilocarpine 4% was at least as effective as, if not more effective than, apraclonidine 1% in post-ALT IOP spike prophylaxis. Pre-ALT apraclonidine prophylaxis was not effective in patients on long-term apraclonidine, and pre-ALT pilocarpine prophylaxis tended to be less effective in patients undergoing long-term pilocarpine therapy.


COPYRIGHT MATERIAL

Literature Summary: prevention of postoperative elevated IOP associated with (b) (4) laser surgery indication

All of the submitted literature articles support the use of pilocarpine for the prevention of postoperative elevated IOP associated with (b) (4) laser surgery.

Dapling, et al, 1994, describes a prospective randomized study in 75 eyes in ALT; despite the use of pilocarpine post-ALT rather than pre-ALT, no rises in IOP post-laser were greater than 10 mmHg in either treatment group. This trial is limited by its lack of negative control arm or description of the incidence of IOP elevation post-ALT.

Elsås, et al, 1991, describes a prospective, randomized study in fifty eyes of 50 patients in ALT; the mean maximum pressure increase was approximately 2.5 mm Hg with pilocarpine pretreatment and approximately 13 mm Hg without pretreatment (p less than 0.05).

Fernandez-Bahamonde, et al, 1990 describes a randomized, double-masked prospective study in argon laser iridotomy; the four subjects with IOP elevations greater than 10 mmHg all had a history of chronic angle-closure glaucoma and were in the pilocarpine-only therapy group. This trial is limited by its lack of negative control arm or description of the incidence of IOP elevation post-argon iridotomy. It does provide support for the miotic effect of pilocarpine in argon iridotomy.

Lewis, et al, 1998, describes a retrospective chart review post iridotomy (primarily Nd:YAG) in patients treated peri-operatively with pilocarpine and apraclonidine; only 1% of patients with narrow occludable angles experienced a rise of more than 10 mmHg 1 to 2 hours after laser peripheral iridotomy. This trial is limited by sample size, homogeneous population, lack of information regarding race and iris color, and retrospective nature.

Liu, et al, 2002, describes a randomized, non-masked, comparator controlled, single center trial in neodymium:Yag laser iridotomy; postoperative pressure spikes were significantly lower ($p = 0.010$) in the latanoprost + pilocarpine group (approximately 4 mmHg) than in the pilocarpine group (approximately 7 mmHg). This trial is limited by its lack of negative control arm or description of the incidence of IOP elevation post-Nd:YAG iridotomy. It does provide support for the miotic effect of pilocarpine in Nd:YAG iridotomy.

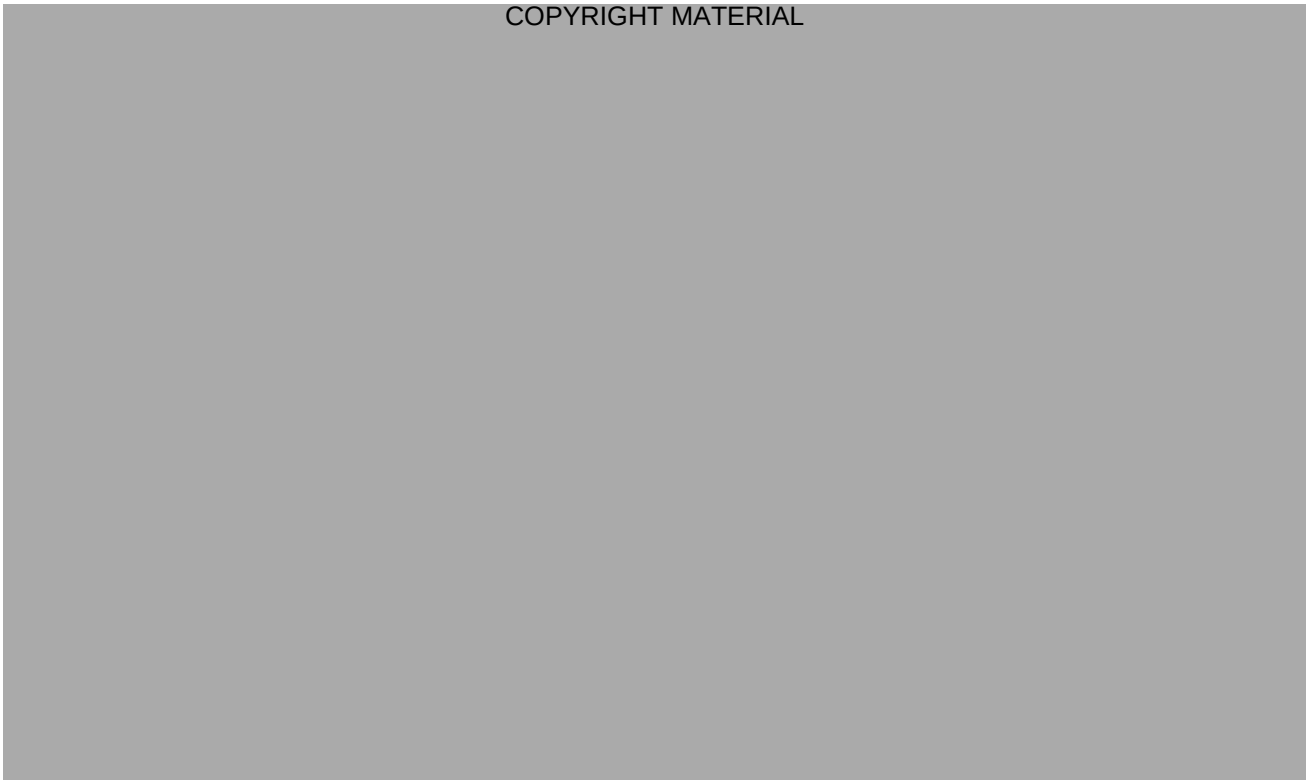
Ren, et al, 1999, describes a prospective, randomized clinical trial in 228 eyes (228 patients) in ALT; incidences of IOP spikes greater than 1, 3, and 5 mmHg at 1 hour post-ALT were roughly 20%, 15%, and 9% for the apraclonidine group and 12%, 5%, and 4% for the pilocarpine group. This trial is limited by its lack of negative control arm or description of the incidence of IOP elevation post-ALT. It also fails to address the

adverse events reported by pilocarpine-naive subjects who received the pilocarpine 4% pre-ALT. It does provide support for the miotic effect of pilocarpine in ALT.

6.4 Indication: The induction of miosis

Pilocarpine is a direct acting cholinergic agonist. It is believed that pilocarpine produces contraction of the ciliary muscle resulting in opening of the trabecular meshwork spaces to facilitate outflow of the aqueous humor, thus lowering intraocular pressure (IOP).

From Allingham, et al, 2005[4]:



The support for the fourth indication (induction of miosis) is therefore supported and derived from the other three indications. Alcon's C-91-47 and C-91-54 contain pupil size evaluations as part of their analyses. See Section 6.1.1. C C-91-47 and Section 6.1.1. D C-91-54 in this review.

4 Allingham R, Damji K, Freedman S, Moroi S, Shafranov G, Shileds M. Shield's Textbook of Glaucoma. Chapter 33: Cholinergic Agents. Lippencott, Williams, & Wilkins. 2005. 501-05.

6.5 Demographics

This is a 505(b)(2) application primarily based on literature but which includes submission of clinical study reports.

See Section 7.2.1 for Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.

Within the Alcon studies, there is adequate representation of the United States population by age, sex, and race. Efficacy and safety in pediatric patients are discussed at length in Section 7.6.3.

6.6 Subpopulations

No clinically relevant differences were observed between the treatment groups comparing the demographic characteristics (i.e., age, race, sex, and iris color) of the population when integrated across studies, as well as within each individual Alcon clinical study. See Appendix 9.1 Additional Tables/Analyses.

Analyses by age category (adults and elderly), gender, race, and iris color did not identify any efficacy (or safety) concerns for any demographic subpopulation. This is supported by the relevant literature references cited in Section 6 of this review.

Within the Alcon studies, there is adequate representation of the United States population by age, sex, and race.

Efficacy and safety in pediatric patients are discussed at length in Section 7.6.3.

6.7 Analysis of Clinical Information Relevant to Dosing Recommendations

The frequency of instillation and concentration of Isopto Carpine are determined by the severity of the glaucoma and miotic response of the patient.

No dose-response or dose ranging studies were carried out by Alcon for Isopto Carpine (pilocarpine hydrochloride ophthalmic solution); pilocarpine has increasing ocular hypotensive effects in concentrations up to 4%, with higher concentrations (e.g. 6%) giving little additional benefit.

From Bartlett, et al, 2008[5]:

5 BartlettJ, Jaanus S. Clinical Ocular Pharmacology. Chapter 10: Ocular Hypotensive Drugs. Butterworth Heinemann. 2008. 167-70.

COPYRIGHT MATERIAL

From Allingham, et al, 2005[6]:

COPYRIGHT MATERIAL

and

COPYRIGHT MATERIAL

Adverse reactions are more frequently observed after repeated instillations of the product and with higher concentrations of pilocarpine.

6.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Alcon proposed the following statement in the Warnings Section of the labeling, (b) (4)

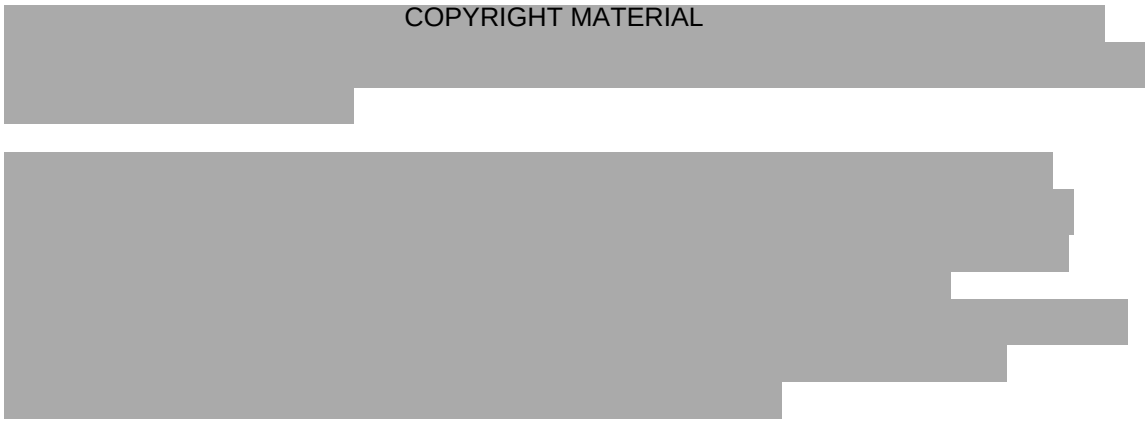
"

After an Agency request for clarification, Alcon subsequently changed this statement (in a May 7, 2010, amendment) to read, (b) (4)

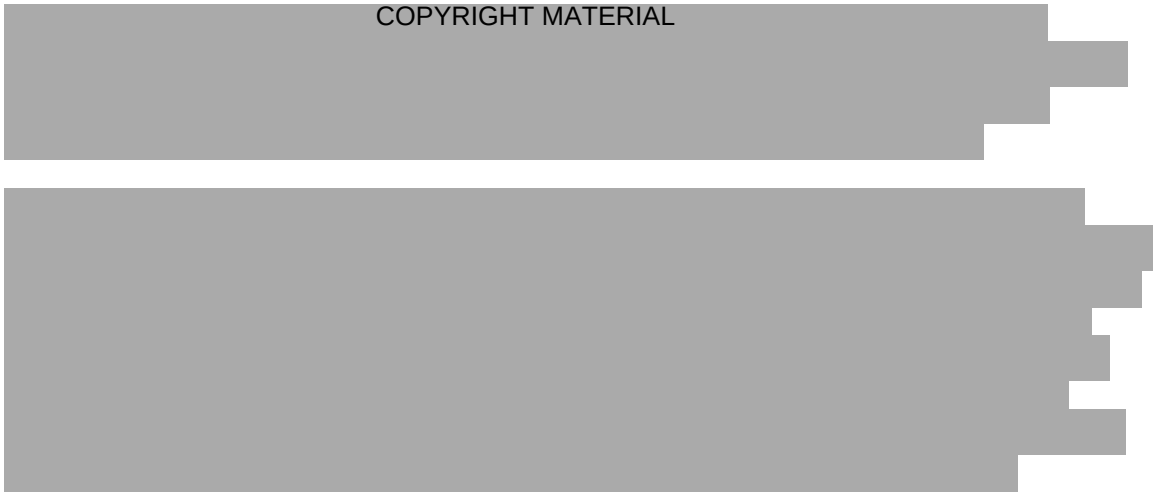
Alcon cites two references to support the proposed language.

From Allingham, et al, 2005[7]

6 Allingham R, Damji K, Freedman S, Moroi S, Shafranov G, Shields M. Shield's Textbook of Glaucoma. Chapter 33: Cholinergic Agents. Lippencott, Williams, & Wilkins. 2005. 501-05.



From Gabelt, et al, 1999[8]:



Both of these cited references utilize animal data to support the proposed Warning language; there is no clinical data provided or referenced to support the statements. An additional literature review conducted by the Medical Officer found no reported human data to support the statements.

This Alcon proposed language regarding (b) (4) not recommended for inclusion in the label.

7 Allingham R, Damji K, Freedman S, Moroi S, Shafranov G, Shields M. Shield's Textbook of Glaucoma. Chapter 33: Cholinergic Agents. Lippencott, Williams, & Wilkins. 2005. 501-05.

8 Gabelt BT, Kaufman P. Chapter 4 Cholinergic Drugs. Ophthalmology Monographs: Glaucoma Medical Therapy. American Academy of Ophthlamology. 1999. 77-96.

6.9 Additional Efficacy Issues/Analyses - Pediatrics

In contrast to the treatment of glaucoma in adults, medical treatment of pediatric glaucomas is often secondary with surgical therapy taking the primary role. This is particularly true of primary congenital glaucoma (or infantile glaucoma) where surgery is necessary to provide effective management.

There is substantial evidence from the literature that pilocarpine has been and continues to be an important component of the medical management of elevated IOP in pediatric glaucoma.

Despite the long-standing use of pilocarpine in the treatment of children, no serious safety concerns have been reported; by implication the safety profile is similar to what has been reported for adults.

The proposed Alcon labeling statements,

> Children under 2 years of age should be dosed one drop of Isopto Carpine 1% should be applied topically in the eye(s) three times daily. Children 2 years of age and over should be dosed as for adults. For the induction of miosis prior to goniotomy or trabeculotomy in children, one drop of Isopto Carpine 1% or 2% should be applied topically in the eye 15 to 60 minutes prior to surgery.
>
> and
>
> Caution is advised when using ISOPTO® Carpine in pediatric patients with primary congenital glaucoma for control of IOP as a paradoxical increase in IOP have been reported. In addition, the use of ISOPTO® Carpine is not recommended in pediatric patients diagnosed with glaucoma secondary to anterior segment dysgenesis or uveitis (especially if uveitis is active).

are supported by Moore, et al, 2007[9]:

9 Moore W, Nischal KK. Pharmacologic management of glaucoma in childhood. Paediatr Drugs. 2007;9(2):71-9.

and

Asrani SG, Wilensky JT. Glaucoma after congenital cataract surgery. Ophthalmology. 1995 Jun; 102(6):863-7.

All consecutive patients who were treated for glaucoma on the Glaucoma Service at the University of Illinois Eye Center, Chicago, during the last 15 years who had a history of congenital cataract surgery were identified. Sixty-four eyes of 38 patients were studied. Open-angle glaucoma was the more frequent type of glaucoma (51 eyes, 80%).

Glaucoma was diagnosed a mean interval of 12 years after cataract surgery, but it could occur at any time from months to decades after the cataract surgery. Medications alone were successful in intraocular pressure control in 21 (64%) of 33 eyes. These included systemic therapy such as acetazolamide and methazolamide and topical therapy such as beta-blockers, Phospholine iodide, pilocarpine, carbachol, and propine. Additional surgical procedures resulted in successful intraocular pressure control in 11 of 14 eyes in which they were performed. The authors could not predict in which eyes glaucoma would develop after surgery for congenital cataracts.

Awad AH, Mullaney PB, Al-Mesfer S, Zwaan JT. Glaucoma in Sturge-Weber syndrome. J AAPOS. 1999 Feb;3(1):40-5.

Sturge-Weber Syndrome (SWS) is one of the systemic hamartomatoses (phakomatoses). It is a rare neuro-oculocutaneous disorder. Glaucoma is more common in SWS than in any other systemic hamartomatosis, but its precise incidence is unknown. The reported incidence ranges between 30% to 45% if both the ophthalmic and maxillary divisions of the trigeminal nerve are involved.

Eighteen consecutive patients with SWS were reviewed retrospectively at the King Khaled Eye Specialist Hospital. An intraocular pressure less than 20 mm Hg, plus stable optic nerve cup-to-disc ratio and corneal diameter (or visual fields where appropriate), were parameters chosen to indicate that the glaucoma was being controlled. RESULTS: Glaucoma was found in 15 of 18 patients (22 eyes). The mean follow-up time was 62 months (range, 12 to 148 months).

Medical treatment alone was successful in 5 patients (7 eyes); the remainder required surgical intervention. Medications used to control the IOP included Betoptic (betaxolol

hydrochloride), Propine (dipivefrin), Adsorbocarpine (pilocarpine hydrochloride), and Diamox (acetazolamide). The initial surgical procedures included cyclocryotherapy, YAG laser goniotomy, surgical goniotomy, and trabeculotomy or trabeculectomy. Eight eyes required subsequent surgery, 5 with Molteno or Ahmed implants.

Barsoum-Homsy M, Chevrette L. Incidence and prognosis of childhood glaucoma. A study of 63 cases. Ophthalmology. 1986 Oct; 93(10):1323-7.

Glaucoma in infants and children has been classified into three groups: group I, primary congenital or infantile glaucoma; group II, glaucoma associated with congenital anomalies; and group III, glaucoma secondary to other ocular pathology. The purpose of this study is to evaluate the relative incidence of glaucoma in the three different groups, to describe and compare the associated clinical findings and treatment modalities, as well as to establish the prognosis in each group.

Sixty-three consecutive cases (95 eyes) of glaucoma in children, seen between 1975 and 1983 at the Pediatric Glaucoma Clinic of Hospital Ste-Justine, were included in this study. Glaucoma associated with congenital anomalies (group II) formed the largest group in this study, accounting for 46% of the cases compared to primary congenital glaucoma (group I) that accounted for 22%. Secondary glaucoma (group III) occurred in 32%.

The presenting signs and symptoms in group I were tearing and corneal edema. In 50% of the cases in groups II and III, diagnosis was made on a routine ophthalmologic examination. Surgery was performed in 96% of eyes in group I, 53% in group II, and 54% in group III. The best visual prognosis occurred in group I where 77% of affected eyes had visual acuity equal to or better than 20/50 with good pressure control in all. This was followed by group II where 42% had vision equal to or better than 20/50 and 42% had 20/200 vision or less. Intraocular pressure remained uncontrolled in 19% of this group. The worst prognosis and morbidity was found in group III where 30% of eyes had 20/50 vision or better and 48% had 20/200 vision or less. In group III, 33% had uncontrolled intraocular pressure.

Treatment in group II was initially medical and consisted of one or more of the following: epinephrine, timolol, pilocarpine, and/or acetazolamide.

Busters JF, Terrine R, Hamel P, Barrette P, Prot-Laborite S. Retrospective cohort study of 163 pediatric glaucoma patients. Can J Ophthalmol. 2009 Jun; 44(3):323-7.

This retrospective cohort study included patients younger than 18 years who were diagnosed with glaucoma between 1980 and 2000 and monitored at the authors' Ophthalmology Clinic and had ocular hypertension or glaucoma in at least one eye. The study identified 163 patients (254 eyes), a total of 374 surgical procedures, and the use of 2885 IOP-lowering drug therapies. For the 4 most frequent pathologies, patients

were monitored for 8.4 years for aphakic glaucoma/pseudophakic glaucoma, 10.0 years for congenital glaucoma, 9.0 years for Axenfeld-Rieger syndrome, and 7.5 years for uveitic glaucoma. In total, 113 patients had at least 1 surgical procedure (70%).

The 2885 IOP-lowering drug therapies were given to 161 patients. Before 1985, only timolol, pilocarpine, epinephrine, acetazolamide, and dipivefrin were used.
Other beta blockers then appeared (betaxolol, levobunolol between 1985 and 1990, and the timolol-pilocarpine association between 1990 and 1995). After 1995, the authors note the arrival of prostaglandin analogues and topical carbonic anhydrase inhibitors.

Papadopoulos M, Cable N, Rahi J, Khaw PT; BIG Eye Study Investigators. The British Infantile and Childhood Glaucoma (BIG) Eye Study.Invest Ophthalmol Vis Sci. 2007 Sep; 48(9):4100-6.

A prospective study was conducted wherein children in the United Kingdom and Republic of Ireland aged ≤16 years with newly diagnosed primary or secondary glaucoma, were identified by consultant ophthalmologists through active surveillance from December 2001 until November 2002.

Of the 99 eligible children with newly diagnosed glaucoma, 47 had primary and 52 secondary glaucoma. The annual incidence of diagnosis of primary congenital glaucoma (PCG) in Great Britain was 5.41 in 100,000 (1/18,500) live births and in the Republic of Ireland, 3.31 in 100,000 (1/30,200). The incidence of PCG in children of Pakistani origin was almost nine times that of Caucasians. IOP control of $\leq$ 21 mm Hg was achieved in 94% with medications (60% without medications) in cases of PCG and in 86% with medications (28% without medications) in cases of secondary glaucoma.

Primary cases were more likely to be treated earlier and surgically with preference to goniotomy. More secondary glaucoma cases were managed medically before surgery and with a greater number of topical medications. The most frequent topical treatment was pilocarpine in primary glaucoma and latanoprost in secondary glaucoma. Sixty percent of children with primary glaucoma and 28% with secondary glaucoma achieved IOP control (≤ 21 mmHg) at 1 year without additional medication.

7 Review of Safety

Safety Summary

This is a 505(b)(2) application primarily based on literature but which includes submission of clinical study reports.

The clinical trials with pilocarpine hydrochloride ophthalmic solution (C-90-42, C-90-105, C-91-47, C-91-54, C-95-17 and C-92-56) were conducted by Alcon between 1990 and 1995 under the IND for betaxolol hydrochloride ophthalmic solution (IND (b) (4)).

The submitted Clinical Study reports were reviewed and are summarized in this review with the exception of C-95-17 (comfort) and C-92-56 (pK).

There is adequate support from the clinical study reports, from Alcon's PSUR for the European Union, and from the literature to support safety for the following indications for pilocarpine ophthalmic solution 1%, 2% and 4 %:

1) the reduction of elevated intraocular pressure in patients with ocular hypertension or open angle glaucoma
2) the management of acute angle closure glaucoma
3) the prevention o (b) (4) postoperative elevated IOP associated with (b) (4) laser surgery
4) the induction of miosis.

The most frequently reported adverse reactions occurring in ≥ 5 % of patients in the pilocarpine study populations (N=317) were: headache, blurred vision, eye irritation, visual impairment (dim, dark, or "jumping" vision), and eye pain. These are in the pooled Alcon trials C-90-105, C-90-42, C-91-47, and C-91-54.

Overall, the majority of the most common adverse events (ocular or nonocular) reported in patients treated with pilocarpine began with the onset of study medication use, were transient in nature, and resolved without treatment with the exception of headaches which in many cases required concomitant therapy to resolve.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Six clinical trials are included in Alcon's Summary of Clinical Safety. These studies included 317 patients diagnosed with open-angle glaucoma or ocular hypertension and 69 healthy subjects that were exposed to pilocarpine 2% or 4% as a single agent or 1%, 1.75%, or 2% in fixed combination with betaxolol.

A five-year Periodic Safety Update Report on pilocarpine hydrochloride (2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml, 60 mg/ml and 40 mg/g) for ophthalmic use was compiled for the regulatory authorities in the European Union. It summarizes the safety data received from world-wide sources by Alcon's Department of Medical Safety from 01 August 2004 to 31 July 2009.

7.1.2 Categorization of Adverse Events

All adverse events in the Alcon trials were coded using the MedDRA dictionary (Version 12.0) and received independent causality assessments from the investigator and Medical Monitor. The causality assessments presented in the adverse event tables and listings are as reported by the investigator on the adverse event form.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Alcon phase 2 (C-90-42, C-91-47 and C-91-54) and Phase 4 (C-90-105) clinical trials were pooled together as these studies were similar in design and patient population. The topical ocular PK (C-92-56) and ocular comfort (C-95-17) clinical trials were presented individually as these studies differed in patient population and design from the other studies.

A five-year Periodic Safety Update Report on pilocarpine hydrochloride (2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml, 60 mg/ml and 40 mg/g) for ophthalmic use was compiled for the regulatory authorities in the European Union. It summarizes the safety data received from world-wide sources by Alcon's Department of Medical Safety from 01 August 2004 to 31 July 2009.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

This is a 505(b)(2) application primarily based on literature but which includes submission of clinical study reports.

Approximately (b) (4) units of Alcon products containing different concentrations of pilocarpine hydrochloride for ophthalmic use were distributed during the period covered by the Alcon European Union PSUR.

Patients/subjects in the 6 clinical trials presented in the Summary of Clinical Safety were exposed to pilocarpine 1.75%, 2% or 4% as a monotherapy. In the ocular comfort study (C-95-17), patients treated with pilocarpine 1.75% received 1 drop twice daily for up to 7 days. During the phase 2 studies, patients treated with pilocarpine 2% received 1 to 2 drops of study medication twice daily (C-90-42) or three times daily (C-91-47 and C-01-57) for up to 90 days. In the phase 4 study (C-90-105), patients received pilocarpine 2% 1 to 2 drops four times daily for up to 2 years. Patients in the topical ocular PK clinical trial received pilocarpine 4% 2 drops 4 times daily for up to 7days.

Within the Alcon studies, there is adequate representation of the United States population by age, sex, and race. Efficacy and safety in pediatric patients are discussed at length in Section 6.9.

Table 2.7.4.1–3 Demographics of Patients in the Pooled Clinical Trials (C-90-42, C-91-47, C-91-54, and C-90-105)

		Pilocarpine 2%	Betaxolol 0.25%/ Pilocarpine 2%	Betaxolol 0.25%/ Pilocarpine 1.75%	Betaxolol 0.25%/ Pilocarpine 1 %	Betaxolol 0.5%	Betaxolol 0.25%	Timolol 0.5%
Total		**157**	**18**	**121**	**21**	**28**	**141**	**27**
Race	Caucasian	123	10	91	14	28	108	24
	Black	26	7	22	6	0	29	1
	Asian	2	0	0	0	0	0	2
	Other	6	1	8	1	0	4	0
Age (years)	18 to 64 years	90	9	65	12	13	69	15
	65 to 74 years	50	7	38	6	8	61	7
	75 years or older	17	2	8	3	7	11	5
Sex	Male	63	11	47	11	15	56	18
	Female	94	17	74	10	13	85	9
Eye Color	Brown	75	10	66	11	6	65	15
	Blue	49	5	41	8	10	45	5
	Other[†]	33	3	14	2	12	31	7

[†]Other = green, gray of hazel irides; Pilocarpine = pilocarpine hydrochloride ophthalmic solution; Betaxolol 0.5% = betaxolol hydrochloride ophthalmic solution, 0.5%; Betaxolol 0.25% = betaxolol hydrochloride ophthalmic suspension, 0.25%; Timolol = timolol maleate ophthalmic solution, 0.5%

7.2.2 Explorations for Dose Response

The frequency of instillation and concentration of Isopto Carpine are determined by the severity of the glaucoma and miotic response of the patient.

No dose-response or dose ranging studies were carried out by Alcon for Isopto Carpine (pilocarpine hydrochloride ophthalmic solution); pilocarpine has increasing ocular hypotensive effects in concentrations up to 4%, with higher concentrations (e.g. 6%) giving little additional benefit. See Section 6.7 this review.

Adverse reactions are more frequently observed after repeated instillations of the product and with higher concentrations of pilocarpine.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was conducted.

7.2.4 Routine Clinical Testing

Clinically relevant changes from baseline in safety parameters which included best corrected visual acuity, intraocular pressure, ocular sign parameters (eyelids/conjunctiva, cornea, iris/anterior chamber, lens, vitreous), pupil diameter, color vision, dilated fundus parameters (retina/macula/choroid, optic disc, optic nerve, horizontal cup/disc ratio), and pulse rate were reported as an adverse event.

No laboratory parameters were assessed in the clinical trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Biopharmacology review.

No laboratory parameters were assessed in the clinical trials.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See 7.2.4 regarding routine clinical testing. The relevant potential adverse events for this drug class (cholinergic agonists) were adequately monitored and evaluated in the Alcon clinical trials.

7.3 Major Safety Results

7.3.1 Deaths

In the six clinical trials with pilocarpine hydrochloride ophthalmic solution (C-90-42, C-90-105, C-91-47, C-91-54, C-95-17 and C-92-56) conducted by Alcon between 1990 and 1995 under the IND for betaxolol hydrochloride ophthalmic solution (IND (b) (4) there were three patient deaths – two deaths occurred in subjects treated with pilocarpine 2% and one death occurred in a betaxolol 0.5% treated subject.

Protocol	Investigator	Sub	Age/Sex	Treatment	Adverse Event
C-91-54	1393	1414	74 yo/male	Pilocarpine 2%	Acute myocardial infarction
C-91-47	970	7701	68 yo/female	Pilocarpine 2%	Acute myocardial infarction
C-90-105	102	161	79 yo/female	Betaxolol 0.5%	Brain herniation 2° trauma

Alcon assessed these events as unrelated to the study medications; this assessment is reasonable.

7.3.2 Nonfatal Serious Adverse Events

Nine patients reported non-fatal serious ADRs during the clinical trials.

Retinal tears were reported in 1 patient treated with pilocarpine 2% and 1 patient treated with betaxolol 0.25%/pilocarpine 2%. Both patients discontinued participation in the trial due to the non-fatal serious ADRs.

The seven additional reported nonfatal serious adverse events included 1 patient treated with betaxolol 0.25%/pilocarpine 1.75% (congestive cardiac failure) and 6 patients treated with betaxolol 0.25% (retinal artery occlusion, breast cancer, coronary artery bypass, arterial bypass operation, cervix carcinoma, hysterectomy, and thrombosis).

7.3.3 Dropouts and/or Discontinuations

Regarding the Alcon studies, the most common pooled adverse events leading to discontinuation of study participation in patients treated with pilocarpine 2% or 4%, or betaxolol 0.25%/pilocarpine 1.75% or 2% were events involving visual disturbances (blurred vision and visual impairment described as dim, dark or jumping vision) and headaches associated with the use of pilocarpine.

The Dropouts and/or Discontinuations for each individual Alcon study are shown in Section 6.1.1.A-D.

7.3.4 Significant Adverse Events

See Section 7.3.2 and Section 7.3.3.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission specific primary safety concerns beyond the relevant potential adverse events for this drug class (cholinergic agonists).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most frequently reported adverse reactions occurring in ≥ 5 % of patients in the pilocarpine study populations (N=317) were: headache, blurred vision, eye irritation, visual impairment (dim, dark, or "jumping" vision), and eye pain. These are in the pooled Alcon trials C-90-105, C-90-42, C-91-47, and C-91-54.

Overall, the majority of the most common adverse events (ocular or nonocular) reported in patients treated with pilocarpine began with the onset of study medication use, were transient in nature, and resolved without treatment with the exception of headaches which in many cases required concomitant therapy to resolve. This table is utilized in the drug product package insert.

Adverse Reactions Occurring at an Incidence of 1% or Greater in Clinical Trials with Pilocarpine 2% or Pilocarpine 1%, 1.75% or 2% in Fixed Combination with Betaxolol 0.25% in Patients with Open-Angle Glaucoma or Ocular Hypertension in Pooled Clinical Trials C-90-105, C-90-42, C-91-47, C-91-54[10]

Adverse Reactions	Pilocarpine 2% N=157	Betaxolol 0.25%/ Pilocarpine 1%, 1.75%, or 2% N = 160	Betaxolol 0.5%, 0.25% or Timolol 0.5% N = 196
Headache	40 (25.5%)	31 (19.4%)	11 (5.6%)
Blurred vision	29 (18.5%)	26 (16.3%)	5 (2.6%)
Eye irritation	11 (7.0%)	5 (3.1%)	3 (1.5%)
Visual impairment	9 (5.7%)	18 (11.3%)	3 (1.5%)
Eye pain	9 (5.7%)	5 (3.1%)	19 (9.7%)
Visual acuity reduced	6 (3.8%)	0 (0.0%)	6 (3.1%)

10 Derived from Alcon Table 2.7.4.7-4

Photopsia	4 (2.5%)	1 (0.6%)	3 (1.5%)
Myo-desopsia (floaters)	3 (1.9%)	7 (4.4%)	0 (0.0%)
Nausea	3 (1.9%)	3 (1.9%)	2 (1.0%)
Dizziness	3 (1.9%)	2 (1.3%)	1 (0.5%)
Foreign body sensation in eye	2 (1.3%)	2 (1.3%)	3 (1.5%)
Ocular hyperaemia	2 (1.3%)	2 (1.3%)	2 (1.0%)
Increased intraocular pressure	2 (1.3%)	0 (0.0%)	1 (0.5%)
Injury	2 (1.3%)	0 (0.0%)	1 (0.5%)

7.4.2 Laboratory Findings

There were no clinical laboratory evaluations conducted for any of the Alcon Isopto Carpine studies.

7.4.3 Vital Signs

There were no clinically significant between group differences in pulse rate found in the Alcon studies.

7.4.4 Electrocardiograms (ECGs)

There were no electrocardiograms conducted for any of the Alcon studies.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials conducted for this application.

7.4.6 Immunogenicity

Not applicable. Drug product is not expected to be immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The frequency of instillation and concentration of Isopto Carpine are determined by the severity of the glaucoma and miotic response of the patient.

No dose-response or dose ranging studies were carried out by Alcon for Isopto Carpine (pilocarpine hydrochloride ophthalmic solution). Pilocarpine has increasing ocular hypotensive effects in concentrations up to 4%, with higher concentrations (e.g. 6%) giving little additional benefit.

Adverse reactions are more frequently observed after repeated instillations of the product and with higher concentrations of pilocarpine.

7.5.2 Time Dependency for Adverse Events

Adverse reactions are more frequently observed after repeated instillations of the product and with higher concentrations of pilocarpine.

7.5.3 Drug-Demographic Interactions

Evaluation of any difference in efficacy based on iris color is of particular interest for pilocarpine as it has been suggested that heavily pigmented eyes may require higher concentrations of pilocarpine in order to achieve similar efficacy seen with less pigmented eyes[11].

No convincing relationship was found between iris color and IOP-lowering efficacy in the Alcon studies. Table 2.7.3.3–5 shows the mean change from baseline in IOP according to iris color (brown versus non-brown) for each of these three studies, C-90-42, C-91-47, and C-91-54.

Table 2.7.3.3–5 Mean Change From Baseline in IOP According to Iris Color for ISOPTO Carpine 2% Ophthalmic Solution

Study No.	Visit Time					
	8AM		12 Noon		4PM	
	Brown	Non-Brown	Brown	Non-Brown	Brown	Non-Brown
C-90-42[a]						
Mean IOP Change	-1.5	-1.1	-5.1	-2.8	-5.8	-3.2
C-91-47[b]						
Mean IOP Change	-2.5	-1.0	-4.5	-2.5	-4.5	-3.4
C-91-54[c]						
Mean IOP Change	-1.8	-1.0	-3.9	-3.6	-3.6	-3.7

[a]No significant iris color by treatment effect was observed at any time point; [b]No significant iris color by treatment effect was observed at 8AM or 4 PM; a significant treatment effect was observed at 12 noon; [c]No significant iris color by treatment effect was observed at any time point.

See Appendix 9.1 Additional Tables/Analyses.

11 BartlettJ, Jaanus S. Clinical Ocular Pharmacology. Chapter 10: Ocular Hypotensive Drugs. Butterworth Heinemann. 2008. 167-70.

7.5.4 Drug-Disease Interactions

Pilocarpine is a direct acting cholinergic agonist. It is believed that pilocarpine produces contraction of the ciliary muscle resulting in opening of the trabecular meshwork spaces to facilitate outflow of the aqueous humor, thus lowering intraocular pressure (IOP).

As with all miotics, rare cases of retinal detachment have been reported when used in certain susceptible individuals and those with pre-existing retinal disease; therefore, a thorough examination of the retina including funduscopy is advised in all patients prior to the initiation of therapy.

7.5.5 Drug-Drug Interactions

The Alcon proposed language regarding (b) (4) not recommended for inclusion in the label. (b) (4)

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Animal reproduction studies have not been conducted with pilocarpine hydrochloride ophthalmic solution. It is also not known whether pilocarpine hydrochloride can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Isopto Carpine should be given to a pregnant woman only if clearly needed.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women. Isopto Carpine ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

As reported by Schmahl D; and Habs M in “Life-Span Investigations for Carcinogenicity of some Immune-Stimulating, Immunodepressive and Neurotropic Substances in Sprague-Dawley Rats” published in Zeitschrift Fur Krebsforschung Und Klinische Onkolo, 1976 May 3; 86 (1) : 77 – 84, pilocarpine is not carcinogenic. Atropine, pilocarpine, nicotine, and phenyl-ethyl-barbituric acid (phenobarbital) which are known to have neurotropic effects were tested. Pilocarpine was given intraparitoneally at a dose of 30 mg/kg/week. Nicotine and phenobarbital were found to diminish the mean survival times. None of these neurotropic substances was found to be carcinogenic.

7.6.3 Pediatrics and Assessment of Effects on Growth

Safety and effectiveness of pilocarpine hydrochloride ophthalmic solution in pediatric patients have been established. The use of Isopto Carpine in pediatric patients is supported by evidence from adequate and well-controlled studies in adults and by reports of pediatric use in medical and scientific literature.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Pilocarpine is a non-narcotic and does not have abuse potential.

Systemic toxicity following topical ocular administration of pilocarpine is rare, but occasionally patients who are sensitive may develop sweating and gastrointestinal overactivity following the suggested dosage and administration. Overdosage of the topical ophthalmic formulation can produce sweating, salivation, nausea, tremors and slowing of the pulse and a decrease in blood pressure. In moderate overdosage, spontaneous recovery is to be expected and is aided by intravenous fluids to compensate for dehydration. For patients demonstrating severe poisoning, atropine, the pharmacologic antagonist to pilocarpine, should be used

7.7 Additional Submissions / Safety Issues

The 120-day Safety Update, submitted on May 7, 2010, provided no new safety information regarding Isopto Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2%, and 4% since the original submission of December 22, 2009.

8 Post-market Experience

EUROPEAN UNION

A five-year Periodic Safety Update Report on pilocarpine hydrochloride (2.5 mg/ml, 5 mg/ml, 10 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml, 60 mg/ml and 40 mg/g) for ophthalmic use was compiled for the regulatory authorities in the European Union. It summarizes the safety data received from world-wide sources by Alcon's Department of Medical Safety from 01 August 2004 to 31 July 2009.

Approximately (b) (4) units of Alcon products containing different concentrations of pilocarpine hydrochloride for ophthalmic use were distributed during the period covered by this safety report. Sales numbers in units are provided as the best estimate of patient exposure. In the following tables from the Alcon European Union PSUR, Isopto Carpine 10 mg/mL corresponds to Isopto Carpine 1%, 20 mg/mL corresponds to 2%, etc. See following Worldwide Sales Numbers table.

Per Alcon, the analysis of cases received during the period reviewed did not reveal new or potentially important safety findings for the ophthalmic use of pilocarpine hydrochloride (2.5 mg/mL, 5 mg/mL, 10 mg/mL, 20 mg/mL, 30 mg/mL, 40 mg/mL, 60 mg/mL). The majority of the adverse events reported were mostly expected for the ophthalmic use of pilocarpine. See the following tables (Table 3) for 1%, 2%, 4% and 6% pilocarpine ophthalmic solution.

Reactions originated from the systemic absorption of the product (such as increased salivation, headache, nausea, bronchospasm, tearing and sweating) have also been reported. These reactions are more frequently observed after repeated instillations of the product and with higher concentrations of pilocarpine.

No reports of suspected drug interactions involving pilocarpine hydrochloride (2.5 mg/mL, 5 mg/mL, 10 mg/mL, 20 mg/mL, 30 mg/mL, 40 mg/mL, 60 mg/mL) for ophthalmic use were received.

There were no medically confirmed reports of overdose received.

WORLDWIDE SALES NUMBERS

(b) (4)

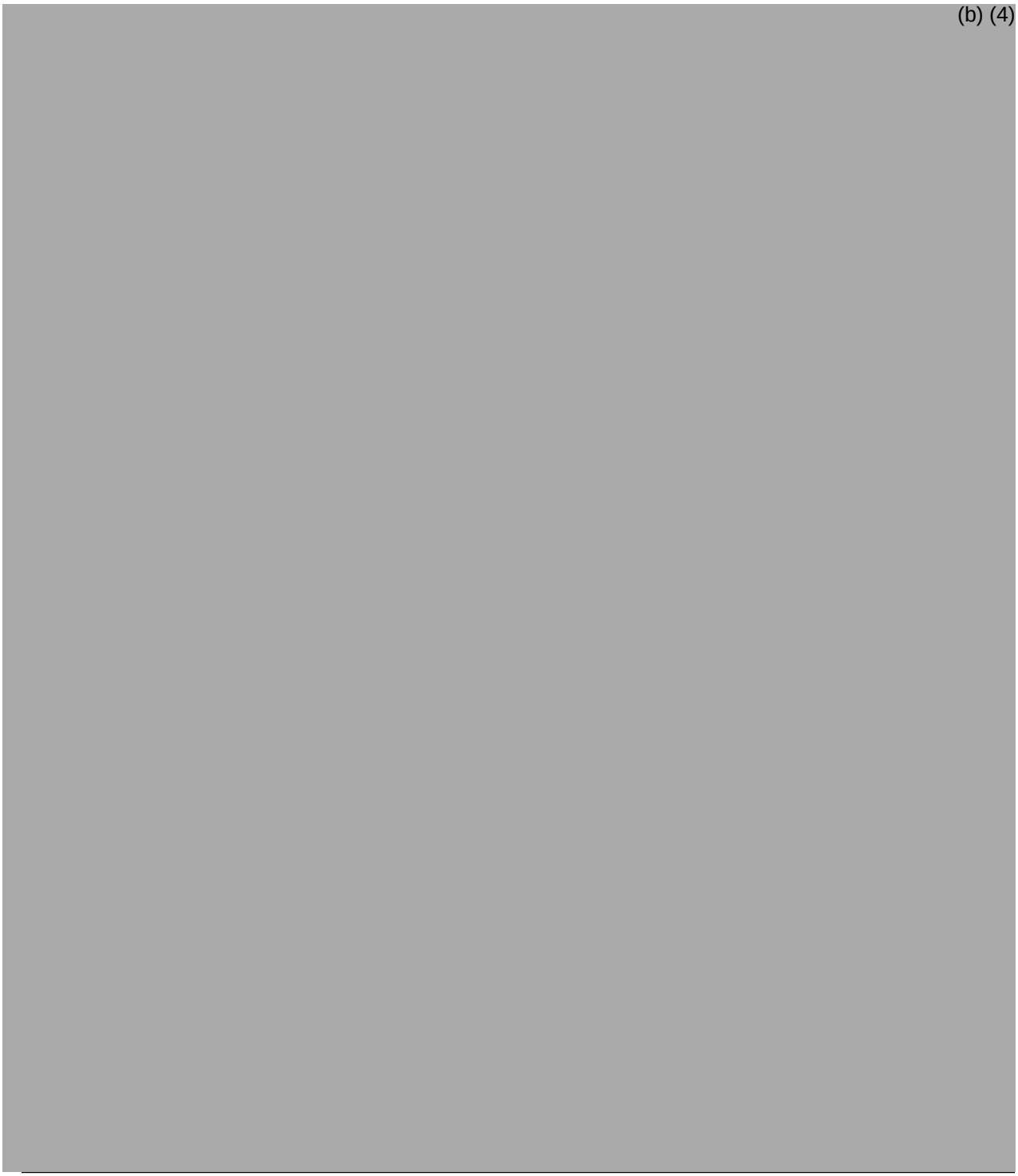


TABLE 3: CODED (MedDRA) TERMS FROM HEALTHCARE PROFESSIONALS, REGULATORY AUTHORITIES, LITERATURE REPORTS AND CLINICAL STUDIES

B. ISOPTO® CARPINE 10 mg/ml Eye Drops

01 August 2004 to 31 July 2009

System Organ Class	Healthcare professionals	Regulatory Authorities	Literature	Clinical studies
ADR Preferred Term (MedDRA 12.0)	**n**	**n**	**n**	**n**
EAR AND LABYRINTH DISORDERS				
Vertigo	1	-	-	-
Sub-total	**1**			
EYE DISORDERS				
Visual acuity reduced	1	2	-	-
Vision blurred	2	-	-	-
Conjunctival hyperaemia	-	-	1	-
Conjunctivitis	-	-	1	-
Eye irritation	-	-	1	-
Lacrimation increased	1	-	-	-
Miosis	1	-	-	-
Symblepharon	-	-	1	-
Sub-total	**11**			
GASTROINTESTINAL DISORDERS				
Nausea	1	-	-	-
Salivary hypersecretion	1	-	-	-
Vomiting	1	-	-	-
Sub-total	**3**			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Malaise	1	-	-	-
Sub-total	**1**			
IMMUNE SYSTEM DISORDERS				
Hypersensitivity	1	-	-	-
Sub-total	**1**			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
Medication error	1	-	-	-
Sub-total	**1**			
INVESTIGATIONS				
Intraocular pressure increased	-	3	-	-
Sub-total	**3**			
NERVOUS SYSTEM DISORDERS				
Dizziness	1	-	-	-
Sub-total	**1**			

TABLE 3: CODED (MedDRA) TERMS FROM HEALTHCARE PROFESSIONALS, REGULATORY AUTHORITIES, LITERATURE REPORTS AND CLINICAL STUDIES

(Cont.)

B. ISOPTO® CARPINE 10 mg/ml Eye Drops
01 August 2004 to 31 July 2009

System Organ Class	Healthcare professionals	Regulatory Authorities	Literature	Clinical studies
ADR Preferred Term (MedDRA 12.0)	**n**	**n**	**n**	**n**
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Epistaxis	1	-	-	-
Lung disorder	1	-	-	-
Sub-total	**2**			
TOTAL	**24**			

During this reporting period, 11 medically confirmed reports were received.

TABLE 3: CODED (MedDRA) TERMS FROM HEALTHCARE PROFESSIONALS, REGULATORY AUTHORITIES, LITERATURE REPORTS AND CLINICAL STUDIES

C. ISOPTO® CARPINE 20 mg/ml Eye Drops

01 August 2004 to 31 July 2009

System Organ Class	Healthcare professionals	Regulatory Authorities	Literature	Clinical studies
ADR Preferred Term (MedDRA 12.0)	**n**	**n**	**n**	**n**
CARDIAC DISORDERS				
Arrhythmia	-	1	-	-
Sub-total	**1**			
EAR AND LABYRINTH DISORDERS				
Ear congestion	1	-	-	-
Sub-total	**1**			
EYE DISORDERS				
Eye irritation	4	-	-	-
Vision blurred	4	-	-	-
Mydriasis	3	-	-	-
Angle closure glaucoma	2	-	-	-
Corneal oedema	2	-	-	-
Eye pain	2	-	-	-
Ocular toxicity	2	-	-	-
Cataract	-	-	1	-
Corneal disorder	1	-	-	-
Eye discharge	1	-	-	-
Maculopathy	-	-	1	-
Posterior segment of eye anomaly	-	-	1	-
Scotoma	-	-	1	-
Sub-total	**25**			
GASTROINTESTINAL DISORDERS				
Vomiting	2	-	-	-
Abdominal discomfort	1	-	-	-
Salivary hypersecretion	1	-	-	-
Sub-total	**4**			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Asthenia	1	-	-	-
Condition aggravated	1	-	-	-
Malaise	1	-	-	-
Sub-total	**3**			
IMMUNE SYSTEM DISORDERS				
Hypersensitivity	2	-	-	-
Sub-total	**2**			

TABLE 3: CODED (MedDRA) TERMS FROM HEALTHCARE PROFESSIONALS, REGULATORY AUTHORITIES, LITERATURE REPORTS AND CLINICAL STUDIES (Cont.)
C. ISOPTO® CARPINE 20 mg/ml Eye Drops
01 August 2004 to 31 July 2009

System Organ Class	Healthcare professionals	Regulatory Authorities	Literature	Clinical studies
ADR Preferred Term (MedDRA 12.0)	**n**	**n**	**n**	**n**
INFECTIONS AND INFESTATIONS				
Eye infection	1	-	-	-
Sub-total	**1**			
INVESTIGATIONS				
Hepatic enzyme increased	1	-	-	-
Sub-total	**1**			
NERVOUS SYSTEM DISORDERS				
Headache	3	-	-	-
Dizziness	1	-	-	-
Syncope	1	-	-	-
Sub-total	**5**			
PSYCHIATRIC DISORDERS				
Confusional state	1	-	-	-
Disorientation	1	-	-	-
Sub-total	**2**			
RENAL AND URINARY DISORDERS				
Bladder discomfort	1	-	-	-
Pollakiuria	1	-	-	-
Sub-total	**2**			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Cough	2	-	-	-
Throat irritation	1	-	-	-
Sub-total	**3**			
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Eczema	1	-	-	-
Hyperhidrosis	1	-	-	-
Sub-total	**2**			
TOTAL	**52**			

During this reporting period, 24 medically confirmed reports were received.

TABLE 3: CODED (MedDRA) TERMS FROM HEALTHCARE PROFESSIONALS, REGULATORY AUTHORITIES, LITERATURE REPORTS AND CLINICAL STUDIES

D. ISOPTO® CARPINE 40 mg/ml Eye Drops

01 August 2004 to 31 July 2009

System Organ Class	Healthcare professionals	Regulatory Authorities	Literature	Clinical studies
ADR Preferred Term (MedDRA 12.0)	**n**	**n**	**n**	**n**
EYE DISORDERS				
Eye irritation	3	-	-	-
Ocular hyperaemia	2	-	1	-
Lens dislocation	-	-	2	-
Eye pain	-	-	2	-
Corneal oedema	-	-	2	-
Eyelid oedema	1	-	-	-
Ocular discomfort	1	-	1	-
Retinopathy	-	1	-	-
Vision blurred	1	-	-	-
Visual acuity reduced	-	-	1	-
Sub-total	**18**			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
Intraocular lens dislocation	-	-	1	-
Sub-total	**1**			
INVESTIGATIONS				
Intraocular pressure increased	1	-	3	-
Sub-total	**4**			
NERVOUS SYSTEM DISORDERS				
Headache	1	-	-	-
Sub-total	**1**			
PSYCHIATRIC DISORDERS				
Anxiety	-	-	1	-
Confusional state	-	-	1	-
Disorientation	-	-	1	-
Fear	-	-	1	-
Hallucination, visual	-	-	1	-
Insomnia	-	-	1	-
Sub-total	**6**			

TABLE 3: CODED (MedDRA) TERMS FROM HEALTHCARE PROFESSIONALS, REGULATORY AUTHORITIES, LITERATURE REPORTS AND CLINICAL STUDIES

(Cont.)

D. ISOPTO® CARPINE 40 mg/ml Eye Drops
01 August 2004 to 31 July 2009

System Organ Class	Healthcare professionals	Regulatory Authorities	Literature	Clinical studies
ADR Preferred Term (MedDRA 12.0)	**n**	**n**	**n**	**n**
SKIN AND SUBCUTANEOUS TISSUE DISORDERS Dry skin	1	-	-	-
Sub-total	**1**			
TOTAL	**31**			

During this reporting period, 10 medically confirmed reports were received.

E. ISOPTO® CARPINE 60 mg/ml Eye Drops
01 August 2004 to 31 July 2009

System Organ Class	Healthcare professionals	Regulatory Authorities	Literature	Clinical studies
ADR Preferred Term (MedDRA 12.0)	**n**	**n**	**n**	**n**
EYE DISORDERS				
Eye irritation	1	-	-	-
Eye pain	1	-	-	-
Eyelids pruritus	1	-	-	-
Vision blurred	1	-	-	-
Sub-total	**4**			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS Medication residue	1	-	-	-
Sub-total	**1**			
TOTAL	**5**			

During this reporting period, 1 medically confirmed report was received.

9 Appendices

9.1 Additional Tables/Analyses

C-90-42 – IOP Changes According to Eye Color

Comparison of Mean Changes in Intraocular Pressure Values From Baseline At Each Visit Time According to Iris Color

	Visit Time							
	8 a.m.		10 a.m.		12 N		2 p.m.	
	Brown	Non-Brown	Brown	Non-Brown	Brown	Non-Brown	Brown	Non-Brown
Combination 2% Mean IOP Change (mmHg)	-3.3	-2.3	-4.7	-4.4	-6.3	-5.0	-6.7	-4.4
Combination 1% Mean IOP Change (mmHg)	-1.7	-3.6	-3.6	-6.7	-4.8	-7.2	-4.4	-7.0
Betaxolol Mean IOP Change (mmHg)	-1.8	-1.9	-3.0	-3.6	-3.3	-4.9	-2.8	-5.2
Pilocarpine Mean IOP Change (mmHg)	-1.5	-1.1	-4.8	-1.6	-5.1	-2.8	-5.8	-3.2

C-91-47 – IOP Changes According to Eye Color

Table 10

Changes in Intraocular Pressure Values From Baseline for Primary Patients at Each Visit Time According to Iris Color[1]

Treatment Group[2]	Visit Time					
	8 A.M.		12 N		4 P.M.	
	Brown	Non-Brown	Brown	Non-Brown	Brown	Non-Brown
Combination						
Mean IOP Change[3]	-3.0	-3.0	-5.3	-5.9	-5.8	-5.8
N Value	28	22	30	19	30	19
Betaxolol						
Mean IOP Change[3]	-1.5	-0.8	-3.3	-3.6	-4.0	-3.8
N Value	25	31	26	32	24	29
Pilocarpine						
Mean IOP Change[3]	-2.5	-1.0	-4.5	-2.5	-4.5	-3.4
N Value	25	21	24	21	23	21
Treatment Comparisons						
Combination vs Betaxolol						
Treatment Difference	-1.5	-2.3	-2.0	-2.3	-1.7	-2.1
P Value	0.02	< 0.01	0.01	< 0.01	0.02	0.01
Combination vs Pilocarpine						
Treatment Difference	-0.5	-2.1	-0.9	-3.4	-1.2	-2.5
P Value	0.45	< 0.01	0.23	< 0.01	0.09	< 0.01

Abbreviations used include the following: IOP (Intraocular Pressure).

1 Repeated measures analysis of variance was done which included the following visit times and treatment days: 8 a.m. (Days 14, 45 and 90); 12 N (Days 14 and 90); and 4 p.m. (Days 14 and 90).

2 Treatment groups include the following: Combination (Betaxolol 0.25%/Pilocarpine HCl 1.75%); Betaxolol 0.25%; and Pilocarpine HCl 2.0%.

3 IOP values (mmHg) are least squares estimates of IOP reductions from baseline.

C-91-47 – IOP Changes According to Sex

Table 11

Changes in Intraocular Pressure Values From Baseline for Primary Patients at Each Treatment Visit According to Sex

Treatment Group[1]	Day 14			Day 45	Day 90		
	8 A.M.	12 N	4 P.M.	8 A.M.	8 A.M.	12 N	4 P.M.
Combination							
Male							
Mean IOP[2]	22.9 ± 2.3	19.4 ± 2.5	19.4 ± 3.0	24.2 ± 3.2	24.7 ± 3.9	20.3 ± 2.4	20.3 ± 3.3
N Value	19	18	18	17	16	15	15
Change from Baseline	-4.2	-7.6	-7.5	-2.8	-2.4	-6.5	-6.6
% Change from Baseline	-15.1	-27.9	-28.0	-10.3	-9.1	-24.1	-24.2
Female							
Mean IOP[2]	21.8 ± 2.8	19.8 ± 2.3	19.4 ± 2.8	21.9 ± 3.3	23.1 ± 3.3	21.1 ± 3.4	20.7 ± 3.1
N Value	31	31	31	29	28	29	28
Change from Baseline	-3.2	-5.3	-5.7	-3.3	-2.3	-4.2	-4.5
% Change from Baseline	-12.7	-20.6	-22.4	-13.3	-8.9	-16.1	-17.6
Betaxolol							
Male							
Mean IOP[2]	23.9 ± 3.6	21.0 ± 3.4	21.2 ± 3.5	23.8 ± 2.8	23.8 ± 3.5	21.4 ± 3.1	21.4 ± 3.5
N Value	20	20	20	19	18	18	18
Change from Baseline	-2.2	-5.1	-4.8	-2.4	-2.2	-4.6	-4.6
% Change from Baseline	-8.5	-19.5	-18.4	-8.6	-8.4	-17.5	-17.5
Female							
Mean IOP[2]	25.0 ± 3.1	22.6 ± 3.5	22.0 ± 3.1	24.3 ± 3.2	25.6 ± 3.9	23.0 ± 3.3	22.1 ± 3.2
N Value	36	38	33	36	29	30	30
Change from Baseline	-0.3	-2.8	-3.4	-1.1	+0.3	-2.3	-3.2
% Change from Baseline	-1.4	-10.8	-13.2	-4.3	+1.4	-8.8	-12.3
Pilocarpine							
Male							
Mean IOP[2]	24.0 ± 5.6	21.7 ± 4.6	21.3 ± 3.9	25.7 ± 5.2	25.5 ± 5.6	23.6 ± 4.8	23.8 ± 5.5
N Value	22	22	22	21	18	19	19
Change from Baseline	-3.2	-5.6	-6.0	-1.3	-1.0	-2.8	-2.6
% Change from Baseline	-12.4	-20.7	-21.8	-5.3	-4.4	-10.8	-10.3
Female							
Mean IOP[2]	22.6 ± 2.8	20.8 ± 2.8	20.8 ± 2.9	22.7 ± 3.2	24.8 ± 4.4	23.1 ± 3.4	22.2 ± 3.9
N Value	24	23	22	22	20	21	21
Change from Baseline	-2.6	-4.4	-4.5	-2.5	-0.7	-2.1	-3.1
% Change from Baseline	-9.8	-17.0	-17.6	-9.7	-2.6	-7.8	-12.1

Abbreviations used include the following: IOP (Intraocular Pressure).

[1] Treatment groups include the following: Combination (Betaxolol 0.25%/Pilocarpine HCl 1.75%); Betaxolol 0.25%; and Pilocarpine HCl 2.0%.

[2] Values are mean ± STD in mmHg for IOP.

C-91-47 – IOP Changes According to Age

Table 12

Changes in Intraocular Pressure Values From Baseline for Primary Patients at Each Treatment Visit According to Age

Treatment Group[1]	Day 14			Day 45	Day 90		
	8 A.M.	12 N	4 P.M.	8 A.M.	8 A.M.	12 N	4 P.M.
Combination							
< 65 years							
Mean IOP[2]	22.2 ± 2.8	19.8 ± 2.6	19.8 ± 3.1	23.4 ± 3.1	23.8 ± 3.2	20.7 ± 3.1	20.2 ± 3.1
N Value	28	27	27	25	23	24	24
Change from Baseline	-3.9	-6.4	-6.4	-2.9	-2.5	-5.5	-6.1
% Change from Baseline	-14.5	-23.8	-24.3	-10.8	-9.4	-20.7	-22.6
≥ 65 years							
Mean IOP[2]	22.3 ± 2.5	19.5 ± 2.1	19.0 ± 2.5	22.0 ± 3.6	23.4 ± 4.1	20.9 ± 3.2	21.1 ± 3.3
N Value	22	22	22	21	21	20	19
Change from Baseline	-3.2	-5.9	-6.3	-3.5	-2.1	-4.3	-4.2
% Change from Baseline	-12.4	-22.7	-24.7	-13.8	-8.5	-16.6	-16.5
Betaxolol							
< 65 years							
Mean IOP[2]	24.8 ± 2.9	22.1 ± 3.5	22.0 ± 3.0	24.2 ± 3.0	24.9 ± 3.9	22.4 ± 3.1	22.3 ± 3.4
N Value	34	36	34	34	29	30	30
Change from Baseline	-0.8	-3.6	-3.7	-1.7	-0.8	-3.3	-3.4
% Change from Baseline	-3.3	-14.0	-14.1	-6.1	-2.8	-12.6	-12.9
≥ 65 years							
Mean IOP[2]	24.2 ± 3.9	21.9 ± 3.5	21.1 ± 3.7	24.1 ± 3.3	24.9 ± 3.7	22.4 ± 3.8	21.1 ± 3.1
N Value	22	22	19	21	18	18	18
Change from Baseline	-1.2	-3.5	-4.4	-1.4	-0.4	-2.9	-4.2
% Change from Baseline	-5.0	-13.6	-17.1	-5.3	-1.6	-11.0	-16.4
Pilocarpine							
< 65 years							
Mean IOP[2]	24.3 ± 4.9	21.8 ± 4.2	21.5 ± 3.3	24.7 ± 4.9	26.0 ± 4.9	23.8 ± 4.4	23.6 ± 5.1
N Value	28	28	28	25	23	24	24
Change from Baseline	-2.1	-4.6	-5.0	-1.6	-0.2	-2.2	-2.4
% Change from Baseline	-8.2	-17.5	-18.5	-6.3	-0.7	-8.3	-9.4
≥ 65 years							
Mean IOP[2]	21.7 ± 3.0	20.3 ± 2.8	20.2 ± 3.5	23.4 ± 3.9	23.7 ± 4.8	22.7 ± 3.5	22.0 ± 4.1
N Value	18	17	16	18	15	16	16
Change from Baseline	-4.1	-5.6	-5.8	-2.4	-1.9	-2.9	-3.6
% Change from Baseline	-15.4	-20.9	-21.9	-9.2	-7.6	-10.7	-14.0

Abbreviations used include the following: IOP (Intraocular Pressure).

[1] Treatment groups include the following: Combination (Betaxolol 0.25%/Pilocarpine HCl 1.75%); Betaxolol 0.25%; and Pilocarpine HCl 2.0%.

[2] Values are mean ± STD in mmHg for IOP.

C-91-47 – IOP Changes According to Race

Table 13

Changes in Intraocular Pressure Values From Baseline for Primary Patients at Each Treatment Visit According to Race

Treatment Group[1]	Day 14			Day 45	Day 90		
	8 A.M.	12 N	4 P.M.	8 A.M.	8 A.M.	12 N	4 P.M.
Combination							
White							
Mean IOP[2]	22.3 ± 2.7	19.6 ± 2.4	19.5 ± 2.8	23.0 ± 3.6	24.0 ± 3.9	20.6 ± 2.8	20.3 ± 3.1
N Value	37	35	35	32	30	30	30
Change from Baseline	-3.6	-6.3	-6.4	-3.0	-2.1	-5.2	-5.6
% Change from Baseline	-13.6	-23.9	-24.4	-11.8	-8.3	-19.7	-21.2
Other[3]							
Mean IOP[2]	21.9 ± 2.5	20.0 ± 2.3	19.3 ± 3.0	22.2 ± 2.9	22.9 ± 2.7	21.2 ± 3.8	21.2 ± 3.3
N Value	13	14	14	14	14	14	13
Change from Baseline	-3.6	-5.6	-6.3	-3.4	-2.7	-4.4	-4.4
% Change from Baseline	-13.6	-21.7	-24.6	-13.1	-10.4	-16.8	-16.9
Betaxolol							
White							
Mean IOP[2]	24.6 ± 3.3	21.7 ± 3.3	21.5 ± 3.2	24.5 ± 2.8	25.0 ± 3.8	22.6 ± 3.3	22.1 ± 3.0
N Value	46	47	43	45	38	38	38
Change from Baseline	-1.0	-3.9	-4.2	-1.2	-0.6	-3.0	-3.6
% Change from Baseline	-4.0	-15.1	-16.2	-4.5	-2.6	-11.5	-13.5
Other[3]							
Mean IOP[2]	24.5 ± 3.6	23.3 ± 4.3	22.7 ± 3.3	22.5 ± 3.8	24.5 ± 4.1	21.8 ± 3.3	21.1 ± 4.5
N Value	10	11	10	10	9	10	10
Change from Baseline	-1.0	-2.2	-2.8	-3.0	-0.9	-3.7	-4.3
% Change from Baseline	-3.8	-8.4	-10.7	-11.5	-3.1	-14.0	-16.9
Pilocarpine							
White							
Mean IOP[2]	23.6 ± 4.7	21.6 ± 4.1	21.2 ± 3.3	24.8 ± 4.6	25.8 ± 4.9	23.9 ± 4.2	23.6 ± 4.9
N Value	37	36	35	34	30	31	31
Change from Baseline	-3.1	-5.2	-5.6	-1.8	-0.5	-2.5	-2.7
% Change from Baseline	-11.6	-19.1	-20.5	-6.9	-2.0	-8.8	-10.2
Other[3]							
Mean IOP[2]	21.9 ± 2.9	19.8 ± 2.1	20.3 ± 3.9	21.8 ± 3.6	22.4 ± 4.1	21.7 ± 3.3	20.6 ± 3.5
N Value	9	9	9	9	8	9	9
Change from Baseline	-2.2	-4.3	-3.9	-2.4	-2.1	-2.5	-3.6
% Change from Baseline	-9.0	-17.8	-16.5	-9.8	-9.0	-10.6	-14.9

Abbreviations used include the following: IOP (Intraocular Pressure).

1 Treatment groups include the following: Combination (Betaxolol 0.25%/Pilocarpine HCl 1.75%); Betaxolol 0.25%; and Pilocarpine HCl 2.0%.

2 Values are mean ± STD in mmHg for IOP.

3 Other races include black, hispanic and asian.

C-91-54 – IOP Changes According to Eye Color

Table 10

Changes in Intraocular Pressure Values From Baseline For Primary Patients at Each Visit Time According to Iris Color[1]

	Visit Time					
	8 A.M.		12 N		4 P.M.	
	Brown	Non-Brown	Brown	Non-Brown	Brown	Non-Brown
Combination[2]						
Mean IOP Change[3]	-3.0	-2.8	-5.5	-5.3	-5.4	-4.6
N Value	25	25	23	25	25	25
Betaxolol[2]						
Mean IOP Change[3]	-1.2	-1.1	-3.1	-3.7	-3.0	-2.8
N Value	31	28	31	28	31	28
Pilocarpine[2]						
Mean IOP Change[3]	-1.8	-1.0	-3.9	-3.6	-3.8	-3.7
N Value	25	25	26	23	26	23
Treatment Comparisons						
Combination vs Betaxolol						
Treatment Difference	-1.8	-1.7	-2.4	-1.6	-2.4	-1.7
P Value	< 0.01	< 0.01	< 0.01	0.02	< 0.01	0.01
Combination vs Pilocarpine						
Treatment Difference	-1.2	1.7	-1.7	-1.7	-1.7	-0.8
P Value	0.03	< 0.01	0.02	0.02	0.01	0.25

Abbreviations used include the following: IOP (Intraocular Pressure).

1 Repeated measures analysis of variance was done which included the following visit times and treatment days: 8 A.M. (Days 14, 45 and 90); 12 N (Days 14 and 90); and 4 P.M. (Days 14 and 90).

2 Treatment groups include the following: Combination (Betaxolol 0.25%/Pilocarpine HCl 1.75%); Betaxolol 0.25%; and Pilocarpine HCl 2.0%.

3 IOP values (mmHg) are least squares estimate of IOP reductions from baseline.

C-91-54 – IOP Changes According to Sex

Table 11

Changes in Intraocular Pressure Values From Baseline For Primary Patients at Each Treatment Visit According to Sex

Treatment Group[1]	Day 14			Day 45	Day 90		
	8 A.M.	12 N	4 P.M.	8 A.M.	8 A.M.	12 N	4 P.M.
Combination[1]							
Male							
Mean IOP[2]	21.8 ± 2.8	19.6 ± 2.9	20.6 ± 3.4	22.6 ± 3.5	21.6 ± 3.5	19.4 ± 3.6	20.6 ± 3.8
N Value	21	21	20	21	19	20	21
Change from Baseline	-3.0	-5.2	-4.3	-2.2	-3.4	-5.5	-4.2
% Change from Baseline	-12.2	-21.0	-17.4	-9.1	-13.8	-22.2	-16.6
Female							
Mean IOP[2]	22.7 ± 2.9	19.6 ± 2.8	20.1 ± 2.8	22.3 ± 3.5	23.0 ± 3.9	20.7 ± 2.4	20.6 ± 2.6
N Value	27	27	28	28	26	25	25
Change from Baseline	-2.9	-5.7	-5.4	-3.2	-2.7	-4.9	-4.9
% Change from Baseline	-11.0	-22.3	-20.7	-12.7	-10.5	-18.6	-19.0
Betaxolol							
Male							
Mean IOP[2]	24.2 ± 2.4	21.9 ± 2.5	22.3 ± 2.5	24.7 ± 2.5	25.0 ± 2.6	22.5 ± 2.7	23.0 ± 3.1
N Value	25	25	25	25	23	24	24
Change from Baseline	-1.3	-3.6	-3.1	-0.7	-0.3	-2.8	-2.4
% Change from Baseline	-4.9	-14.1	-12.3	-2.9	-1.3	-11.2	-9.3
Female							
Mean IOP[2]	23.5 ± 2.9	22.1 ± 3.4	22.6 ± 3.2	23.7 ± 3.5	23.7 ± 3.2	21.3 ± 3.4	21.7 ± 3.8
N Value	34	34	34	33	31	32	32
Change from Baseline	-1.5	-2.9	-2.4	-1.3	-1.3	-3.8	-3.3
% Change from Baseline	-6.0	-11.8	-9.7	-5.4	-5.4	-15.1	-13.6
Pilocarpine							
Male							
Mean IOP[2]	24.4 ± 3.3	21.4 ± 2.8	21.2 ± 2.5	24.8 ± 4.5	23.9 ± 3.8	20.5 ± 2.9	21.0 ± 3.1
N Value	18	16	16	14	12	12	12
Change from Baseline	-2.0	-5.2	-5.5	-2.3	-3.1	-6.5	-6.0
% Change from Baseline	-7.1	-18.8	-19.7	-8.6	-11.3	-23.1	-21.3
Female							
Mean IOP[2]	24.0 ± 3.1	22.1 ± 3.1	22.4 ± 3.5	24.6 ± 3.3	24.6 ± 3.3	22.5 ± 3.8	22.6 ± 3.4
N Value	32	33	33	29	29	29	29
Change from Baseline	-1.5	-3.6	-3.2	-1.1	-1.0	-3.1	-3.0
% Change from Baseline	-6.0	-13.6	-12.5	-3.9	-3.8	-11.9	-11.5

Abbreviations used include the following: IOP (Intraocular Pressure).

[1] Treatment groups include the following: Combination (Betaxolol 0.25%/Pilocarpine HCl 1.75%); Betaxolol 0.25%; and Pilocarpine HCl 2.0%.

[2] Values are mean ± STD in mmHg for IOP.

C-91-54 – IOP Changes According to Age

Table 12

Changes in Intraocular Pressure Values From Baseline For Primary Patients at Each Treatment Visit According to Age

Treatment Group[1]	Day 14			Day 45	Day 90		
	8 A.M.	12 N	4 P.M.	8 A.M.	8 A.M.	12 N	4 P.M.
Combination[1]							
≤ 65							
Mean IOP[2]	22.9 ± 3.4	20.8 ± 2.4	20.8 ± 2.9	22.8 ± 4.2	23.5 ± 4.0	21.1 ± 3.1	21.3 ± 3.2
N Value	25	24	26	25	24	24	24
Change from Baseline	-2.7	-4.6	-4.7	-2.9	-2.3	-4.6	-4.5
% Change from Baseline	-10.7	-18.0	-18.2	-11.6	-8.9	-17.9	-17.2
≥ 65							
Mean IOP[2]	21.7 ± 2.1	18.4 ± 2.8	19.4 ± 2.8	22.1 ± 2.6	21.1 ± 3.1	19.0 ± 2.6	19.9 ± 2.7
N Value	23	24	24	24	21	21	21
Change from Baseline	-3.1	-6.4	-5.5	-2.7	-3.8	-5.8	-4.8
% Change from Baseline	-12.4	-25.4	-21.6	-10.8	-15.2	-22.9	-19.6
Betaxolol							
≤ 65							
Mean IOP[2]	22.5 ± 1.7	21.1 ± 2.5	21.8 ± 2.3	23.1 ± 2.6	23.6 ± 2.2	21.5 ± 2.5	21.3 ± 2.8
N Value	25	25	25	24	23	23	23
Change from Baseline	-2.3	-3.7	-3.0	-1.8	-1.3	-3.3	-3.6
% Change from Baseline	-9.1	-15.0	-12.0	-7.4	-4.9	-13.3	-14.3
≥ 65							
Mean IOP[2]	24.7 ± 2.9	22.6 ± 3.2	22.9 ± 3.2	24.9 ± 3.3	24.8 ± 3.4	22.0 ± 3.6	23.0 ± 3.9
N Value	34	34	34	34	31	33	33
Change from Baseline	-0.8	-2.8	-2.5	-0.5	-0.6	-3.4	-2.5
% Change from Baseline	-3.0	-11.1	-9.9	-2.1	-2.7	-13.6	-9.9
Pilocarpine							
≤ 65							
Mean IOP[2]	24.3 ± 3.3	22.2 ± 2.6	22.0 ± 2.4	24.5 ± 3.7	24.3 ± 3.2	22.1 ± 3.2	22.0 ± 2.9
N Value	30	30	30	28	27	27	27
Change from Baseline	-1.4	-3.7	-3.9	-1.3	-1.4	-3.6	-3.8
% Change from Baseline	-5.5	-13.6	-14.4	-5.1	-5.4	-13.4	-14.1
≥ 65							
Mean IOP[2]	24.0 ± 3.0	21.4 ± 3.4	22.1 ± 4.3	24.8 ± 3.6	24.6 ± 3.8	21.6 ± 4.5	22.5 ± 4.2
N Value	20	19	18	15	14	14	14
Change from Baseline	-2.1	-4.7	-4.1	-1.7	-1.9	-4.9	-4.1
% Change from Baseline	-7.8	-17.9	-15.6	-6.1	-7.1	-18.6	-14.9

Abbreviations used include the following: IOP (Intraocular Pressure).

[1] Treatment groups include the following: Combination (Betaxolol 0.25%/Pilocarpine HCl 1.75%); Betaxolol 0.25%; and Pilocarpine HCl 2.0%.

[2] Values are mean ± STD in mmHg for IOP.

C-91-54 – IOP Changes According to Race

Table 13

Changes in Intraocular Pressure Values From Baseline For Primary Patients at Each Treatment Visit According to Race

Treatment Group[1]	Day 14			Day 45	Day 90		
	8 A.M.	12 N	4 P.M.	8 A.M.	8 A.M.	12 N	4 P.M.
Combination							
White							
Mean IOP[2]	22.1 ± 3.0	19.6 ± 3.0	20.2 ± 3.1	22.1 ± 3.5	22.1 ± 3.8	19.9 ± 3.2	20.5 ± 3.2
N Value	39	39	39	38	37	37	37
Change from Baseline	-2.9	-5.3	-4.7	-2.9	-3.0	-5.2	-4.5
% Change from Baseline	-11.5	-21.2	-18.7	-12.0	-12.2	-20.5	-18.1
Other[3]							
Mean IOP[2]	23.1 ± 2.2	19.4 ± 2.1	19.7 ± 2.3	23.7 ± 3.3	23.7 ± 3.2	21.0 ± 2.2	21.0 ± 1.6
N Value	9	9	11	11	8	8	8
Change from Baseline	-3.2	-6.3	-6.2	-2.2	-2.8	-5.1	-5.1
% Change from Baseline	-11.6	-24.1	-20.2	-8.5	-10.4	-19.0	-19.1
Betaxolol							
White							
Mean IOP[2]	23.4 ± 2.4	21.7 ± 2.7	22.5 ± 2.8	24.2 ± 2.9	24.0 ± 2.7	21.8 ± 3.1	21.9 ± 2.6
N Value	44	44	44	43	39	41	41
Change from Baseline	-1.7	-3.4	-2.6	-0.9	-1.1	-3.3	-3.2
% Change from Baseline	-6.7	-13.5	-10.3	-3.8	-4.3	-13.3	-12.7
Other[3]							
Mean IOP[2]	24.8 ± 3.3	22.8 ± 3.7	22.3 ± 3.1	24.0 ± 3.9	25.0 ± 3.8	21.9 ± 3.5	23.2 ± 5.4
N Value	15	15	15	15	15	15	15
Change from Baseline	-0.6	-2.6	-3.1	-1.4	-0.4	-3.5	-2.2
% Change from Baseline	-2.4	-10.5	-12.4	-5.8	-2.0	-13.9	-9.0
Pilocarpine							
White							
Mean IOP[2]	24.1 ± 3.4	22.2 ± 3.1	22.1 ± 3.4	24.6 ± 3.8	24.0 ± 3.1	21.2 ± 3.0	21.8 ± 3.2
N Value	34	32	32	27	25	25	25
Change from Baseline	-1.4	-3.3	-3.4	-1.0	-1.5	-4.3	-3.7
% Change from Baseline	-5.3	-12.8	-13.2	-4.1	-5.6	-16.5	-14.0
Other[3]							
Mean IOP[2]	24.4 ± 2.7	21.3 ± 2.7	21.9 ± 3.0	24.7 ± 3.4	25.1 ± 3.8	23.2 ± 4.3	22.7 ± 3.7
N Value	18	17	17	16	16	16	16
Change from Baseline	-2.4	-5.5	-4.9	-2.2	-1.8	-3.7	-4.2
% Change from Baseline	-8.8	-20.0	-18.1	-7.8	-6.6	-13.2	-15.0

Abbreviations used include the following: IOP (Intraocular Pressure).

[1] Treatment groups include the following: Combination (Betaxolol 0.25%/Pilocarpine HCl 1.75%); Betaxolol 0.25%; and Pilocarpine HCl 2.0%.

[2] Values are mean ± STD in mmHg for IOP.

[3] Other races include black, hispanic and asian.

6 Page(s) of Draft Labeling has 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/

WILEY A CHAMBERS
06/22/2010

WILLIAM M BOYD
06/22/2010