CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-890

SUMMARY REVIEW

Division Director Review for NDA 200-890

Date	June 21, 2010
From	Wiley A. Chambers, M.D.
NDA #	200-890
Applicant	Alcon Research, Ltd.
Date of Submission	December 22, 2009
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
Action:	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 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. This application is a 505(b)(2) application based primarily on literature but which includes submission of clinical study reports conducted in support of prior applications for other formulations of pilocarpine.

Other formulations/dosage forms of pilocarpine are the subject of approved new drug applications. These include 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 (Alcon) for BetopticPilo was approved 4/17/97, but the drug product has never been marketed.

3. CMC

Isopto Carpine is a sterile aqueous solution presented in a multiple-dose container, benzalkonium chloride (0.01%) is added [redacted].

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] shrink band, which when heated shrinks to conform around the neck and closure area of the bottle.

Composition	**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]			
Benzalkonium chloride	0.01	0.01	0.01	Preservative
Hypromellose 2910	[redacted]			
HCl/NaOH	[redacted]			pH adjustment
Purified water	[redacted]			

Acceptance Specifications

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

Endotoxin	NMT (b) (4)
Sterility	Meets USP

Approval from a CMC prospective was recommended in the second CMC Review.

4. Nonclinical Pharmacology/Toxicology

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

Alcon's original labeling proposal references Salagen, however, Salagen was not identified as part of the 505(b)(2) reference. Labeling sections from Salagen were not incorporated in the final labeling amendments and no portions of the Salagen application have been used in the review of this application. Reference to Alcon's previous approved NDAs for pilocarpine alone provide sufficient non-clinical information to support this application.

5. Clinical Pharmacology/Biopharmaceutics

Alcon conducted one ocular PK study (C-92-56) to assess systemic exposure of pilocarpine following ocular topical administration of Isopto Carpine 4%. Pilocarpine concentrations following topical ocular administration of 4% were found to be low. Mean Cmax value at steady-state following topical ocular dosing was approximately 3.7 ng/mL on both Days 5 and 8. 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.

Similar to the non-clinical sections, Alcon's original labeling proposal references Salagen, however, Salagen was not identified as part of the 505(b)(2) reference. No portions of the Salagen application have been used in the review of this application. Reference to Alcon's previous approved NDAs and their ocular pK studies for pilocarpine provide sufficient information to support this application.

6. Sterility Assurance

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). 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 (b) (4) of label and no significant decrease was observed through the shelf life of the product. All three lots met the acceptance criteria.

7. Clinical/Statistical - Efficacy

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)). 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 studies support the efficacy of pilocarpine in both adults and pediatric patients. The submitted literature articles support the use of pilocarpine for the reduction of elevated intraocular pressure, the management of angle closure glaucoma. The overall reduction in intraocular pressure for this indication is roughly 3-7 mm Hg.

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, and 60 mg/mL) 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.

The most frequently reported adverse reactions occurring in ≥ 5 % of patients pilocarpine populations 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.

POSTMARKETING EXPERIENCE

A five-year Periodic Safety Update Report 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.

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.

9. Pediatrics

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

10. 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.

11. Labeling

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

12. Action

NDA 200890, Isopto Carpine (pilocarpine ophthalmic solution) 1%, 2%, and 4%, with the labeling submitted on June 16, 2010, will be approved 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

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products

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

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/s/

WILEY A CHAMBERS
06/22/2010