CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-890

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review for NDA 200-890

Date	June 4, 2010
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	200-890
Applicant	Alcon Research, Ltd.
Date of Submission	December 22, 2009
PDUFA Goal Date	June 22, 2010
Type of Application	505(b)(2)
Name	Isopto Carpine (pilocarpine ophthalmic solution) 1%, 2%, and 4%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	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 laser surgery 4) the induction of miosis
Recommended:	Recommended for Approval

1. Introduction

Pilocarpine hydrochloride ophthalmic solution (0.25%, 0.5%, 1%, 2%, 3%, 4%, 6% and 8%) 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).

2. Background

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.

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.

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

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.

3. CMC

Approval from a CMC prospective was recommended from the first and second CMC Reviews finalized 5/15/10 and 6/16/10.

Since Isopto Carpine is a sterile aqueous solution presented in a multiple-dose container, benzalkonium chloride (0.01%) is added [redacted (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 [redacted (b) (4)] shrink band, which when heated shrinks to conform around the neck and closure area of the bottle.

Composition of IsoptoCarpine 1%, 2% and 4% drug product

	Concentration (%w/v)			
Component	Isopto Carpine 1%	Isopto Carpine 2%	Isopto Carpine 4%	Function
Pilocarpine hydrochloride	1.0	2.0	4.0	Active
Boric acid Sodium chloride Sodium citrate Dihydrate	[redacted (b) (4)]			
Benzalkonium chloride	0.01	0.01	0.01	Preservative
Hypromellose 2910	[redacted (b) (4)]			
HCl/NaOH	[redacted (b) (4)]			pH adjustment
Purified water	[redacted (b) (4)]			

Acceptance Specifications

Pilocarpine hydrochloride identity (HPLC)	Positive
Pilocarpine hydrochloride identity (TLC)	Positive
Pilocarpine hydrochloride assay	(b) (4) of label
Pilocarpine impurities:	
(b) (4)	NMT (b) (4)
	NMT
	NMT
	NMT
Any single unspecified impurity	NMT
Total impurities	NMT
Benzalkonium chloride identity	Positive
Benzalkonium chloride assay	(b) (4) of label
pH	3.5 to 5.5
Osmolality	290-350 mOsmol (1 or 2% product) 550-600 mOsmol (4% product)
Viscosity	(b) (4)
Particulate matter	NMT (b) (4)
Endotoxin	NMT
Sterility	Meets USP

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology Toxicology Review finalized 5/17/10:

The ocular toxicity potential of pilocarpine hydrochloride has been assessed previously by Alcon and was approved for ophthalmic use in Pilopine HS Gel (NDA 18-796) and BetopticPilo Ophthalmic Suspension (NDA 20-619).

Regarding labeling of the Isopto Carpine drug product: Alcon's initial references to Salagen in the Isopto Carpine annotated labeling are problematic; Alcon did not otherwise cite reliance on the Salagen product in their application. Neither their 356h form nor cover letter state that they are relying on that product, nor did they submit a patent certification or statement with the application.

The preclinical study synopses and exposure calculations from the Pharmacology Toxicology review are noted, but are not necessary to support this application and an alternate version of the labeling has been used for approval with Sections 8.1 (Pregnancy) and 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) replaced using the language found in the approved Alcon Pilopine HS labeling. No information from the Salagen application has been used to support this application nor is any additional information needed.

8.1 Pregnancy

Pregnancy. Category C. Animal reproduction studies have not been conducted with pilocarpine hydrochloride. 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.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There have been no long-term studies done using pilocarpine hydrochloride in animals to evaluate carcinogenic potential.

5. Clinical Pharmacology/Biopharmaceutics

From the Clinical Pharmacology Review finalized 5/21/10:

In support of this NDA, the applicant conducted one ocular PK study (C-92-56) to assess systemic exposure of pilocarpine following ocular topical administration of Isopto Carpine 4%. The applicant also conducted four clinical efficacy studies and one comfort/acceptability study with an Isopto Carpine 2% treatment.

One human PK study (C-92-56) with Isopto Carpine 4% (pilocarpine hydrochloride ophthalmic solution) was performed by Alcon. Pilocarpine concentrations following topical ocular administration were found to be low relative to the reported pilocarpine concentrations following oral dosing. The total daily dose for Isopto Carpine 4% administered as 2 drops to each eye QID was 27.52 mg (43µl × 2 drop/eye × 2 eyes × 4 time/day × 40 mg/mL). Mean Cmax value at steady-state following topical ocular dosing was approximately 3.7 ng/mL on both Days 5 and 8. A larger margin is expected with 1 drop QID and at lower concentrations (i.e., 1% and 2%) of Isopto Carpine.

The Clinical Pharmacology Review references systemic levels of pilocarpine from the Salagen application to show a comparison between this application and the Salagen application. These comparisons are not necessary for the review of this application and no information from the Salagen application has been used in support of this application.

No dose adjustment for Isopto Carpine is warranted based on intrinsic factors including age and organ dysfunction (i.e. renal or hepatic impairment).

Pilocarpine is metabolized by esterase and CYP2A6. CYP2A6 can be inhibited by pilocarpine (Ki =1- 4 µM). Given the low systemic exposure following topical ocular administration of Isopto Carpine, clinically relevant drug-drug interactions based on CYP450 interactions is not expected for Isopto Carpine.

6. Sterility Assurance

From the Product Quality Microbiology review completed 5/10/10:

Container-Closure and Package Integrity

Container closure integrity testing was performed by microbial ingress using sterile Trypticase Soy Broth filled units on three different sterilized component lots. Each lot tested 10 units that

were torqued to the minimum level of 5 in-lb and 10 units that were torqued at the maximum level of 9 in-lb. Positive controls were units that had been pierced with a sterile 27 gauge needle. Positive controls and challenge units were submerged in a microbial suspension of approximately 10^8 cfu/mL of *Escherichia coli* for 10 minutes. Following the challenge, the units were incubated inverted at 30-35°C for 7 days. All challenged and negative control units were negative for growth, positives controls were positive for growth. Growth promotion of the media was performed at the completion of the container closure testing and was acceptable. It was concluded that the container closure system was an effective barrier to microbial ingress.

Preservative Effectiveness

Benzalkonium chloride (0.01%) is added (b) (4) . Antimicrobial effectiveness test was performed per USP <51> and the counting method was validated (Technical Report 0308-338PQ). Per USP <51>, this is a Category 2 product and the acceptance criteria are:

1) Bacteria: Not less than (b) (4) from the initial count at 14 days, and (b) (4) (b) (4) from the 14 days count at 28 days.
2) Mold (b) (4) from the initial calculated count at 14 and 28 days.

Three stability lots were tested at 48 months (12 months past the 36 month expiration date). The stability testing acceptance criteria for benzalkonium chloride is unchanged from the release specification (b) (4)); therefore no significant decrease is expected through the shelf life for this product. All three lots met the acceptance criteria. This reviewer finds this testing acceptable in light of the results for the test in conjunction with the long marketing history for this product.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review finalized 6/21/2010:

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)). 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.

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

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

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.

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) and Pilocarpine ($p < 0.02$) (1.9, 3.6 and 3.8 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.

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).

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

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.

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.

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).

Literature

All of the submitted literature articles support the use of pilocarpine for the reduction of elevated intraocular pressure prior to surgery in patients with acute angle closure glaucoma. The overall reduction in intraocular pressure for this indication is roughly 3-7 mm Hg.

Three Alcon literature references are summarized here.

Diestelhorst M, et al, 2000, studied 242 patients with primary open-angle glaucoma or ocular hypertension in a multicenter, randomized, open-label study. 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.

Drance, et al, 1999, describes a 24 month, single center, randomized, partially masked clinical trial comparing betaxolol 0.5% twice daily, timolol 0.5% twice daily, and 2% pilocarpine four times daily. 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.

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.

Indication: The 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 also provides 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.

Indication: The prevention postoperative elevated IOP associated with laser surgery

All of the submitted literature articles support the use of pilocarpine for the prevention of postoperative elevated IOP associated with 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 also provides 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.

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 also provides 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 also provides support for the miotic effect of pilocarpine in ALT.

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).

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.

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.

See Section 6.9 of the Medical Officer's review for a detailed literature discussion.

Efficacy Summary Statement

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 the Medical Officer's 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 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 and thinning of the iris prior to gonioscopic and surgical procedures involving the peripheral iris or trabecular meshwork indication) 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.

8. 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.

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.

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).

COMMON ADVERSE EVENTS

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[1]

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 (26%)	31 (19%)	11 (6%)
Blurred vision	29 (19%)	26 (16%)	5 (3%)
Eye irritation	11 (7%)	5 (3%)	3 (2%)
Visual impairment	9 (6%)	18 (11%)	3 (2%)
Eye pain	9 (6%)	5 (3%)	19 (10%)
Visual acuity reduced	6 (4%)	0	6 (3%)
Photopsia	4 (3%)	1 (1%)	3 (2%)
Myo-desopsia (floaters)	3 (2%)	7 (4%)	0
Nausea	3 (2%)	3 (2%)	2 (1%)
Dizziness	3 (2%)	2 (1%)	1 (1%)
Foreign body sensation in eye	2 (1%)	2 (1%)	3 (2%)
Ocular hyperaemia	2 (1%)	2 (1%)	2 (1%)
Increased intraocular pressure	2 (1%)	0	1 (1%)
Injury	2 (1%)	0	1 (1%)

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.

[1] Derived from Alcon Table 2.7.4.7-4

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.

POSTMARKETING EXPERIENCE
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.

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. The adverse events reported were previously known and expected from the ophthalmic use of pilocarpine.

See Section 8, Medical Officer's review for detailed tables.

Safety Summary Statement

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). These studies were completed 15-20 years ago.

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 of (b) (4) postoperative elevated IOP associated with 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.

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.

9. Advisory Committee Meeting

There were no new issues needing discussion at an Advisory Committee Meeting for Isopto Carpine (pilocarpine ophthalmic solution) 1%, 2%, and 4%.

10. Pediatrics

See Section 7 this review.

Safety and effectiveness of pilocarpine hydrochloride ophthalmic solution in pediatric patients have been established.

11. Other Relevant Regulatory Issues

DSI
A Division of Scientific Investigations (DSI) audit was requested. No significant issues have been identified.

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

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).

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.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Risk Assessment sought input from pertinent disciplines involved with the review of this application and considered it accordingly. Their evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA found the proposed proprietary name, Isopto Carpine, acceptable for this product. The Division of Anti-Infective & Ophthalmology Products concurred with this assessment.

DMEPA was invited to the May 12, 2010, labeling meeting and provided recommendations on the packaging configuration and the package insert labeling. These are incorporated into the final labeling where appropriate.

DDMAC
DDMAC reviewed the Division's draft proposed product labeling for Isopto Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2% and 4% and their comments have been considered in the review of the labeling.

BIOSTATISTICS
Per the Biostatistics consultative review finalized 5/26/10:

There is substantial evidence from the literature to support the efficacy of pilocarpine 2% or 4% for the two following indications:

1) Reduction of elevated IOP in patients with open angle glaucoma or ocular hypertension
2) Induction of Miosis

There is insufficient evidence to support the efficacy of pilocarpine for the two following indications:

3) (b) (4) for acute angle-closure glaucoma
4) Prevention of (b) (4) postoperative elevated IOP associated with (b) (4) laser surgery

Per the review: "Note that the clinical review team considered the indication of '**management of acute angle closure glaucoma'** instead of the indication sought by the applicant of (b) (4) (b) (4) Since it is unclear to me how the management of acute angle closure glaucoma can be assessed and quantified, I leave it to the clinical review team to comment on this indication."

The Biostatistics Team Leader review finalized 5/27/10, addresses, the remaining indication, i.e. prevention of postoperative elevated IOP associated with laser surgery. Per that review:

For the sub-indication "the prevention of post-operative elevated IOP associated with [redacted] laser surgery [redacted]", there is a difference of opinion between the statistical team leader and the primary statistical reviewer. Based on the following detailed efficacy evaluation, the statistical team leader concludes that there is substantial efficacy evidence to support this indication.

The efficacy of the pilocarpine treatment for the indication "the prevention of post-operative elevated IOP associated with [redacted] laser surgery [redacted]" has been evaluated in 7 studies from 7 publications. Among them, 5 studies demonstrated statistically significant results and the remaining 2 studies showed supporting evidence of a numerical trend favoring pilocarpine over no treatment (Leung and Gillies1986) and favoring pilocarpine over timolol or dipivefrin or acetazolamide (Robin 1989). Furthermore, the positive conclusion of the primary statistical reviewer on the efficacy evaluation for indication #1 (the reduction of elevated IOP in patient with open angle glaucoma or ocular hypertension) and indication #4 (the induction of miosis) provides additional supporting evidence for the indication of interest. Thus this review concludes that there is substantial efficacy evidence of pilocarpine 2% and 4% for the indication "the prevention of post-operative elevated IOP associated with [redacted] laser surgery [redacted]."

12. Labeling

The labeling revisions recommended by the review team have been incorporated by Alcon in an amendment to the application.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED 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 laser surgery
4) the induction of miosis

with the labeling submitted by Alcon on 6/16/10 and found in this CDTL review (see Appendix 1).

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

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).

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 pilocarpine study populations were: headache, blurred vision, eye irritation, visual impairment (dim, dark, or "jumping" vision), and eye pain.

Pharmacology/Toxicology, Clinical Microbiology, CMC, Clinical, Biostatistics and Clinical Pharmacology have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements.

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