

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200-890

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 200-890

Supporting document/s: Electronic submission

Applicant's letter date: December 22, 2009

CDER stamp date: December 22, 2009

Product: Isopto Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2% and 4%

Indication: The reduction of IOP in patients with open angle glaucoma or ocular hypertension, (b) (4) (b) (4) for acute angle-closure glaucoma, for the prevention of (b) (4) postoperative elevated IOP associated with (b) (4) laser surgery and (b) (4) as a potent miotic.

Applicant: Alcon Research, Ltd., Fort Worth, Texas

Review Division: Division of Anti-Infective and Ophthalmology Products

Reviewer: Conrad H. Chen, Ph.D.

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Review Completion Date: April 30, 2010

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1 Executive Summary

1.1 Recommendations

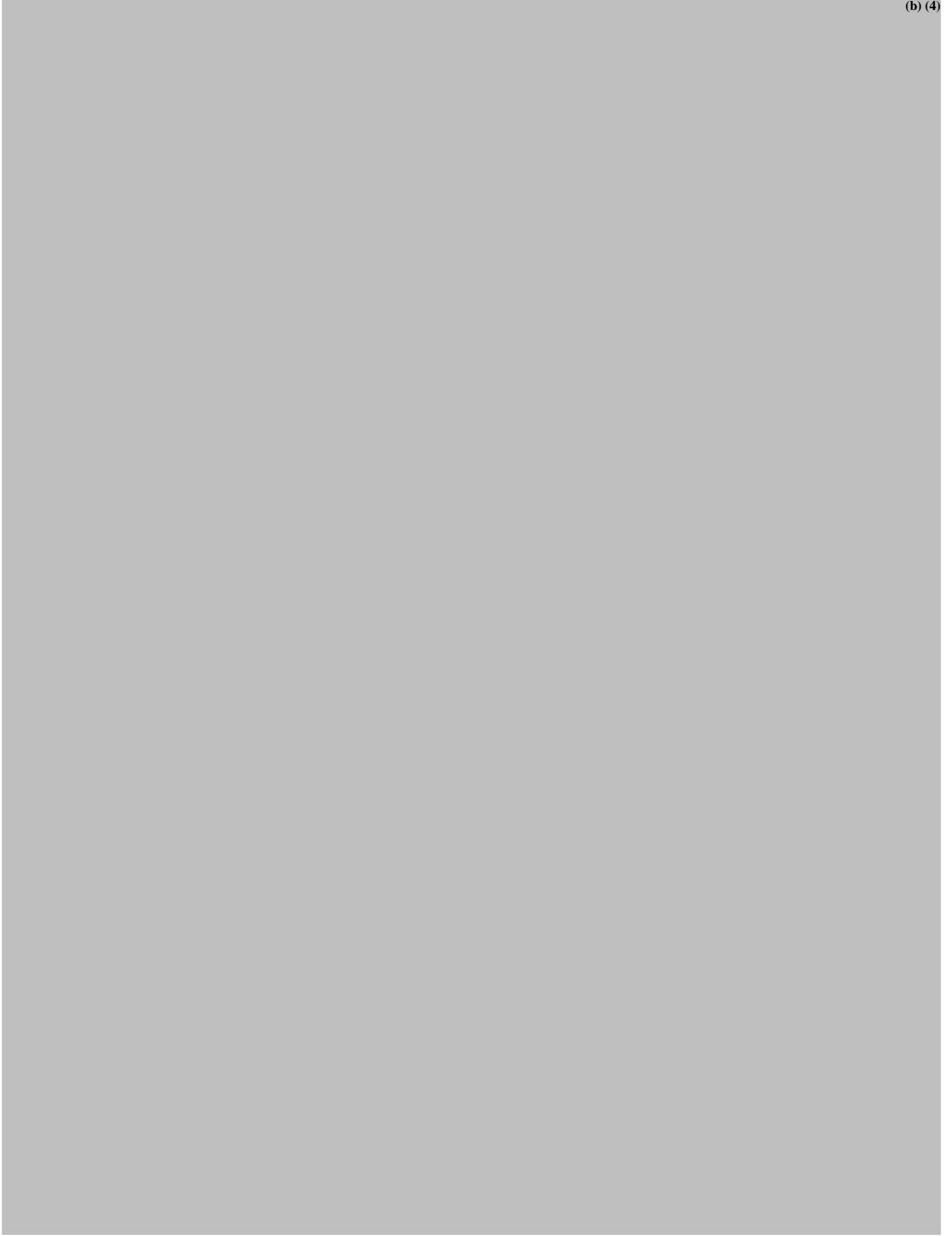
1.1.1 Approvability: The approval of NDA 200-890 is recommended.

1.1.2 Additional Non Clinical Recommendations: None

1.1.3 Labeling:



(b) (4)



1.2 Brief Discussion of Nonclinical Findings

NDA 200-890, Isopto Carpine (pilocarpine hydrochloride ophthalmic solution 1%, 2% and 4%), is filed under 505(b)(2).

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 (Barany 1962 and Kaufman 1979). Pilocarpine is a direct acting cholinergic agonist that 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) (Barany 1962, Davidson 1974, Kaufman 1979, and Gelatt et al. 1997).

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 BETOPTIC® PILO Ophthalmic Suspension (NDA 20-619). Pilocarpine hydrochloride has also been approved as an oral medication, SALAGEN® Tablets (NDA 20-237), for the treatment of xerostomia from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck as well as for the treatment of xerostomia and xerophthamia in patients with Sjogren's Syndrome.

Three repeated-dose topical ocular toxicity studies were conducted using concentrations of up to 6% pilocarpine hydrochloride for 3 weeks to 6 months. Two of the studies were non-GLP and one was GLP. Based on the results from these studies it was concluded that up to 6% pilocarpine hydrochloride ophthalmic solution, administered 2 drops QID to each eye, will not elicit any significant ocular or systemic toxicities in rabbits.

The mutagenic toxicity, carcinogenicity, and reproductive and developmental toxicity studies were previously conducted for oral formulation of pilocarpine hydrochloride (NDA 20-237, Salagen).

2 Drug Information

2.1 Drug: Isopto Carpine (pilocarpine hydrochloride ophthalmic solution 1%, 2% and 4%)

2.1.1 CAS Registry Number (Optional): 54-71-7

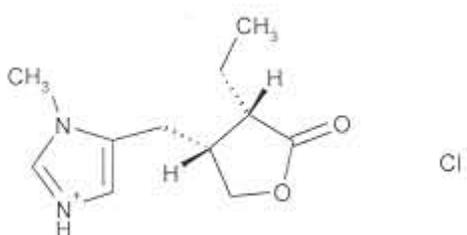
2.1.2 Generic Name: Pilocarpine Hydrochloride

2.1.3 Code Name: AL-2910A, AL 1528

2.1.4 Chemical Name: 3-ethylidihydro-4-[(1-methyl-1H-imidazol-5-yl)-methyl]2-(3H)-furanone hydrochloride

2.1.5 Molecular Formula/Molecular Weight: C₁₁H₁₆N₂O₂ HCl/244.72

2.1.6 Structure



2.1.7 Pharmacologic class: Muscarinic cholinergic agonist

2.2 Relevant IND/s, NDA/s, and DMF/s: NDA 18-796 (Pilopine HS Ophthalmic Gel, pilocarpine hydrochloride ophthalmic solution 4%, approved 10/01/1984, Alcon), NDA 20-619 (Betoptic Pilo, betaxolol hydrochloride 0.25%/pilocarpine hydrochloride 1.75%, approved 04/17/1997, Alcon), NDA 20-237 (Salagen, pilocarpine hydrochloride 5 mg and 7.5 mg tablet, approved 03/22/1994, Eisai).

Pilopine HS® (pilocarpine hydrochloride ophthalmic gel) 4% is a sterile topical ophthalmic aqueous gel which contains more than 90% water and employs CARBOPOL 940, a synthetic high molecular weight cross-linked polymer of acrylic acid, to impart a high viscosity.

2.3 Clinical Formulation:

2.3.1 Drug Formulation:

Table 2.3.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 ^d | 2.0 ^d | 4.0 ^d | Active Ingredient | USP |
| Boric acid | (b) (4) | | | | NF |
| Sodium chloride | | | | | USP |
| Sodium citrate, dihydrate | | | | | USP |
| Benzalkonium chloride | 0.01 | 0.01 | 0.01 | Preservative | NF |
| Hypromellose 2910 (HPMC) | (b) (4) | | | | USP |
| Hydrochloric Acid and/or Sodium Hydroxide | (b) (4) | | | pH Adjustment | NF |
| Purified Water | (b) (4) | | | | NF |
| | (b) (4) | | | | USP |

^a Formulation ID No. 10026; ^b Formulation ID No. 11631; ^c Formulation ID No. 99222;

^d Up to (b) (4) coverage may be added to (b) (4)

2.3.2 Comments on Novel Excipients: All excipients are USP/NF compendial ingredients and have been used in the approved ophthalmic drug products to the strength to be utilized.

2.3.3 Comments on Impurities/Degradants of Concern: See Chemist's review.

2.4 Proposed Clinical Population and Dosing Regimen:

Open-Angle Glaucoma or Ocular Hypertension, Acute Angle-Closure Glaucoma, prevention of (b) (4) Postoperative Elevated IOP, Induction of Miosis

One or two drops of ISOPTO® Carpine 1%, 2% or 4% would be applied topically in the eye(s) up to four times daily. The frequency of instillation and concentration

of ISPOTO® Carpine are determined by the severity of the glaucoma and miotic response of the patient.

2.5 Regulatory Background:

The NDA is submitted under 505(b)(2).

3 Studies Submitted

3.1 Studies Reviewed: The following 3 studies (1 GLP and 2 non-GLP studies) are reviewed.

Table 2.4.4-1 Repeated-Topical Ocular Dose Toxicity Studies with Pilocarpine Hydrochloride

| Species/ Strain | Dosing Regimen | Posology | Doses | No./group | Noteworthy Findings | TR No. (Study No.) |
|--------------------|---|--|---|--|---|--|
| Rabbit/ NZW | 2 drops, QID, OU, for 3 weeks | QID QID QID | pilocarpine hydrochloride vehicle pilocarpine hydrochloride 4% ^b degraded pilocarpine hydrochloride 4% ^b | 5M/3F for Vehicle group 4/sex for test article treated groups | No treatment-related findings. | 045:3320:0888 (N-88-79) GLP Final report |
| Rabbit/ NZW | 0.1 mL, OU, for 21 days | TID TID TID TID TID TID | AL1528 gel 6% ^a AL1528 gel 2% ^a AL1528 gel vehicle pilocarpine hydrochloride 6% ^b pilocarpine hydrochloride 4% ^b pilocarpine hydrochloride 2% ^b | 5/sex | AL1528 gel 2 and 6%^a: Minimal conjunctival discharge and fluorescein staining. | 151:7320:75/76 (T-767) Non- GLP Final report |
| Rabbit/ NZW | 0.05 mL OD, for up to 182 days | NA BID BID QD BID TID Every 7 days | Untreated AL1528 Gel Vehicle AL1528 Gel 2% ^a AL1528 Gel 4% ^a AL1528 Gel 4% ^a pilocarpine hydrochloride 4% ^b Ocusert Pilo-40 | 120 treatment days (10 animals); 140 treatment days, 92-day reversibility observation period (12 animals); 182 treatment days (14 animals) | AL1528 Gel Vehicle and AL1528 Gel formulations: Corneal neovascularization due to the gel formulation, not pilocarpine hydrochloride. | 030:3320:0480 (75-Y-18N) Non - GLP Final report |

^apilocarpine hydrochloride gel

AL1528 = pilocarpine hydrochloride

^bpilocarpine hydrochloride ophthalmic solution

3.2 Studies Not Reviewed: Studies previously submitted under NDAs 18-796, 20-619, and 20-237 are not reviewed. The outlines of the findings are summarized.

3.3 Previous Reviews Referenced: Reviews for NDAs 18-796, 20-619, and 20-237.

4 Pharmacology

4.1 **Primary Pharmacology:** According to the published literature, pilocarpine has been used as a miotic for the clinical therapy of primary open-angle glaucoma and other forms of chronic glaucoma for more than 100 years. Pilocarpine is a direct acting cholinergic agonist that produces miosis through contraction of the iris sphincter resulting in opening of the trabecular meshwork spaces to facilitate outflow of the aqueous humor, thus lowering IOP.

4.2 **Secondary Pharmacology:** No data are submitted.

4.3 **Safety Pharmacology:** No data are submitted.

5 Pharmacokinetics/ADME/Toxicokinetics:

Limited nonclinical pharmacokinetic and drug-disposition data are available on ISOPTO® Carpine and pilocarpine itself. Nevertheless, the available data show a favorable pharmacokinetic profile that supports the safety of this drug.

Following topical ocular administration to rabbits, pilocarpine is absorbed rapidly into the eye ($T_{max} \approx 30$ minutes) and then eliminated rapidly (aqueous humor $t_{1/2} < 1$ hour). The plasma half-life of radioactive drug equivalents in rats after intravenous and oral doses of ^{14}C -pilocarpine is approximately 9 hours. In dogs, the half-life of pilocarpine is about 1.3 hours. The longer half-life of radioactivity in rats is considered to be due to metabolites.

In rats administered oral doses of ^3H -pilocarpine, radioactive drug equivalents distribute widely and are generally eliminated in parallel with plasma. Greater than 90% of the dose is excreted in the first 24 hours with essentially the entire radioactivity excreted in urine.

Radioactive drug equivalents distribute to the fetus of pregnant rats; however, fetal tissue concentrations are approximately one-half of those in maternal plasma except for fetal liver which is similar to maternal plasma. Secretion of radioactive equivalents in the milk of lactating rats occurs with milk levels similar to plasma levels of the dam. Both milk and plasma concentrations decline in parallel resulting in milk:plasma ratios of approximately unity.

Pilocarpine is metabolized to isopilocarpine, pilocarpic acid and 3-hydroxypilocarpine. Isopilocarpine and pilocarpic acid are metabolites found in rabbit aqueous humor, cornea and iris-ciliary body following a topical ocular dose. Cornea appears to be the major site of metabolism due to the presence of esterases that are presumed responsible for formation of pilocarpic acid. Circulating pilocarpine metabolites in animal species have not been reported.

Isopilocarpine and pilocarpic acid are found in human plasma and urine.

3-(*R*)-Hydroxypilocarpine is the major metabolite in human plasma and urine accounting for at least one third of an oral dose and is produced by first pass metabolism. Interestingly, the 3-(*S*) diastereomer is not observed indicating a high degree of metabolic stereoselectivity. Cytochrome P450 (CYP 2A6) is considered to be responsible for formation of this metabolite.

Pilocarpine inhibits *in vitro* rabbit hepatic microsomal metabolism of nicotine and aniline showing an induced differential spectral change characterized as a class Type II change.

CYP2A6 and CYP2E1 are now known to be the major isozymes responsible for the metabolism of these substrates, respectively. Since plasma levels of pilocarpine in humans are low following topical ocular doses, drug-drug interactions involving cytochrome P450 metabolism are not likely. In addition, drug-drug interactions involving protein binding are not likely since pilocarpine does not significantly bind to plasma proteins. In addition, the principal metabolites of pilocarpine, isopilocarpine, pilocarpic acid and isopilocarpic acid, also bind significantly (<5%) to human plasma proteins.

6 General Toxicology

6.1 Single-Dose Toxicity: The single-dose toxicity of pilocarpine hydrochloride has not been assessed by Alcon.

6.2 Repeat-Dose Toxicity

Study title: Three-Week Subacute Topical Ocular Irritation Evaluation of Degraded Pilocarpine Ophthalmic Solution in Rabbits. Final Report

Study no.: N-88-79. Alcon Technical Report No. TR 045:3320:0888

Study report location: Module 4, Section 4.2.3.2

Conducting laboratory and location: Alcon Laboratories, Inc., Fort Worth, Texas

Date of study initiation: 6/29/88

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: Pilocarpine Solution Vehicle 0.0%, Lot Number All-075
Pilocarpine Hydrochloride Ophthalmic Solution 4.0%, Lot Number All-094
Degraded Pilocarpine Hydrochloride Ophthalmic Solution 4.0%, Lot Number All-092

Key Study Findings:

In a 3-week GLP-regulated ocular irritation evaluation (TR: 045:3320:0888), 4% pilocarpine hydrochloride ophthalmic solution and degraded 4% pilocarpine hydrochloride (3% pilocarpine hydrochloride, 14% isopilocarpine, and 8% pilocarpic acid) ophthalmic solution were administered 4 times daily. Biomicroscopic evaluation of the eyes treated with degraded 4% pilocarpine hydrochloride ophthalmic solution or 4% pilocarpine hydrochloride ophthalmic solution demonstrated minimal ocular irritation, including conjunctival congestion and single instances of conjunctival discharge. High incidences of altered light reflex were noted in animals treated with degraded 4% pilocarpine hydrochloride and 4% pilocarpine hydrochloride. This finding was expected since pilocarpine hydrochloride is used as a miotic and was therefore considered pharmacologic in nature. No adverse compound or treatment-related findings were observed following gross examination of all organs and tissues at necropsy. Histopathological evaluation of the ocular tissues was unremarkable. This study demonstrated that pilocarpine hydrochloride ophthalmic solution or the presence of the degradation products, pilocarpic acid and isopilocarpine hydrochloride in ophthalmic formulations, do not induce significant ocular toxicity when administered topically to New Zealand White rabbits.

Methods

Doses: 2 drops (60 μ L) of control, 4% pilocarpine, or 4% heat degraded pilocarpine were administered to right eye of each animal. The left eyes were not treated.

The heat degraded pilocarpine contained 3.08% (77% of 4%) pilocarpine, 0.56% (14% of 4%) isopilocarpine, and 0.32% (8% of 4%) pilocarpic acid.

Frequency of dosing: Four times per day for three consecutive weeks

Route of administration: Topical ocular

Dose volume: Approximately 30 μ L/drop

Formulation/Vehicle:

Table 2

Composition of Test and Control Articles Used in the Three-Week Subacute Topical Ocular Irritation Evaluation of Degraded Pilocarpine Ophthalmic Solution in Rabbits

| Ingredient | Vehicle (Lot AII-075) (Of Label) | 4.0% Pilocarpine HCl (Lot AII-094) (Of Label) | Degraded 4.0% Pilocarpine HCl* (Lot AII-092) (Of Label) |
|---|--|---|--|
| Pilocarpine HCl | - | 4.0% w/v | 4.0% w/v |
| Benzalkonium Chloride | 0.01% w/v + 10% Excess** | 0.01% w/v + 10% Excess** | 0.01% w/v + 10% Excess** |
| Sodium Hydroxide and/or Hydrochloric Acid | QS pH 5 | QS pH 5 | QS pH 5 |
| Purified Water | QS 100 | QS 100 | QS 100 |
| Sodium Chloride | 0.9% w/v | - | - |

*Refer to Table 4 for actual chemical composition following degradation.

**Refers to 10% of label concentration.

Reviewer's comment:

The formulation used in this study is different from that used in clinical study in which inactive ingredients such as boric acid, sodium citrate, and hypromellose 2910 are also included. However, these inactive ingredients have been used in other approved ophthalmic drug products. The absence of these ingredients in the study drug may not affect the toxicity evaluation of this study.

Species/Strain: New Zealand Albino rabbits
 Number/Sex/Group: 4/sex/group (5 males and 3 females in control by mistake)
 Age: Not stated
 Weight: 2.4 to 3.0 kg
 Satellite groups: None

Observations and Results:

There were no compound- or treatment-related pharmacotoxic signs observed in any of the treatment or control groups throughout the duration of the study. In addition, each treatment and control group exhibited a positive mean body weight gain during the study.

Biomicroscopic observation of eyes treated with degraded 4.0% pilocarpine hydrochloride ophthalmic solution revealed only minimal conjunctival congestion (hyperemia) and single instances of conjunctival discharge. Comparable ocular changes were observed among animals treated with the pilocarpine vehicle and 4.0% pilocarpine hydrochloride ophthalmic solution. High incidences of altered light reflex (pupillary response) noted in the groups treated with degraded 4% pilocarpine hydrochloride or 4% pilocarpine hydrochloride ophthalmic solutions were expected and were judged to be related to the pharmacological actions of pilocarpine.

No adverse compound- or treatment-related findings were observed following gross examination of all organs and tissues at necropsy. In addition, histopathological evaluation of the ocular tissues as well as representative samples from all tissues and organs was unremarkable.

Based on the results of this study, it was concluded that the ocular effects elicited by a 3 - week topical ocular exposure to degraded 4.0% pilocarpine hydrochloride ophthalmic solution containing approximately 8.0% pilocarpic acid and 14.0% isopilocarpine relative to original 4.0% pilocarpine hydrochloride concentration prior to degradation were minimal in nature, comparable to those effects observed in the control groups and judged to be of no clinical significance. In addition, evaluation of the ante and postmortem data (pharmacotoxic signs, body weight data, gross observations at necropsy, and histopathological evaluation of representative samples of all tissues or organs) revealed that topical ocular administration of the pilocarpine hydrochloride degradation products, pilocarpic acid and isopilocarpine, did not result in any systemic toxicity.

Based on the results of this study, it was concluded that pilocarpine hydrochloride ophthalmic solution or the presence of the degradation products, pilocarpic acid and isopilocarpine, or pilocarpine hydrochloride in ophthalmic formulations, does not present an ocular or systemic toxicity hazard in the New Zealand White rabbit. The presence of pilocarpic acid and isopilocarpine should not present an ocular or systemic toxicity hazard to humans following topical ocular treatment with ophthalmic formulations containing pilocarpine hydrochloride.

Study title: Twenty-One Day Ocular Irritation Evaluation of AL1528 in Albino Rabbits. Final Report.

Study no.: T-767. Alcon Technical Report No.: TR151:7320:75/76

Study report location: Module 4, Section 4.2.3.2

Conducting laboratory and location: Alcon Laboratories, Inc., Fort Worth Texas

Date of study initiation: June 1976

GLP compliance: No

QA statement: No

Drug, lot #, and % purity:

TABLE 1
Composition of Test Formulations

| Component | Theoretical Concentration % (w/v) | | | | | | |
|------------------------------|-----------------------------------|-------------------|--------|----------------------|----------------------|-------------------|--------------|
| | Lot: WI-172 | WE-1269 | WI-182 | R54612T ^a | R54437T ^a | WI-168 | WI-170 |
| AL1528 | 14.16 ^b | 4.73 ^c | - | - | - | - | - |
| Pilocarpine HCl | - | - | 6.00 | 4.00 | 2.00 | - | - |
| Carbopol 940 | - | - | - | - | - | 3.02 ^d | - |
| Benzalkonium Chloride | 0.008 | 0.008 | 0.01 | 0.01 | 0.01 | 0.008 | 0.008 |
| Disodium Edetate | 0.01 | 0.01 | - | 0.01 | 0.01 | 0.01 | 0.01 |
| Sodium Hydroxide 3N | qs pH 5.1 | qs pH 5.1 | - | - | - | qs pH 5.1 | qs pH 5.1 |
| Boric Acid | - | - | 1.0 | - | - | - | - |
| Sodium Citrate Dihydrate | - | - | 0.14 | - | - | - | - |
| Hydroxypropylmethylcellulose | - | - | - | 0.33 | 0.33 | - | - |
| H ₂ O | qs | qs | qs | - | - | qs | qs |

^a [Redacted] (b) (4)

Alcon in-house lot numbers are: WI-184 = R54612T; WI-183 = R54437T

^b Equivalent to 6% pilocarpine hydrochloride.

^c Equivalent to 2% pilocarpine hydrochloride.

^d Carbopol 940 is a component of AL1528; WI-168 is equivalent to WE-1269 without pilocarpine HCl.

Key Study Findings:

In a non-GLP ocular irritation evaluation (TR:151:7320:75/76) of AL1528 gel (2 or 6% pilocarpine hydrochloride) or pilocarpine hydrochloride ophthalmic solution (2%, 4%, or 6%), doses were administered three times per day over a 21-day period. Minimal ocular

changes were observed in all animals treated with AL1528 gel, regardless of pilocarpine concentration, and included conjunctival congestion, conjunctival discharge, impaired light reflex, and fluorescein staining. These ocular changes were minimal and consistent with those commonly seen in rabbits. Impaired light reflex was considered pharmacologic in nature since pilocarpine is used as a miotic. These expected pharmacologic responses are not considered adverse. No significant ocular toxicity was observed when pilocarpine hydrochloride administered topically as either an ophthalmic gel or solution to New Zealand White rabbits. Pilocarpine hydrochloride ophthalmic solution and AL1528 gel (pilocarpine hydrochloride 6%) exceed the proposed clinical concentrations for this application.

Methods

Doses: 0.1 mL/dose, AL1528 (2 or 6% pilocarpine hydrochloride) or pilocarpine hydrochloride ophthalmic solution (2%, 4% or 6%), TID for 21 consecutive days, only right eyes are treated. AL1528 is a complex of pilocarpine hydrochloride and carbopol 940. Carbopol 940 is a water-soluble resin. It is a carboxy vinyl polymer of extremely high molecular weight (b) (4). (b) (4) The toxicity of carbopol is negligible (Adams and Davis, 1973). Carbopol produced no-significant irritation after topical ocular instillation-to rabbits or dermal application to humans (b) (4). (b) (4).

Frequency of dosing: Three times per day for 21 consecutive days
 Route of administration: Topical ocular
 Dose volume: 0.1 mL
 Formulation/Vehicle: See Table 1 above
 Species/Strain: New Zealand White rabbits
 Number/Sex/Group: 5/sex/group
 Age: Not described
 Weight: 2.5-3.5 kg
 Satellite groups: None

Observations and Results

There were no treatment-related changes in body weights or appearance. Instillation of AL1528 gel (pilocarpine hydrochloride 2% and 6%) elicited minimal ocular changes including conjunctival congestion, conjunctival discharge, impaired light reflex, and fluorescein staining. Conjunctival congestion was minimal and comparable to the intensity observed in the Pilocar competitor controls, vehicle, and untreated controls. Conjunctival congestion was considered pharmacological in nature due to the vasodilating effects of parasympathomimetic drugs. Conjunctival discharge was

transient, and therefore was not considered adverse. Impaired light reflex was an expected pharmacologic response since pilocarpine is a miotic. Fluorescein staining observed in the AL1528 gel (pilocarpine hydrochloride 2%) treated animals was minimal and comparable to the Pilocar competitor controls, vehicle, and untreated controls. These ocular changes were not considered adverse.

A single animal in the AL1528 gel (pilocarpine hydrochloride 2%) treatment group exhibited significant ocular changes in the treated eye. These changes included severe conjunctival congestion, minimal swelling, severe discharge, minimally impaired light reflex, corneal cloudiness of moderate severity and area, fluorescein staining of minimal intensity and area, and pannus. These changes began on Day 12, but were preceded by gross observations of moderate discharge beginning on Day 10. When these changes occurred, 10 extra animals were added to the AL1528 gel (pilocarpine hydrochloride 2%) group. These ocular changes were not observed in any other animals and thought to be due to accidental scratching of the cornea by the metal tip of the dosing tube. Therefore, these findings were not considered related to the test article. Macroscopic lesions observed at necropsy were comparable between the AL1528 gel (pilocarpine hydrochloride 2% and 6%) treated animals and Pilocar competitor control treated animals (pilocarpine hydrochloride 2%, 4%, and 6%).

Based on these observations, AL1528 gel and pilocarpine hydrochloride 2%, 4%, and 6% (Pilocar, competitor control) are safe for clinical use. This data supports the clinical use of pilocarpine hydrochloride ophthalmic solution 1%, 2%, and 4%.

Study title: Chronic Topical Ocular Irritation/Systemic Toxicity Evaluation of AL1528 Gel in Rabbits. Final Report

Study no.: 75-Y-18N. Alcon Technical
Report No. TR 030:3320:0480

Study report location: Module 4, Section 4.2.3.2

Conducting laboratory and location: Alcon Laboratories, Inc., Fort Worth,
Texas

Date of study initiation: 10/31/78

GLP compliance: No

QA statement: Yes

Drug, lot #, and % purity:

Key Study Findings:

A study in New Zealand White rabbits (TR: 030:3320:0480) assessed various drug delivery formulations of pilocarpine hydrochloride, including AL1528 gel (pilocarpine hydrochloride 2%, 4%), pilocarpine hydrochloride ophthalmic solution, 4% and Ocusert Pilo-40, for up to 182 days with 92 days of recovery. The AL1528 gel delivery formulation elicited moderate corneal neovascularization, moderate conjunctival congestion, and minimal corneal cloudiness within the vehicle treated animals, as well as each of the pilocarpine concentrations. There was no recovery of the corneal neovascularization in any of the AL1528 gel treated animals; however, corneal cloudiness and conjunctival congestion were reversible. There were no significant

findings in the pilocarpine hydrochloride ophthalmic solution, 4% or the Ocusert Pilo-40 treated animals. This study demonstrated that the AL1528 drug delivery vehicle elicited corneal neovascularization in rabbits with repeated chronic administration in rabbits. There were no treatment-related effects in animals dosed with 4% pilocarpine hydrochloride ophthalmic solution or Ocusert Pilo-40.

Methods

Doses: One drop (approximately 0.05 mL) of 0, 2, and 4% pilocarpine hydrochloride (AL1528 Gel, Pilocar, or Ocusert Pilo-40). AL1528 is a complex of pilocarpine hydrochloride and carbopol 940. Carbopol 940 is a water-soluble resin. It is a carboxy vinyl polymer of extremely high molecular weight (b) (4). The toxicity of carbopol is negligible (Adams and Davis, 1973). Carbopol produced no-significant irritation after topical ocular instillation-to rabbits or dermal application to humans (b) (4).

Frequency of dosing: 1, 2, or 3 times daily for the duration as shown in Table 1

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| Table 1 | | | | | | | |
| <u>Test and Control Articles, Treatment Groups and Treatment Regimen</u> | | | | | | | |
| Group No. | Treatment | Conc. of Pilocarpine HCl (%) | Lot No. | Rabbits/Dose | Dose/Treatment (mg) | Dose/Day | Treatment Days |
| 1a | Untreated ¹ | - | - | 10 | - | - | 121 ₂ |
| b | | - | - | 12 | - | - | 140 ₃ |
| c | | - | - | 14 | - | - | 182 ₃ |
| 2a | AL1528 Gel Vehicle | 0.0 | PB5648C1 | 10 | 50.0 | 2 | 121 ₂ |
| b | | 0.0 | | 12 | 50.0 | 2 | 140 ₃ |
| c | | 0.0 | | 14 | 50.0 | 2 | 182 ₃ |
| 3a | AL1528 Gel | 2.0 | PB5649C2 | 10 | 50.0 | 2 | 120 ₂ |
| b | | 2.0 | | 12 | 50.0 | 2 | 139 ₃ |
| c | | 2.0 | | 14 | 50.0 | 2 | 182 ₃ |
| 4a | AL1528 Gel | 4.0 | PB5658C6 | 10 | 50.0 | 1 | 120 ₂ |
| b | | 4.0 | | 12 | 50.0 | 1 | 139 ₃ |
| c | | 4.0 | | 14 | 50.0 | 1 | 182 ₃ |
| 5a | AL1528 Gel (2X/day) | 4.0 | PB5658C6 | 10 | 50.0 | 2 | 120 ₂ |
| b | | 4.0 | | 12 | 50.0 | 2 | 138 ₃ |
| c | | 4.0 | | 14 | 50.0 | 2 | 182 ₃ |
| 6a | Pilocar | 4.0 | R83871 | 10 | 1 ⁴ | 3 | 120 ₂ |
| b | | 4.0 | | 12 | 1 | 3 | 138 ₃ |
| c | | 4.0 | | 14 | 1 | 3 | 182 ₃ |
| 7a | Ocusert Pilo-40 | - | 07635 | 10 | 1 ⁵ | 1 ⁶ | 56 |
| b | | - | and | 12 | 1 | 1 | 56 |
| c | | - | 03649 | 14/10 ⁷ | 1 | 1 | 119 |

¹ Right eyes were manipulated three times/day.

² The treatment was terminated after approximately 140 days due to the development of neovascularization. These animals were observed for 93 days to determine the remission of this condition.

³ Treatment was terminated prior to 365 days at the Study Director's discretion.

⁴ 1 Drop = approximately 0.05 ml

⁵ Ocusert Pilo-40 delivers 40 ug/hr/week or a total of dose of 11 mg pilocarpine/week.

⁶ A new Ocusert Pilo-40 device was inserted every 7 days.

⁷ Due to the high rate of rejection by the rabbits of the Ocusert Pilo-40 device, treatment was terminated in all rabbits except the 10 animals with the longest retention time for the device, regardless of the animal's original group assignment.

Route of administration: Topical Ocular, only right eyes are treated

Dose volume: One drop is approximately 0.05 mL

Formulation/Vehicle: As shown in Table 2

Table 2
Composition of Test Articles

| Ingredients | AL1528 Gel Vehicle (Lot No. PB5648C1) | AL1528 Gel 2% Pilocarpine HCl (Lot No. PB5649C2) | AL1528 Gel 4% Pilocarpine HCl (Lot No. PB5658C6) | Pilocar 4% ¹ (Lot No. R83871) | Ocusert Pilo-40 ² (Lot No. 07635) |
|--|--|--|--|---|---|
| Pilocarpine HCl | - | 2.0% + 10% xs | 4.0% + 10% xs | 4.0% | - |
| Carbopol 940 | 4.0% | 4.0% | 4.0% | - | - |
| Benzalkonium Chloride | 0.008% + 10% xs | 0.008% + 10% xs | 0.008% + 10% xs | * | - |
| Disodium Edetate | 0.01% | 0.01% | 0.01% | * | - |
| Hydrochloric Acid and Sodium Hydroxide | qs (pH 5) | qs (pH 5) | qs (pH 5) | - | - |
| Purified Water | qs | qs | qs | - | - |
| 1 | (b) (4) | | | | |
| | The exact percentage of each component of this formulation is not known. | | | | |
| 2 | (b) (4) | | | | |
| | (b) (4) Exact percentages of each are not known. | | | | |
| * | Exact percentage in manufactured product unknown. | | | | |

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Species/Strain: New Zealand White rabbits
 Number/Sex/Group: 10 to 14 rabbits/group
 Age: Not stated
 Weight: 1.8 -3.4 kg
 Satellite groups: None

Observations and Results:

In those eyes treated with the AL1528 gel formulations (vehicle or pilocarpine hydrochloride), the ocular changes generally consisted of moderate corneal neovascularization, minimal-moderate conjunctival congestion and minimal corneal cloudiness. The development of corneal neovascularization was more rapid in the AL1528 gel vehicle group (17/33 on Day 28, 22/33 on Day 42, 30/32 on Day 57, and 31/31 on Day 70) than in the other AL1528 gel test articles containing pilocarpine hydrochloride (AL1528 gel 2% pilocarpine hydrochloride group – 8/35 Day 42, 17/35 Day 57, 33/34 Day 119; AL1528 gel 4% pilocarpine hydrochloride (1X/day) 5/36 Day 57, 14/33 Day 119, 19/24 Day 171; and AL1528 gel 4% pilocarpine hydrochloride (2X/day) group 9/33 Day 70, 22/33 Day 98, 29/33 Day 119). In all instances, corneal cloudiness, if it appeared, developed after the corneal neovascularization. The corneal cloudiness did not persist. The corneal neovascularization which developed in those groups treated with AL1528 gel vehicle or AL1528 gel 2% and 4% developed without any accompanying inflammatory changes. In those animals treated with Pilocar 4% and Ocusert Pilo-40, ocular changes generally consisted of minimal conjunctival congestion. Additionally, isolated instances or low incidences of minimal discharge, minimal corneal

fluorescein staining, iritis, and abnormal lenses were also observed sporadically throughout the study in the various groups.

In the reversal of ocular effects phase of the study, corneal neovascularization was not reversed in any of the AL1528 gel-treated groups. Partial or total reversal of conjunctival congestion and corneal cloudiness occurred in all of the AL1528 gel 2% and 4% pilocarpine hydrochloride groups. None of the ocular changes in the AL1528 gel vehicle group had reversed after 92 days of nontreatment.

Evaluations were performed to determine if the corneal neovascularization was due to either a hypersensitization phenomenon or of bacterial origin. The results from the skin sensitization tests and bacterial swabs were negative.

There was no apparent systemic effect from treatment in any of the groups as evidenced by unremarkable pharmacotoxicity, growth patterns, and gross pathology. A microscopic evaluation of the eyes from the rabbits in the AL1528 gel vehicle, and AL1528 gel 2% and 4% (QD) groups in this phase of the study showed vascularization at the limbus of the corneas of the right eyes. This change was evident in 6 of 10 rabbits in the AL1528 vehicle control group, 6 of 9 rabbits in the AL1528 gel 2% group, and 3 of 10 rabbits in the AL1528 gel 4% (QD) group. These changes were not observed in the left (untreated) eyes of these rabbits. Additionally, these changes were not observed in the eyes of rabbits from the AL1528 gel 4% (BID), untreated control, Pilocar 4%, or Ocusert Pilo-40 groups. The presence of these changes in the AL1528 gel vehicle group, with a slightly greater degree of incidence and severity than in the other AL1528 gel groups, suggests that the lesion may be related to the vehicle used in this study. There was no apparent difference between the eyes of the male and female rabbits used in this study.

Based on the results of this study, it was apparent that all of the formulations of AL1528 gel vehicle or AL1528 containing pilocarpine hydrochloride were capable of eliciting corneal neovascularization in rabbit eyes with repeated, chronic administration. In those dosed with AL1528 gel formulations containing pilocarpine hydrochloride, the development of corneal neovascularization was delayed and of lesser incidence.

Therefore, it was concluded that the rabbit may not be a suitable species for the safety evaluation or assessment of toxicity of this unique drug dosage form due to development of corneal neovascularization with both the vehicle and active drug formulations. There were no treatment-related effects in the animals dosed with Pilocar 4 % (pilocarpine hydrochloride ophthalmic solution, 4%) or Ocusert-Pilo 40. This data supports the clinical use of pilocarpine hydrochloride ophthalmic solution 1%, 2%, and 4%.

7 Genetic Toxicology

Pilocarpine hydrochloride was not found to be mutagenic in a series of studies including: *in vitro* Ames test, *in vitro* chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, *in vitro* unscheduled DNA synthesis test in primary rat hepatocytes, and *in vivo* chromosomal aberration in the mouse micronucleus test (SALAGEN® NDA 20-237).

8 Carcinogenicity

Lifetime oral carcinogenicity studies for pilocarpine hydrochloride were conducted in mice and rats by (b) (4) (SALAGEN® NDA 20-237). In mice, no tumors were induced at any dosage of up to 30 mg/kg/day. In rats, increased incidences of benign pheochromocytomas were observed in both males and females and increased incidences of hepatocellular adenomas were observed in female rats at a dosage of 18 mg/kg/day.

9 Reproductive and Developmental Toxicology

In a teratology study, pregnant rats were dosed between gestational days 6 through 15 with 0, 7.5, 26, or 90 mg/kg/day pilocarpine hydrochloride via oral gavage. Reduction in mean fetal body weight and increased incidence of skeletal variations were observed at the 90 mg/kg/day pilocarpine hydrochloride dose. It was not determined whether these effects were directly related to the drug or secondary to maternal toxicity.

A teratology study was performed in New Zealand White rabbits dosed between gestational day 6 through 18 via oral gavage with 0.1, 3, or 9 mg/kg/day pilocarpine hydrochloride. Test article related maternal mortality and reduced body weight gain were observed in the 9 mg/kg/day dose. Clinical signs in all groups consisted of excessive salivation and diarrhea, which are known pharmacologic responses to pilocarpine. No effects on the fetus were observed (SALAGEN® NDA 20-237).

In peri- and postnatal development study, pregnant rats were dosed between gestation and lactation with up to 36 mg/kg/day pilocarpine hydrochloride via oral gavage. At 18 mg/kg/day, increased still births, decreased neonatal survival, and reduced mean fetal body weight were observed (SALAGEN® NDA 20-237).

Impaired reproductive function was observed in male and female rats administered 18 mg/kg/day via oral gavage, including reduced fertility, decreased sperm motility, and morphologic evidence of abnormal sperm. It was unclear whether the impaired fertility was due to the effects on males, females, or both males and females. In dogs, evidence of impaired spermatogenesis was observed at an oral dosage of 3 mg/kg/day for 6 months (SALAGEN® NDA 20-237).

10 Special Toxicology Studies: No submission

11 Integrated Summary and Safety Evaluation

NDA 200-890, Isopto Carpine (pilocarpine hydrochloride ophthalmic solution 1%, 2% and 4%), is filed under 505(b)(2).

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 (Barany 1962 and Kaufman 1979). Pilocarpine is a direct acting cholinergic agonist that 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) (Barany 1962, Davidson 1974, Kaufman 1979, and Gelatt et al. 1997).

ISOPTO® Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2%, and 4%, is the intended trade name for the product presented in this application. It contains the same concentrations of pilocarpine hydrochloride as the approved product PILOPINE HS® Gel.

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 BETOPTIC® PILO Ophthalmic Suspension (NDA 20-619). Pilocarpine hydrochloride has also been approved as an oral medication, SALAGEN® Tablets (NDA 20-237), for the treatment of xerostomia from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck as well as for the treatment of xerostomia and xerophthamia in patients with Sjogren's Syndrome.

All excipients in Isopto Carpine (pilocarpine hydrochloride ophthalmic solution 1%, 2% and 4%) are USP/NF compendial ingredients and have been used in the approved ophthalmic drug products.

Three repeated-dose topical ocular toxicity studies were conducted using concentrations of up to 6% pilocarpine hydrochloride for up to 1 year. Two of the studies were non-GLP and one was GLP.

In a 3-week GLP-regulated ocular irritation evaluation (TR: 045:3320:0888), 4% pilocarpine hydrochloride ophthalmic solution and degraded 4% pilocarpine hydrochloride (3% pilocarpine hydrochloride, 14% isopilocarpine, and 8% pilocarpic acid) ophthalmic solution were administered 4 times daily. Biomicroscopic evaluation of the eyes treated with degraded 4% pilocarpine hydrochloride ophthalmic solution or 4% pilocarpine hydrochloride ophthalmic solution demonstrated minimal ocular irritation, including conjunctival congestion and single instances of conjunctival discharge.

Based on the results of this study, it was concluded that the presence of the degradation products, pilocarpic acid and isopilocarpine, of pilocarpine hydrochloride in ophthalmic formulations and pilocarpine hydrochloride ophthalmic solution itself, do not present an ocular or systemic toxicity hazard in the New Zealand White rabbit.

In a non-GLP ocular irritation evaluation (TR:151:7320:75/76) of AL1528 gel (2 or 6% pilocarpine hydrochloride) or pilocarpine hydrochloride ophthalmic solution (2%, 4%, or 6%), doses were administered three times per day over a 21-day period. Minimal ocular changes were observed in all animals treated with AL1528 gel, regardless of pilocarpine concentration, and included conjunctival congestion, conjunctival discharge, impaired light reflex, and fluorescein staining. These ocular changes were minimal and consistent with those commonly seen in rabbits. Impaired light reflex was considered pharmacologic in nature since pilocarpine is used as a miotic. These expected pharmacologic responses are not considered adverse. No significant ocular toxicity was observed when pilocarpine hydrochloride administered topically as either an ophthalmic gel or solution to New Zealand White rabbits.

Another non-GLP study in New Zealand White rabbits (TR: 030:3320:0480) assessed various drug delivery formulations of pilocarpine hydrochloride (1 to 3 times daily), including AL1582 gel (pilocarpine hydrochloride 2%, 4%), pilocarpine hydrochloride ophthalmic solution, 4% and Ocusert Pilo-40, for up to 182 days with 92 days of recovery. As shown in Table 2 in Study 75-Y-18N, the formulations differ for these test drugs.

The AL1528 gel delivery formulation elicited moderate corneal neovascularization, moderate conjunctival congestion, and minimal corneal cloudiness within the vehicle treated animals, as well as each of the pilocarpine concentrations. There was no recovery of the corneal neovascularization in any of the AL1528 gel treated animals; however, corneal cloudiness and conjunctival congestion were reversible. Based on the results of this study, it was apparent that all of the formulations of AL1528 gel vehicle or AL1528 containing pilocarpine hydrochloride were capable of eliciting corneal neovascularization in rabbit eyes with repeated, chronic administration. In those animals treated with Pilocar 4% and Ocusert Pilo-40, ocular changes generally consisted of minimal conjunctival congestion. This data supports the clinical use of pilocarpine hydrochloride ophthalmic solution 1%, 2%, and 4%.

Pilocarpine hydrochloride was not found to be mutagenic in a series of studies including: *in vitro* Ames test, *in vitro* chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, *in vitro* unscheduled DNA synthesis test in primary rat hepatocytes, and *in vivo* chromosomal aberration in the mouse micronucleus test (SALAGEN® NDA 20-237).

Lifetime oral carcinogenicity studies for pilocarpine hydrochloride were conducted in mice and rats by (b) (4) (SALAGEN® NDA 20-237). In mice, no tumors were induced at any dosage of up to 30 mg/kg/day. In rats, increased incidences of benign pheochromocytomas were observed in both males and females and increased incidences of hepatocellular adenomas were observed in female rats at a dosage of 18 mg/kg/day.

(b) (4) conducted studies to address the reproductive and developmental toxicity of pilocarpine hydrochloride on fertility, embryofetal development, and peri- and postnatal development. Impaired reproductive function was observed in male and female rats administered 18 mg/kg/day via oral gavage, including reduced fertility, decreased sperm motility, and morphologic evidence of abnormal sperm. In a teratology study, pregnant Sprague Dawley rats were dosed between gestational days 6 through 15 with 0, 7.5, 26, or 90 mg/kg/day pilocarpine hydrochloride. Fetal observations included, reduction in mean fetal body weight and increased incidence of skeletal variations at the 90 mg/kg/day pilocarpine hydrochloride dose. Reduced ossification and increased incidence of rudimentary fourteenth ribs were observed more frequently in fetuses from the 90 mg/kg/day group compared to controls. In another study, pregnant rats were dosed during gestation and lactation with up to 36 mg/kg/day pilocarpine hydrochloride via oral gavage. At 18 mg/kg/day, increased still births, decreased neonatal survival, and reduced mean fetal body weight were observed. In the proposed label by the sponsor, the dose level 18 mg/kg/day in this study was misquoted as 10

mg/kg/day. The error has been corrected in the Suggested Label in Executive Summary.

The findings of genetic toxicology, carcinogenicity, and reproductive and developmental toxicology for pilocarpine have been appropriately described in the labeling for Salagen. The proposed label for Isopto Carpine by the sponsor is similar to that for Salagen.

The proposed clinical dose of Isopto Carpine 1%, 2% and 4% is 1 drop in each eye up to four times daily. Given 43 μ L as a drop, each drop of Isopto Carpine contains approximately 1.7 mg pilocarpine hydrochloride. Therefore, the maximum daily dose of 4% (40 mg/mL) Isopto Carpine is 1.7 mg X 1 drop/eye x 2 eyes x 4 times/day = 13.6 mg/day (per person). In a 70 kg body weight person, the daily ocular dose of pilocarpine hydrochloride will be 0.2 mg/kg/day. This figure will be used in calculating the multiples of animal dose to MROHD (maximum recommended ophthalmic human dose) in the label.

The previous calculations were based on the sponsor's response to a query on the origin of the figures. Thus, the final ratios of animal doses to human doses on a body weight basis are as follows:

For pregnancy data:

Rat #1: 90 mg/kg / 0.2 mg/kg = 450

Rat #2: 36 mg/kg / 0.2 mg/kg = 180

Rabbit: 18 mg/kg / 0.2 mg/kg = 90

For carcinogenicity:

Mice: 30 mg/kg / 0.2 mg/kg = 150

Rats; 18 mg/kg / 0.2 mg/kg = 90

For Seg I:

Rats: 18 mg/kg / 0.2 mg/kg = 90

Dog: 3 mg/kg / 0.2 mg/kg = 15

12 Appendix/Attachments

NDA 18-796 (Pilopine HS Ophthalmic Gel, pilocarpine hydrochloride ophthalmic solution 4%, approved 10/01/1984, Alcon), NDA 20-619 (Betoptic Pilo, betaxolol hydrochloride 0.25%/pilocarpine hydrochloride 1.75%, approved 04/17/1997, Alcon), NDA 20-237 (Salagen, pilocarpine hydrochloride 5 mg and 7.5 mg tablet, approved 03/22/1994, Eisai).

| 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/

CONRAD H CHEN
05/17/2010

WENDELYN J SCHMIDT
05/17/2010

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA Number: 200890

Applicant: Alcon Research, Ltd.

Stamp Date: December 22,
2009

Drug Name: Isopto® Carpine
(pilocarpine hydrochloride
ophthalmic solution) 1%, 2% and
4%

IS THE PHARM/TOX SECTION OF THE APPLICATION FILABLE? Yes [X] No []

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

| | Parameters | Yes | No | Comment |
|----|--|-----|----|---|
| 1 | On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review to begin? | X | | |
| 2 | Is the Pharmacology/Toxicology section of the NDA indexed and paginated in a manner to allow substantive review begin? | X | | |
| 3 | On its face, is the Pharmacology/Toxicology section of the NDA legible so that substantive review can begin? | X | | |
| 4 | Are ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? | X | | |
| 5 | If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required? | X | | The drug formulation to be marketed was used in the animal toxicity studies. The inactive ingredients in the formulation are USP/NF compendial products and are used in the FDA approved ocular products. |
| 6 | Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in mg/m ² or comparative serum/plasma levels) and in accordance with 201.57? | X | | The human ocular dose multiples (to animal doses) were based on mg/kg/day. |
| 7 | Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions? | X | | There was no request made. |
| 8 | On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route? | X | | |
| 9 | Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? | X | | One pivotal GLP toxicity study was conducted. |
| 10 | Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? | X | | |
| 11 | From a pharmacology perspective, is this NDA fileable? | X | | |

Note: The NDA filing meeting is on 1-25-2010

Reviewing Pharmacologist:

Conrad Chen, Ph.D.

Date: 1-21-2010

Team Leader:

Wendelyn Schmidt, Ph.D.

Date

| 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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CONRAD H CHEN
01/22/2010

WENDELYN J SCHMIDT
01/22/2010