CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217064Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 217064
Assessment # 1

Drug Product Name	Phentolamine Ophthalmic solution
Dosage Form	Ophthalmic solution
Strength	0.75%
Route of Administration	Topical ophthalmic
Rx/OTC Dispensed	Rx
Applicant	Ocuphire Pharma, Inc.
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Nov 28, 2022	All disciplines
Quality Amendment	Feb 7, 2023	Drug substance, biopharmaceutics
Quality Amendment	May 8, 2023	Quality microbiology
Quality Amendment	Jun 13, 2023	Quality microbiology
Quality Amendment	Jul 17, 2023	Drug product
Quality Amendment	Jul 21, 2023	Manufacturing process
Quality Amendment	Jul 24, 2023	Drug product
Quality Amendment	Aug 4, 2023	Drug product
Quality Amendment	Aug 10, 2023	Drug product
Quality Amendment	Aug 11, 2023	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Joseph Leginus	Sithamalli Chandramouli
Drug Product	Anne Marie Russell	Danae Christodoulou
Manufacturing	Kejun Cheng	Nallaperumal Chidambaram
Microbiology	David Bateman	Laura Wasil
Biopharmaceutics	NA	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	2/15/2023	LoA dated 6/3/2022
	III			Adequate	NA	LoA dated 7/21/2021
	III			Adequate	NA	LoA dated 7/20/2022

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

Document	Application Number	Description
IND	70499	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology	Complete	Adequate	8/2/2023	Dr. Maria Rivera
CDRH	NA			
Clinical				
Other	NA			

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 217064, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product Phentolamine ophthalmic solution, 0.75%. All information requests and review issues have been addressed.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable recommendation for all the facilities on Jul 29, 2023.

The drug product is regulated as a dug device combination product per the Genus decision. CDRH confirmed that no CDRH GMP/QS consults is necessary as the single dose BFS vial is considered a low risk on Dec 6, 2022.

Therefore, NDA 217064 is recommended for approval from Product Quality perspective.

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

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Phentolamine ophthalmic solution, 0.75% is a sterile, non-preservative, aqueous solution and packaged in a 0.5 mL LDPE single-dose BFS vial with 0.31 mL fill volume.

Proposed Indication(s) including Intended Patient Population	For the treatment of pharmacologically-induced mydriasis produced by adrenergic agonists (e.g., phenylephrine) parasympatholytic (e.g., tropicamide) agents, or a combination thereof.
Duration of Treatment	One or two drops topically to the dilated eye for adults and children aged 12 years or older; One drop for children aged 3-11 years

Maximum Daily Dose	1.2 mg/day (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

Phentolamine Mesylate is a white crystalline powder. Phentolamine Mesylate has a USP monograph and the specification for the drug substance is aligned with this monograph. All the CMC information is referenced in DMF (b) (4) which is found adequate by Dr. Joseph Leginus on 2/15/2023.

Drug Product: Adequate

Phentolamine ophthalmic solution, 0.75%, is a sterile, single-dose, clear, colorless (b) (4) ophthalmic solution. All the excipients are compendial.

The revised drug product specifications are acceptable and the following quality attributes are included: appearance, ID, pH, osmolality, assay, related substances, uniformity of dosage, particulate matter, minimum fill volume, container closure integrity, and sterility. Dr. Maria Rivera confirmed on 8/2/2023 that (b) (4) at NMT (b) (4)% is qualified for the proposed short-term dosing regimen. All the analytical methods are adequately validated. Evaluation of the risk assessment of the elemental impurities was performed and indicates the results are lower than the permitted daily exposure (PDE) as noted in ICH Q3D guidance. There is one leachable (b) (4) observed at level (b) (4) ppm at 3-months at the accelerated condition. Dr. Maria Rivera confirmed on 8/2/2023 that there is minimal safety concern at a leachable level of (b) (4) ppm.
Per the agency's request, the applicant included (b) (4) with the acceptance criteria of ≤ (b) (4) ppm (LOQ) in the drug product specifications on 8/10/2023. The updated drug product specifications including (b) (4) is provided through email communications on 8/11/2023.

The commercial container closure for the proposed product is a 0.5 mL LDPE BFS single-dose vials separated into cards of 5 vials each and packaged into an aluminum foil overwrap pouch. The container closure system was demonstrated to be suitable for the proposed drug product and cause no safety concerns.

The applicant has submitted 21 months stability data at long term long term refrigerated (5°C) and accelerated condition (25°C/40%RH) conditions for the three registration batches of phentolamine ophthalmic solution in BFS vials in foil pouch. All the quality attributes met the

specifications, and no obvious trend was observed. Photostability studies indicate the product is photo sensitive. In-use stability supports that the product can be stable for (b) (4) days at room temperature after opening the pouch. There is no data to support a (b) (4) (b) (4) Therefore, an expiry of 24 months at 5°C in the container closure and a (b) (4) days In-Use period at room temperature in the open foil pouch is granted.

The storage statement is "Store at 2°C to 8°C (36°F to 46°F) and protect from freezing. After opening the foil pouch, the product should be used within (b) (4) days, not to exceed the expiration date printed on the vial. The single dose vial, once opened, (b) (4) should be discarded immediately after use." 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: Adequate

The manufacturing process for Phentolamine ophthalmic solution, 0.75% includes (b) (4) (b) (4)

OPMA has issued an overall acceptable recommendation for all the facilities based on the profile review and inspectional history on July 29, 2023.

Biopharmaceutics: N/A

NA

Microbiology (if applicable): Adequate

The manufacturing process includes (b) (4) This application is recommended for approval on the basis of product quality microbiology.

C. Risk Assessment

I. From Initial Risk Identification	Review Assessment

Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations
Sterility	Formulation Container closure Process parameters Scale/equipment Site	H		L	Post-approval stability protocol will test sterility.
Assay (API), stability	Formulation Container closure Raw materials	L	(b) (4)	L	
pH	Formulation Container closure Process parameters Scale/equipment	L		L	
Particulate matter	Formulation Container closure Process parameters Scale/equipment	M		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

NA

5. Manufacturing Deficiencies

NA

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., Aug 11, 2023

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	217064
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Phentolamine Ophthalmic solution 0.75% single-dose vial
Route of Administration	Topical ocular ophthalmic solution
Applicant Name	Ocuphire Pharma, Inc.
Therapeutic Classification/ OND Division	Division of Ophthalmology
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:
The drug product is (b) (4) blow fill seal 0.5 mL vials.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD Seq #0001	November 28, 2022
eCTD Seq #0007	May 8, 2023
eCTD Seq #0008	June 13, 2023

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

Remarks: The drug product is supplied as a solution in single-dose 0.5 mL vials.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): None

Supporting Documents: None.

P.1 Description of the Composition of the Drug Product

- **Description of drug product:** A non-preserved aqueous solution containing within a 0.5 mL single-dose blow fill seal vial intended for topical administration directly to the eye.

- **Drug product composition:**

Ingredient	Content per mL
Phentolamine Mesylate, USP	10.0 mg
Mannitol, USP	(b) (4)
Sodium acetate trihydrate, USP	
Sodium hydroxide, NF	To pH adjust to 4.5-(b) (4)
Hydrochloric acid, NF	To pH adjust to 4.5 (b) (4)
Water for injection, USP	Quantity sufficient to 1 mL

- **Description of container closure system:** (b) (4)

Adequate

Reviewer's Assessment:
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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/s/

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