CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200-890

CHEMISTRY REVIEW(S)

NDA 200-890

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

Applicant: Alcon Research, Ltd.

Rao V. Kambhampati, Ph.D.
Senior Regulatory Review Scientist
Branch V
Division of Pre-Marketing Assessment II
ONDQA

CMC Review #2 for Division of Antiinfective and Ophthalmic Products

Table of Contents

Chemistry Review Data Sheet

1. NDA **200-890**
2. REVIEW #: 2
3. REVIEW DATE: 6-18-2010
4. REVIEWER: **Rao V. Kambhampati, Ph.D.**
5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	EDR Entry Date
Original 0000	11-23-09
Amendment 0001	11-23-09
Amendment 0002	1-21-10
Amendment 0003	2-19-10
Amendment 0004	2-8-10
Amendment 0005	3-17-10
Amendment 0006	4-16-10
Amendment 0008	5-26-10
Amendment 0009	6-16-10
Amendment 0010	6-17-10

7. NAME & ADDRESS OF APPLICANT:

Name:	Alcon Research, Ltd.
Address:	6201 South Freeway Forth Worth, TX 76134-2099
Representative:	Same as applicant
Telephone:	817-551-8120

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Isopto® Carpine
b) Non-Proprietary Name: pilocarpine hydrochloride ophthalmic solution

c) Code Name/#: AL-2910 Ophthalmic Solution
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Type 505 (b)(2)

10. PHARMACOL. CATEGORY: Alkaloid

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 1% (10 mg/mL), 2% (20 mg/mL), and 4% (40 mg/mL) of pilocarpine hydrochloride.

13. ROUTE OF ADMINISTRATION: topical ocular

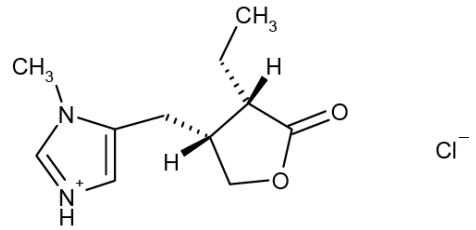
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, & MOLECULAR WEIGHT OF DRUG SUBSTANCE:

Chemical Name:
i) 3-Ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)-methyl]-2(3*H*)-furanone hydrochloride
or
ii) 2(3*H*)-Furanone, 3-ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)-methyl]-monohydrochloride, (3S-cis)-
Established Name: Pilocarpine hydrochloride (USAN, USP, Ph Eur)
Code Number/Name: AL-2910
Structural Formula:



Molecular Formula: $C_{11}H_{16}N_2O_2 \cdot HCl$

Molecular Weight: 244.72

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF Number	Holder	Description	Status	Comment
[redacted] (b) (4)			Adequate	Review #3, 6/16/10 (Rao Kambhampati, Ph.D., ONDQA). Review #2, 12-20-96 (Allan Fenselau, Ph.D., ONDQA).
			Adequate	Information in NDA is sufficient (see Denise Miller's Product Quality Microbiology Review in DARRTS, 5-10-10)
			Adequate	Information in NDA is sufficient (see Denise Miller's Product Quality Microbiology Review in DARRTS, 5-10-10
			Adequate	Information in NDA is sufficient; Rao Kambhampati
			Adequate	Information in NDA is sufficient; Rao Kambhampati

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Initial Quality Assessment (IQA)	200-890	Reviewed by PAL, Linda Ng, Ph.D., see her review in DARRTS.
Product Microbiology Review	200-890	Reviewed by Denise Miller, Ph.D., see her review in DARRTS. Recommendation: Acceptable.
Chemistry Review #3	DMF (b) (4) (Pilocarpine Hydrochloride USP)	Reviewed by Rao V. Kambhampati, see his review in DARRTS. Recommendation Adequate.
E-Mail Communication between ONDQA PM and Alcon on 5/13/10	200-890	Entered in DARRTS by Jeannie David, M.S., ONDQA PM

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Evaluation	Acceptable	6/16/10	E. Johnson (HFD-320, DMPQ, OC)
Product Microbiology	Acceptable	5/10/10	Denise Miller, Ph.D. (Product Microbiology Staff, OPS)
LNC	N/A (Pre-38 drug; USP Monograph)	5/13/10	Rao V. Kambhampati, Ph.D.
Proprietary Name Review	Acceptable	3/22/10	Judy Park, Carlos Mena-Grillasca, and Carol Holquist (DMEPA)
Methods Validation	Not submitted to FDA Lab per current ONDQA Policy	5/13/10	Rao V. Kambhampati, Ph.D.
EA	Categorical exclusion request acceptable	5/13/10	Rao V. Kambhampati, Ph.D.
Labeling and Container Labels	Acceptable	6/16/10	DAIOP

The Chemistry Review for NDA 200-890

Note: This is the updated final Executive Summary for this NDA

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA #200-890 provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product, therefore, from the CMC perspective this NDA is recommended for approval. The following packaging configuration was provided in the NDA:

15 mL size DROP-TAINER® package system containing 15-mL of 1%, 2%, or 4% strength pilocarpine hydrochloride ophthalmic solution per bottle. The recommended storage condition is store at 15º to 25ºC (59º to 77ºF) and protect from freezing.

1%: **NDC** 0998-0203-15
2%: **NDC** 0998-0204-15
4%: **NDC** 0998-0206-15

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Substances and Drug Product

Introduction: This is a 505 (b)(2) NDA for a pre-38 drug. The applicant received priority review status for this NDA because the drug product fulfills the unmet medical need. The active component of Isopto® Carpine is pilocarpine hydrochloride, which is a muscarinic cholinergic agonist. Isopto Carpine (pilocarpine hydrochloride ophthalmic solution) is a sterile, benzalkonium-preserved ophthalmic solution containing 1%, 2% or 4% of pilocarpine hydrochloride.

Isopto Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2% and 4%, sterile topical ophthalmic drops are intended for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Isopto Carpine 1%, 2% and 4% also may be used for the treatment of acute angle-closure glaucoma, as a prophylaxis for (b) (4)

post-operative elevated IOP associated with (b) (4) surgery, and (b) (4) (b) (4) as a potent miotic.

Drug Substance: The proposed drug product contains pilocarpine hydrochloride USP as the active pharmaceutical ingredient (API). Pilocarpine is an alkaloid obtained from Jaborandi leaves (*Pilocarpus microphyllus*). The CMC information for the API was cross-referenced to (b) (4) which was reviewed previously and found to be adequate (12/20/96) by Allan Fenselau, Ph.D. (Chemist, ONDQA). Since then an amendment and annual reports were submitted to this DMF and they were reviewed by this reviewer and the DMF is still adequate. On the basis of DMF Holder's drug substance specification, Alcon initially proposed an acceptance criterion (AC) of NMT (b) (4) content in the NDA drug substance specification. However, since the drug product will be used as an ophthalmic, Alcon was asked to tighten the AC for (b) (4). Initially Alcon was unable to tighten the AC because of disagreement with (b) (4). Therefore, we negotiated with (b) (4) directly and in the 6/14/10 teleconference, (b) (4) agreed to tighten the AC to (b) (4), which is acceptable to us. Pilocarpine hydrochloride is manufactured by (b) (4) (b) (4) and supplied to the Applicant. Alcon also conducts testing of the drug substance and their specification was provided in the NDA. The initially proposed specification did not include microbial limits test, however, upon comment the applicant agreed to include it in the specification indicating that the test is performed by (b) (4) and the results are obtained from (b) (4) Batch analysis results were provided for three batches and the assay values ranged from (b) (4) by the titration method. The total impurities content was (b) (4) It was demonstrated that the drug substance can be manufactured with consistent quality and purity. In the batch analysis table, the impurities were shown as NMT of a certain percentage, however, (b) (4) contained the actual percentages, therefore, the applicant was asked to include the actually observed values in the batch analysis table. In the e-mail communication (5/13/10) and later in the amendment dated 5/26/10, the applicant provided revised batch analysis tables containing the actually observed values. The drug substance is packaged in sealed (b) (4) bags and then placed in (b) (4) drums and closed with LDPE caps. Based on the (b) (4) stability studies on three batches at 30±2ºC and 75±5% humidity, the applicant assigned a shelf-life of (b) (4) for the drug substance.

Drug Product:
The proposed drug product, Isopto® Carpine (pilocarpine hydrochloride ophthalmic solution) is a sterile, preserved ophthalmic solution containing either 1% (10 mg/mL), 2% (20 mg/mL), or 4% (40 mg/mL) of pilocarpine hydrochloride as the active ingredient. It is manufactured at the Applicant's facility in Forth Worth, TX. The drug product is packaged in a plastic bottle with a plastic dispensing plug and plastic closure. The excipients include boric acid, sodium chloride (1% strength only), sodium citrate, dihydrate, benzalkonium chloride (preservative), hypromellose 2910 (HPMC), hydrochloric acid and/or sodium hydroxide (for pH adjustment), and purified water. The API is USP grade and all excipients are USP/NF grade. The proportions of the excipients (boric acid, sodium chloride, and sodium citrate, dihydrate) in the three strengths are slightly different. The applicant initially requested an overage of (b) (4) for the all three strengths. However, upon comment, the (b) (4) overage was withdrawn for the 1% strength, and adequate justification for 2% and 4% strengths was provided in the e-mail communication dated 5-13-10 and later in the amendment dated 5/26/10. Since this product has been marketed for several years, the applicant did not conduct much pharmaceutical development. The manufacturing process consists of (b) (4)

(b) (4) The batch formula was provided for the full production scale batch of (b) (4) The drug product specification included identity by HPLC and TLC, assay by HPLC, impurities by HPLC, benzalkonium chloride (preservative) identity and assay by HPLC, pH, osmolality, color, clarity, viscosity, particulate matter, bacterial endotoxins, and sterility. Upon comment, the acceptance criteria for impurities were tightened for (b) (4) and total impurities. Adequate description was provided for the Alcon analytical procedures and the particulate matter test is conducted as according to USP <789>. Analytical method validation reports were provided for pilocarpine hydrochloride identity, assay, and degradation products by HPLC method, identity by TLC method, benzalkonium chloride identity and assay by HPLC method, bacterial endotoxins, sterility, and antimicrobial effectiveness methods. The reports are acceptable. Batch analyses results were provided for three batches for each strength. The data demonstrated that the drug product can be manufactured with consistent quality and purity. The assay values ranged from (b) (4) and the total impurities content ranged from (b) (4) Stability study results were provided for three batches of all three strengths. The studies were conducted in the proposed commercial container/closure at 25ºC/40%RH. Stability data for 36 months were provided for two batches and 24 months data were provided for one batch. There was no significant change in the assay values. However, there was an increase of (b) (4) , and total impurities. According to the literature, this drug product is expected to produce these impurities upon storage. All results are within the proposed specification for the drug product. Based on the real time stability data, the proposed expiration dating period of 36 months is acceptable. The applicant requested a storage condition of (b) (4) however, since no stability data were provided for the refrigerated condition, the applicant was asked to change the storage condition to 15º-25ºC with protection from freezing. Since the stability data contained testing points for 12, 24, and 36 months only, the applicant was also asked to study the next three annual commercial batches using the ICH recommended testing points.

B. Description of How the Drug Product is Intended to be Used

In the revised package insert (6/15/10), it was stated that the Isopto® Carpine is a muscarinic cholinergic agonist indicated for the following: i) The reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension; ii) The management of acute angle-closure glaucoma; iii) The prevention of postoperative elevated IOP associated with laser surgery; and iv) The induction of miosis. The drug product is manufactured in three strengths, 1% (10 mg/mL), 2% (20 mg/mL), and 4% (40 mg/mL) of pilocarpine hydrochloride. One drop of the solution is instilled in the eye (s) up to four times daily. Isopto® Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2% and 4% is supplied sterile in 15 mL natural LDPE plastic ophthalmic DROP-TAINER® dispensers containing 15 mL of the solution with appropriate color-coding (green LDPE tips and green polypropylene caps).

It is stored at 15º to 25ºC (59º to 77ºF) and protected from freezing.

C. Basis for Approvability or Not-Approval Recommendation

The applicant proposed to use the drug substance (pilocarpine hydrochloride USP) from the same source (b) (4)) which is supplying the same drug substance for the manufacturing of (b) (4) The drug substance is manufactured according to the process in the DMF (b) (4) which has been reviewed and found to be adequate. It was demonstrated that the drug product solution can be manufactured and packaged with

consistent quality and purity and it can be stored at 25ºC. Adequate in-process controls are in place during various stages of the manufacturing and packaging processes. The review of the NDA from product quality microbiology stand point is acceptable. The drug substance manufacturing facility (b) (4) the drug product manufacturing and packaging facility (Alcon, Ft. Worth, TX), and the testing facilities are acceptable and an Overall Acceptable Recommendation was issued by the Office of Compliance. The trademark, Isopto® Carpine, was found to be acceptable by DMEPA. Per current ONDQA policy, this drug product does not require analytical method validation by the FDA laboratory. The applicant satisfactorily addressed all the comments and recommendations in the IR letters dated 3/19/10, 5/7/10, and 5/25/10. The draft responses to the 5/7/10 IR letter were initially provided by e-mail communication to the ONDQA Project Manager and later the final responses were provided in the 5/25/10 amendment. Comments on the draft package insert and container and carton labels were communicated to the clinical reviewer (William Boyd, M.D., DAIOP) and the revised PI and container/carton labels (6/15/10) contained the suggested changes. Categorical exclusion from the requirement from preparing EA for the NDA for the proposed drug product is acceptable because the drug has already been marketed in the US for over 40 years, therefore, it will not increase the use of active moiety if this NDA is approved. Therefore, from the CMC stand point this NDA #200-890 is recommended for approval.

III. Administrative

A. Primary Reviewer:

Rao V. Kambhampati, Ph.D.
Senior Regulatory Review Scientist
Branch V, DPA II, ONDQA, OPS

B. Secondary Reviewer:

Stephen P. Miller, Ph.D.
Acting Chief, Branch V, DPA II, ONDQA, OPS

84 Pages has been withheld in full immediately following this page as B4 (CCI/TS)

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

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

/s/

RAO V KAMBHAMPATI
06/18/2010

STEPHEN P MILLER
06/18/2010
I concur - approval of this NDA is recommended from the CMC perspective

NDA 200-890

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

Applicant: Alcon Research, Ltd.

Rao V. Kambhampati, Ph.D.
Senior Regulatory Review Scientist
Branch IV
Division of Pre-Marketing Assessment II
ONDQA

CMC Review #1 for Division of Antiinfective and Ophthalmic Products

Table of Contents

Chemistry Review Data Sheet

1. NDA **200-890**

2. REVIEW #: 1

3. REVIEW DATE: 5-14-2010

4. REVIEWER: **Rao V. Kambhampati, Ph.D.**

4. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

4. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	eCTD Entry Date	EDR Date
Original 0000	11-23-09	
Amendment 0001	11-23-09	
Amendment 0002	1-21-10	
Amendment 0003	2-19-10	
Amendment 0004	2-8-10	
Amendment 0005	3-17-10	
Amendment 0006	4-16-10	
E-Mail Communication between ONDQA PM and Alcon	5-13-10	

7. NAME & ADDRESS OF APPLICANT:

Name:	Alcon Research, Ltd.
Address:	6201 South Freeway Forth Worth, TX 76134-2099
Representative:	Same as applicant
Telephone:	817-551-8120

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Isopto® Carpine
b) Non-Proprietary Name: pilocarpine hydrochloride ophthalmic solution

c) Code Name/#: AL-2910 Ophthalmic Solution
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Type 505 (b)(2)

10. PHARMACOL. CATEGORY: Alkaloid

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 1%, 2%, and 4%

13. ROUTE OF ADMINISTRATION: topical ocular

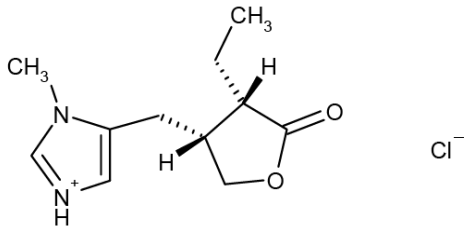
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
___X___SPOTS product – Form Completed Yes

_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:
i) 3-Ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)-methyl]-2(3*H*)-furanone hydrochloride
or
ii) 2(3*H*)-Furanone, 3-ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)-methyl]-monohydrochloride, (3S-cis)-
Established Name: Pilocarpine hydrochloride (USAN, USP, Ph Eur)
Code Number/Name: AL-2910
Structural Formula:



Molecular Formula: $C_{11}H_{16}N_2O_2 \cdot HCl$

Molecular Weight: 244.72

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF Number	Holder	Description	Status	Comment
[redacted] (b) (4)			Adequate	Reviewed by Allan Fenselau, Ph.D. (ONDQA). Minor amendments were submitted afterwards and they are acceptable; Rao Kambhampati.
			Adequate	Information in NDA is sufficient (see Denise Miller, Product Quality Microbiology Review in DARRTS, 5-10-10)
			Adequate	Information in NDA is sufficient (see Denise Miller, Product Quality Microbiology Review in DARRTS, 5-10-10
			Adequate	Information in NDA is sufficient; Rao Kambhampati
			Adequate	Information in NDA is sufficient; Rao Kambhampati

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Initial Quality Assessment (IQA)	200-890	Reviewed by PAL, Linda Ng, Ph.D., see her review in DARRTS.
Product Microbiology Review	200-890	Reviewed by Denise Miller, Ph.D., see her review in DARRTS. Recommendation: Acceptable.

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Evaluation	Pending	5/13/10	(HFD-320, DMPQ, OC)
Product Microbiology	Acceptable	5/10/10	Denise Miller, Ph.D. (Product

			Microbiology Staff, OPS)
LNC	N/A (Pre-38 drug; USP Monograph)	5/13/10	Rao V. Kambhampati, Ph.D.
Proprietary Name Review	Acceptable	3/22/10	Judy Park, Carlos Mena-Grillasca, and Carol Holquist (DMEPA)
Methods Validation	Not submitted to FDA Lab per current ONDQA Policy	5/13/10	Rao V. Kambhampati, Ph.D.
EA	Categorical exclusion request acceptable	5/13/10	Rao V. Kambhampati, Ph.D.
Labeling and Container Labels	Pending	5/13/10	DAIOP

The Chemistry Review for NDA 200-890

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

At this point, this NDA did not provide sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The following issues need to be resolved:

- Package Insert and Container and Carton labeling
- Overall site recommendation from the Office of Compliance
- Tightening of the acceptance criterion for (b) (4) content in the drug substance specification from the current (b) (4)

Therefore, from the CMC perspective, this NDA is not recommended for approval as of this date. The following packaging configuration was provided in the NDA:

15 mL size DROP-TAINER® package system containing 15-mL of 1%, 2%, or 4% strength pilocarpine hydrochloride ophthalmic solution per bottle.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Substances and Drug Product

Introduction: This is a 505 (b)(2) NDA for a pre-38 drug. The applicant received priority review status for this NDA because the drug product fulfills the unmet medical need. The active component of Isopto® Carpine is pilocarpine hydrochloride, which is a muscarinic cholinergic agonist. Isopto Carpine (pilocarpine hydrochloride ophthalmic solution) is a sterile, benzalkonium-preserved ophthalmic solution containing 1%, 2% or 4% of pilocarpine hydrochloride.

Isopto Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2% and 4%, sterile topical ophthalmic drops are intended for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Isopto Carpine 1%, 2% and 4% also may be used for the treatment of acute angle-closure glaucoma, as a prophylaxis for (b) (4) post-operative elevated IOP associated with (b) (4) surgery, and (b) (4) (b) (4) as a potent miotic.

Drug Substance: The proposed drug product contains pilocarpine hydrochloride as the pharmaceutical active ingredient (PAI). The CMC information for the API was cross-referenced to the DMF (b) (4) which was reviewed by Allan Fenselau, Ph.D. (Chemist, ONDQA) and determined to be acceptable. The applicant also provided some CMC information directly in the NDA. Pilocarpine is an alkaloid obtained from Jaborandi leaves (*Pilocarpusmicrophyllus*). It is manufactured by (b) (4) and supplied to the Applicant. Alcon also conducts testing of the drug substance and their specification was provided in the NDA. The initially proposed specification did not include microbial limits test, however, upon comment the applicant agreed to include it in the specification indicating that the test is performed by (b) (4) and the results are obtained from (b) (4). Since the drug substance is used for the formulation of ophthalmic solution, the Applicant was asked to tighten the (b) (4) acceptance criterion from the current NMT (b) (4) (reported batches range from NMT (b) (4) (b) (4)). Batch analysis results were provided for three batches and the assay values ranged from (b) (4) by the titration method. The total impurities content was (b) (4) It was demonstrated that the drug substance can be manufactured with consistent quality and purity. In the batch analysis table the impurities were shown as NMT of a certain percentage, however, (b) (4) contained the actual percentages, therefore, the applicant was asked to include the actually observed values in the batch analysis table. In the e-mail (5/13/10) communication, the applicant provided revised batch analysis tables containing the actually observed values. The drug substance is packaged in sealed (b) (4) bags and then placed in (b) (4) drums and closed with LDPE caps. Based on the (b) (4) stability studies on three batches at 30±2ºC and 75±5% humidity, the applicant assigned a shelf-life of (b) (4) for the drug substance which is adequately supported by the data.

Drug Product:
The proposed drug product, Isopto® Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2% and 4% is a sterile, preserved ophthalmic solution containing either 1%, 2% or 4% of pilocarpine hydrochloride as the active ingredient. It is manufactured at Applicant's facility in Forth Worth, TX. The drug product is packaged in a plastic bottle with a plastic dispensing plug and plastic closure. The excipients include boric acid, sodium chloride (1% strength only), sodium citrate, dihydrate, benzalkonium chloride (preservative), hypromellose 2910 (HPMC), hydrochloric acid and/or sodium hydroxide (for pH adjustment), and purified water. The API is USP grade and all excipients are USP/NF grade. The proportions of the excipients (boric acid, sodium chloride, and sodium citrate, dihydrate) in the three strengths are slightly different. The applicant initially requested an overage of (b) (4) for the API, however, upon comment, the (b) (4) overage was requested for the 2% and 4% strengths only by providing adequate justification in the e-mail communication dated 5-13-10. Since this product has been marketed for several years, the applicant did not conduct much pharmaceutical development. The manufacturing process consists of (b) (4) The batch formula was provided for the full production scale batch of (b) (4) The drug product specification included identity by HPLC and TLC, assay by HPLC, impurities by HPLC, benzalkonium chloride (preservative) identity and assay by HPLC, pH, osmolality, color, clarity, viscosity, particulate matter, bacterial endotoxins, and sterility. Upon comment, the acceptance criteria for impurities were tightened for (b) (4), and total impurities but the applicant stated that (b) (4) acceptance criterion cannot be tightened at this point because it is same as for the drug substance. Adequate description was provided for the all Alcon analytical procedures and the particulate matter test is conducted as

according to USP <789>. Analytical methods validation reports were provided for pilocarpine hydrochloride identity, assay, and degradation products by HPLC method, identity by TLC method, benzalkonium chloride identity and assay by HPLC method, bacterial endotoxins, sterility, and antimicrobial effectiveness methods. The reports are acceptable. Batch analyses results were provided for three batches for each strength. The data demonstrated that the drug product can be manufactured with consistent quality and purity. Initial batch analysis results did not contain the actually observed results for the impurities, however, upon comment they were incorporated in the revised batch analysis tables. The assay values ranged from (b) (4) and the total impurities content ranged from (b) (4) Stability study results were provided for three batches of all three strengths. The studies were conducted in the proposed commercial container/closure at 25ºC/40%RH. Stability data for 36 months were provided for two batches and 24 months data were provided for one batch. There was no significant change in the assay values. However, there was an increase of (b) (4), and total impurities. According to the literature, this drug product is expected to produce these impurities upon storage. All results are within the proposed specification for the drug product. Based on the real time stability data, the proposed expiration dating period of 36 months is acceptable. The applicant requested a storage condition of (b) (4) however, since no stability data were provided for the refrigerated condition, the applicant was asked to change the storage condition to 15º-25ºC with protection from freezing. Since the stability data contained testing points for 12, 24, and 36 months only, the applicant was also asked to study the next three annual commercial batches using the ICH recommended testing points.

B. Description of How the Drug Product is Intended to be Used

Isopto® Carpine is a muscarinic cholinergic agonist indicated for the following: i) open-angle glaucoma or ocular hypertension; ii) acute angle-closure glaucoma; iii) prevention of (b) (4) postoperative elevated IOP; and iv) induction of miosis. The drug product is manufactured in three strengths, 1%, 2%, and 4% and each mL of these solutions contains 10 mg, 20 mg, and 40 mg of pilocarpine hydrochloride, respectively. One to two drops of the solution is instilled in the eye (s) up to four times daily. Isopto® Carpine (pilocarpine hydrochloride ophthalmic solution) 1%, 2% and 4% is supplied sterile in 15 mL natural LDPE plastic ophthalmic DROP-TAINER® dispensers containing 15 mL of the solution with green LDPE tips and green polypropylene caps as follows:

1%: **NDC** 0998-0203-15
2%: **NDC** 0998-0204-15
4%: **NDC** 0998-0206-15

It is stored at 15º to 25ºC (59º to 77ºF) and protected from freezing.

C. Basis for Approvability or Not-Approval Recommendation

The applicant proposed to use the drug substance (pilocarpine hydrochloride) from the same source (b) (4) which is supplying the same drug substance for the manufacturing of (b) (4). The drug substance is manufactured as according to the process in the DMF (b) (4) which was reviewed previously by the FDA chemist and found to be adequate. It was demonstrated that the drug product solution can be manufactured and packaged with consistent quality and purity and it can be stored at 25ºC. Adequate in-process controls are in place during various stages of the manufacturing and packaging processes. The review of the NDA from product quality microbiology stand point is acceptable. The

inspection status of the drug substance manufacturing facility (b) (4) is pending and the drug product manufacturing and packaging facility (Alcon, Ft. Worth, TX) was found to be acceptable on the basis of the file review by the OC. The trademark, Isopto® Carpine, was found to be acceptable by DMEPA. Per current ONDQA policy, this drug product does not require analytical method validation by the FDA laboratory. The applicant satisfactorily addressed all the comments and recommendations in the IR letters dated 3/19/10 and 5/7/10 except tightening of the (b) (4) content in the drug substance specification. The responses to the 5/7/10 IR letter were provided by e-mail communication to the ONDQA Project Manager. Comments on the draft package insert and container and carton labels were communicated to the clinical reviewer (William Boyd, M.D., DAIOP). Per DIAOP's practice, comments from all disciplines will be incorporated in the draft labeling documents and then they will be communicated to the applicant for their incorporation in the final labeling documents. Therefore, the package insert and container and carton labels are pending as of this date. Categorical exclusion from the requirement of preparing EA for the NDA for the proposed drug product is acceptable because the drug has already been marketed in US for over 40 years, therefore, it will not increase the use of active moiety if this NDA is approved. Because of the pending CMC, inspectional, and labeling issues, this NDA cannot be approved at this time.

III. Administrative

A. Primary Reviewer:

Rao V. Kambhampati, Ph.D.
Senior Regulatory Review Scientist
Branch IV, DPA II, ONDQA, OPS

B. Secondary Reviewer:

Stephen P. Miller, Ph.D.
Acting Chief, Branch IV, DPA II, ONDQA, OPS

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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/

RAO V KAMBHAMPATI
05/14/2010

STEPHEN P MILLER
05/14/2010
I concur - from the CMC perspective we cannot recommend approval at this time

Initial Quality Assessment
Branch __IV__
Pre-Marketing Assessment Division __II__

OND Division:	Division of Anti-Infective and Ophthalmology Produ
NDA:	200-890
Applicant:	Alcon Research Ltd
Stamp Date:	December 22, 2009
PDUFA Date:	June 22, 2010
Trademark:	Isopto Carpine
Established Name:	(pilocarpine hydrochloride ophthalmic solution) 1%, 2% and 4%
Dosage Form:	Ophthalmic Solution
Route of Administration:	Topical
Indication:	Treatment of various IOP indications
PAL:	Linda Ng, Ph.D.

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☒

Summary and Critical Issues:

Summary

This NDA, 3S, dated December 22, 2009, is an ophthalmic solution compared to the approved ophthalmic gel 4% in NDA 18-796. The product is a self preserved multi-use ophthalmic solution in 3 strengths for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension, (b) (4) for acute angle-closure glaucoma, for the prevention of (b) (4) postoperative elevated IOP associated with (b) (4) laser surgery, and (b) (4) (b) (4) as a potent miotic. This is a 505(b) (b) (4) NDA, submitted in eCTD format and was accepted for priority review. The trade name is the same as the one marketed in the US without approval.

A microbiology consult was submitted by the OND PM, Lori Gorski and Dr. Denise Miller was assigned. The trade name consult was sent directly from the applicant to OSE. The EES evaluation was performed by ONDQA PM Jeannie David who confirmed sites with the applicant and finalized the request with the CMC reviewer Rao Kambhampati.

The drug substance, pilocarpine hydrochloride is manufactured by (b) (4) (b) (4) Pilocarpine is an alkaloid extracted from Jaboradni leaves (*Pilocarpus microphyllus*) and acidified. An LOA dated December 8, 2009 was submitted, referencing the synthesis, controls and stability information to DMF (b) (4). The drug substance and drug product USP monographs are available. Information is also available in *Analytical Profiles of Drug Substances and Excipients.* The applicant claims that Pilocarpine has been marketed for more

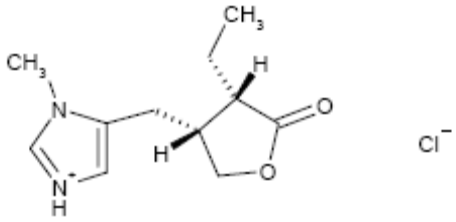
than 50 years in the US. The compound is claimed to be very stable with a retest period of (b) (4) proposed.

The drug product has (b) (4) a preservative. (b) (4) in the stability of the product. Thus the product is maintained at pH range of 3.5 to 5.5. The product is manufactured, packaged, labeled, release and stability tested at Alcon's ASPEX facility in Fort Worth, Texas.

The drug product is stored in Alcon's natural LDPE 'Drop-tainer" bottle, green LDPE plug, and a green polypropylene cap with pressure sensitive label and shrink band around the neck and cap. The container and plug resins are described in DMF (b) (4) and the cap resin, (b) (4) is in DMF (b) (4). (b) (4) referenced in DMF (b) (4), is the sterilization technique is used for the closures; and (b) (4) sterilization, DMF (b) (4) (b) (4), for the bottles and plugs. The trade sample is a 15 mL fill in a 15 mL bottle. No professional sample size proposed.

The batch size is claimed to be (b) (4). The stability data were generated using 3 batches at each strength, with horizontal position (claimed worst position), and (b) (4) size. For each strength, two batches for 36 months and 1 batch for 24 months data are provided. An expiry of 36 months is claimed. Product is claimed to be stored between (b) (4)

Structural Formula:



Molecular Formula:

$C_{11}H_{16}N_2O_2\,HCl$

Molecular Weight: 244.72

Critical issues for review

- This is a SPOT product and should be entered in database.
- All tests should be evaluated for meaningful conditions and criteria for both drug substance and drug product. In the drug substance specification, values should be reported instead of "NMT (b) (4) and microbial limits may need to be included. In the drug product, the endotoxin level is expressed on a per dose basis that converts to (b) (4) per mL. This is higher than products approved in the past. Micro will have to evaluate.

- Osmolality in the drug product specification is set between [redacted]. The 1% and 2% have lower upper limit. The range seems large for the 4% and reviewer should evaluate need for this wide acceptance criterion.
- In the drug product specification, any individual unspecified impurity should be set at NMT than [redacted].
- The applicant claims to monitor [redacted] as residual solvents, but the drug substance specification only indicates test for [redacted]. [redacted] is used in late stages. Reviewer should evaluate for contradiction.
- The overage is claimed to [redacted] Reviewer should evaluate need. Overage is not granted for [redacted]
- An average drop size study seems to be missing. Also not claimed is a physician sample size.
- The [redacted] information appears to be missing. Reviewer should follow up.
- Molecular formula seems to be missing in the description of the package insert. Also missing is the fill size in the How Supplied. The storage room temperature should not start at [redacted].
- The preservative effectiveness test is missing in the drug product specification. Micro should be alerted to evaluate. If a study to support the preservative, benzalkonium chloride is effective, it is acceptable to drop the preservative effectiveness test in the specification.

- Comments for 74-Day Letter

None recommended.

D. Review, Comments and Recommendation:

Acceptable for filing. Dr. Rao Kambhampati has been assigned to review this NDA.

_____Linda Ng, Ph.D._____ _____ _
Pharmaceutical Assessment Lead Date

___Stephen Miller, Ph.D._____ _____
Acting Branch Chief Date

Cc: OND PM LGorshi
ONDQA PM JDavid

Appendix 1. Composition of the Drug Product

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 NF
Purified Water				(b) (4)	USP

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

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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/

LINDA L NG
02/19/2010

STEPHEN P MILLER
02/23/2010

NDA FILEABILITY CHECKLIST

NDA Number: 200890
Applicant: Alcon Research Ltd
Letter Date: December 22, 2009
Stamp Date: December 22, 2009
Drug Name: Isopto Carpine (pilocarpine hydrochloride Ophthalmic Solution) 1, 2 and 4%

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) __Yes__

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

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	Y		
2	Is the section indexed and paginated adequately?	Y		This is an eCTD NDA
3	On its face, is the section legible?	Y		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	Y		Not complete CFN list
5	Is a statement provided that all facilities are ready for GMP inspection?	Y		In cover letter
6	Has an environmental assessment report or categorical exclusion been provided?	Y		1.12.14
7	Does the section contain controls for the drug substance?	Y		Pilocarpine HCl supplied by (b) (4) DMF (b) (4)
8	Does the section contain controls for the drug product?	Y		
9	Has stability data and analysis been provided to support the requested expiration date?	Y		Three strengths @ 1, 2 and 4%. All 15 mL fill size in 15 mL bottles. 2 batches each strength at 36 months and 1 batch each at 24 months stability RT horizontal only provided.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		N	Product marketed over 40 years in the US without approval
11	Have draft container labels been provided?	Y		Mock-up provided for all three strengths
12	Has the draft package insert been provided?	Y		
13	Has an investigational formulations section been provided?		N	Product marketed over 40 years in the US without approval
14	Is there a Methods Validation package?		N	Information found in 3.2.P.5.3
15	Is a separate microbiological section included?		N	Incorporated in the CMC section

NDA 200-890

Chemistry Reviewer: Rao Kambhampati, Ph.D.
Pharmaceutical Assessment Lead: Linda Ng, Ph.D.
Branch Chief: Stephen Miller, Ph.D.
Prepared by: LN 1/21/10

DMF Number	Holder	Description	LOA Included	Status
[redacted]	[redacted]	(b) (4)	December 8, 2009	
			May 20, 2008	
			May 11, 2009	
			November 24, 2009	
			February 15, 2008	

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/

LINDA L NG
01/22/2010

STEPHEN P MILLER
01/22/2010