CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217836Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 217836

From: Chunchun Zhang, ATL, Branch 6, OPQ/ONDP

Date: Sep 29, 2023

Re: NDA 217836, Pilocarpine hydrochloride ophthalmic solution, 0.4%

Product quality final recommendation: Approval

NDA 217836, Pilocarpine hydrochloride ophthalmic solution, 0.4% was originally recommended for Complete Response because the facilities compliance status was not acceptable, refer to IQA #1 dated Sep 1, 2023. The drug product manufacturing site, (b) (4) was initially out of compliance (pOAI) in recent PAI and surveillance inspection occurred from (b) (4), and it is found acceptable based on review of the findings from the inspection, including the firm responses and other considerations as applicable on 9/26/2023. All other facilities are found acceptable based on profile review and inspectional history. Therefore, OPMA issued an overall recommendation of "Approve" on Sep 27, 2023. All the other OPQ disciplines uphold the approval recommendation. Therefore, NDA 217836 is recommended for approval from product quality perspective.

____Chunchun Zhang, Ph.D._____
ATL for 217836

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/s/

CHUNCHUN N ZHANG
09/29/2023 11:23:04 AM

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 217836
Assessment # 1

Drug Product Name	Pilocarpine hydrochloride ophthalmic solution
Dosage Form	Solution
Strength	0.4%
Route of Administration	Topical ophthalmic
Rx/OTC Dispensed	Rx
Applicant	Orasis Pharmaceuticals, Ltd.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Dec 22, 2022	All disciplines
Quality Amendment	Feb 3, 2023	Manufacturing process
Quality Amendment	Mar 24, 2023	Facilities
Quality Amendment	Apr 13, 2023	Drug substance
Quality Amendment	May 22, 2023	Manufacturing process
Quality Amendment	Jun 14, 2023	Quality microbiology
Quality Amendment	Aug 22, 2023	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Daniel Jansen	Zhengfu Wang
Drug Product	Anne Marie Russell	Danae Christodoulou
Manufacturing	Kejun Cheng	Aditi Thakur
Microbiology	Sallie Crenshaw	John Metcalfe
Biopharmaceutics	NA	
Regulatory Business Process Manager	Shazma Aftab	
Application Technical Lead	Chunchun Zhang	

Laboratory (OTR)	NA	
Environmental	Anne Marie Russell	Danae Christodoulou

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	10/2019	
	III			NA		

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	131464	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics		NA		
Pharmacology/Toxicology		Adequate	8/15/2023	Erin Ruhland
CDRH		NA	1/13/2023	CDRH confirmed no consult is necessary.
Clinical		NA		
Other		NA		

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Satisfactory information and responses have been submitted to support the drug substance, drug product, manufacturing process, and quality microbiology aspects.

The product is regulated as a drug and device combination product per the Genus decision. However single dose (b) (4) *vials are considered low risk and CDRH confirmed that a CDRH consult is not necessary on 1/13/2023.*

The compliance status of the drug product manufacturing facility, (b) (4) (b) (4) *was determined unacceptable based on the most recent inspection performed ending* (b) (4)*. OPMA issued an overall recommendation of "Withhold" on* (b) (4) *Therefore, NDA 217836 is recommended Complete Response from Product Quality perspective.*

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

The following CR comments should be included in the Action Letter:

Facilities deficiency:

1. *Following surveillance inspection of the* (b) (4) *manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of the observations is required before this NDA may be approved.*

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product Pilocarpine hydrochloride ophthalmic solution, 0.4% is stored in 1 mL LDPE single (b) (4) *vials with a fill volume of 0.4 mL. In the proposed commercial packaging, the product is packaged as a 5-vial card in a* (b) (4) *non-sterile foil pouch.*

Proposed Indication(s) including Intended Patient Population	For treatment of presbyopia in adults
Duration of Treatment	Up to 2 drops per eye up to 2 times per day (b) (4) drops/day)

Maximum Daily Dose	(b) (4) mg; As above (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance Pilocarpine hydrochloride USP is a colorless, translucent, odorless, faintly bitter crystalline. CMC information is referenced in DMF (b) (4) which is currently adequate.

Drug Product: Adequate

Pilocarpine hydrochloride ophthalmic solution, 0.4% is a sterile, clear, colorless to slightly yellow solution. All the excipients are compendial.

The revised drug product specifications are acceptable and include the following quality attributes: appearance, identification, API assay, viscosity, particulate matter, osmolality, pH, leak test, minimum fill, impurities/degradants, and sterility. All the analytical methods are adequately validated. (b) (4) Impurities risk assessment concludes that the risk of (b) (4) content is low. Extractable/leachable studies were performed; Leached elemental impurities were present in the drug product at levels below ICH Q3D PDEs and Control Limits.

Pilocarpine hydrochloride ophthalmic solution, 0.4% is stored in 1 mL LDPE single (b) (4) vials with a fill volume of 0.4 mL. In the proposed commercial packaging, the product is packaged as a 5-vial card in a (b) (4) (b) (4), non-sterile foil pouch. The container closure system was demonstrated to be suitable for the proposed drug product and cause no safety concerns.

The applicant has submitted three drug product primary stability batches with 24 months stability data when stored at long term storage condition (5°C) and 6 months at accelerated condition (25°C/40%RH). All the quality attributes met the specifications. Photostability study indicated the drug product is sensitive to light and the foil pouch will protect from light. The in-use stability study demonstrated that the drug product is stable for 30 days at 25 °C after opening the pouch. Freeze-thaw study with three cycles were conducted to support the proposed shipping plan. Therefore, the expiration date of 24 months for commercial products is granted when stored at 2 °C to 8 °C.

The storage statement is “Store refrigerated at 36°F to 46°F (2°C to 8°C). Product may also be stored at room temperature [up to 77°F (25°C)]

for up to 30 days. Once a pouch is open, single (b) (4) vials should be used within 30 days" and will be finalized at the OND's labeling meeting.

Labeling: Adequate

Labeling recommendations from the Product Quality perspective will be communicated to the OND PM.

Manufacturing: Inadequate

The manufacturing process includes (b) (4) Several process related deficiencies are identified. The drug product facility (b) (4) was inspected in (b) (4) and was classified OAI. All the other manufacturing sites are acceptable based on the inspection history and manufacturing capability. Therefore, OPMA issued an overall recommendation of "Withhold" on (b) (4)

Biopharmaceutics: N/A

Microbiology (if applicable): Adequate

The applicant has provided adequate sterility assurance. The drug product is (b) (4)
Sterility is tested for release of finished drug product.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay (API), stability	• Formulation • Container closure • Raw materials	L	(b) (4)	L	
Impurities	• Formulation • Container closure • Process parameters • Scale/equipment	H		L	

Particulate matter	• Formulation • Container closure	L	(b) (4)	L	
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment	H		L	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

NA

4. Labeling Deficiencies

Communicate to the OND PM

5. Manufacturing Deficiencies

See the Section I

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

8. Other Deficiencies *(Specify discipline, such as Environmental)*

NA

Application Technical Lead Name and Date:

Chunchun Zhang, Ph. D., Sep 1, 2023

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R REGIONAL INFORMATION

Environmental

1.12.14.1 Claim for Categorical Exclusion

Pursuant to 21 CFR 25.31(b), Orasis Pharmaceuticals, Ltd. (Orasis) hereby claims a categorical exclusion from the requirement of an environmental assessment.

The estimated concentration of pilocarpine hydrochloride at the point of entry into the aquatic environment is estimated to be below 1 part per billion (ppb). To Orasis' knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment per 21 CFR 25.15(d).

Pilocarpine hydrochloride qualifies for this categorical exclusion because the theoretical maximum expected introduction concentration (EIC) is below 1 ppb.

Conclusion: Acceptable

Methods Validation or Verification Package: N/A

Comparability Protocols: N/A

Post-Approval Commitments: N/A

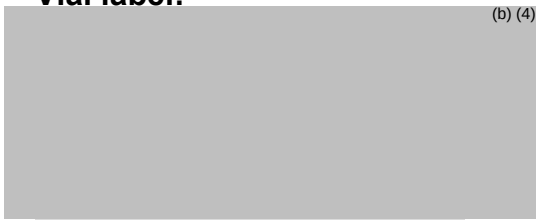
DRUG PRODUCT LIST OF DEFICIENCIES

None.

Labeling:
The submitted Prescribing Information (PI) has been reviewed and is accurate/acceptable from the quality perspective for the following sections: Highlights/Dosage Form and Strengths, Section 3 Dosage Forms and Strength, Section 11 Description, Section 16 How Supplied/Storage and Handling. No comments. At this time, OND has not finalized labeling with the sponsor, including PI, vial, container and carton.

Vial label:

(b) (4)



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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	217836
Assessment Cycle Number	MR01
Drug Product Name/Strength	Pilocarpine Hydrochloride 0.4% ophthalmic solution (Qlosi)
Route of Administration	Topical Ocular
Applicant Name	Orasis Pharmaceuticals, Ltd.
Therapeutic Classification/ OND Division	CDER/OND/OID/DAI
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Original Submission	**12/22/2022**
1111-response-to-fda-cmc-ir.pdf	**2/3/2023**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is a single (b) (4), non-preserved, sterile solution intended for the treatment of presbyopia in adults.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents:

- Microbiology Reviews of NDA (b) (4).pdf) dated 10/12/2022 and deemed adequate.

S DRUG SUBSTANCE-N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product-** A sterile, preservative-free, clear, colorless to slightly yellowish and slightly viscous solution packaged in LDPE units intended for topical administration to the eye.

Drug product composition-

(b) (4)

Table 1 CSF-1 Ophthalmic Solution Composition

Component	Concentration		Quantity per unit[1] (mg)	Function	Quality Standard
	mg/mL	% w/v			
Pilocarpine hydrochloride	4.0	0.4	1.6	Drug substance	USP
Hypromellose (b) (4)	(b) (4)				USP-NF
Sodium chloride					USP-NF
Sodium hyaluronate					Ph. Eur.
Disodium edetate[2]					USP-NF
Sodium hydroxide[3]	q.s. to target pH	q.s. to target pH	q.s. to target pH	pH adjuster	USP-NF
Hydrochloric acid[3]					USP-NF
Water for Injection (WFI)	(b) (4)				USP-NF

USP: United States Pharmacopeia; mg: milligram; mL: milliliter; NF: National Formulary; Ph. Eur.: European Pharmacopeia; q.s: *quantum satis;* w/v: weight/volume

1 Unit: is 0.4 mL ophthalmic solution per vial

2 As dihydrate

3 Used as (b) (4) solution

- **Description of container closure system-**

(b) (4)

Table 1 Description of Primary Packaging Vial Components

Component	Description	Manufacturer	Quality Standard
(b) (4)	Low-density polyethylene polymer used to form vial (b) (4)	(b) (4)	

Assessment: *Adequate*

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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