CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217603Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 217603
Assessment # 1

Drug Product Name	Xdemvy (lotilaner ophthalmic solution)
Dosage Form	Ophthalmic solution
Strength	0.25%
Route of Administration	Topical ophthalmic
Rx/OTC Dispensed	Rx
Applicant	Tarsus Pharmaceuticals, Inc.
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Aug 25, 2022	All disciplines
Quality Amendment	Oct 21, 2022	Drug product, manufacturing process
Quality Amendment	Jan 4, 2023	Drug substance
Quality Amendment	Jan 11, 2023	Manufacturing process
Quality Amendment	Jan 19, 2023	Quality microbiology
Quality Amendment	Jan 24, 2023	Quality microbiology
Quality Amendment	Jan 31, 2023	Manufacturing process
Quality Amendment	May 1, 2023	Quality microbiology
Quality Amendment	May 3, 2023	Quality microbiology

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Jing Li	Sithamalli Chandramouli
Drug Product	Elise Luong	Chunchun Zhang
Manufacturing	Sureshbabu Dadiboyena	Kamal Tiwari
Microbiology	Karthik Krishnan	Laura Wasil
Biopharmaceutics	NA	NA

Regulatory Business Process Manager	Shazma Aftab	
Application Technical Lead	Chunchun Zhang	
Laboratory (OTR)	NA	
Environmental	Elise Luong	Chunchun Zhang

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Adequate	NA	LoA dated 7/16/2021
	III			Adequate	NA	LoA dated 9/22/2021
	III			Adequate	NA	LoA dated 11/23/2021
	V			Adequate	NA	LoA dated 7/19/2022

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

Document	Application Number	Description
IND	143686	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology	Complete	Adequate	11/7/2022	Dr. Muriel Saulnier
CDRH	NA			
Clinical				
Other (OLDP)	Complete	Acceptable	2/23/2023	Dr. Libaniel Rodriguez

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 217603, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product Xdemvy (lotilaner ophthalmic solution), 0.25%. 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 April 24, 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 for this product on Sep 28, 2022.

Therefore, NDA 217603 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.

Additionally, the following statement should be included in the action letter:

The comparability protocol for the drug substance and the proposed submission category of CBE-30 are acceptable. The drug product comparability protocol as provided, can be part of the Drug Substance comparability protocol, since the demonstration of equivalence is usually done as part of the Drug Substance comparability protocol.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Xdemvy (lotilaner ophthalmic solution), 0.25% is a sterile, preservative, aqueous solution and packaged in a 11 mL LDPE multi- dose (b) (4) with 10 mL fill volume and 3 mL with 1.5 mL fill volume for the physician sample.

Proposed Indication(s)	For the treatment of demodex blepharitis

including Intended Patient Population	
Duration of Treatment	One drop topically to the eye; twice daily
Maximum Daily Dose	(b) (4) mg/day (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

Lotilaner is a white to beige or brownish solid. All the CMC information including the drug substance synthesis, specifications, stability is adequate. A retest period of (b) (4) months for the Lotilaner drug substance is appropriate when stored at (b) (4) .

(b) (4)

Drug Product: Adequate

Xdemvy (lotilaner ophthalmic solution), 0.25%, is a sterile, multi-dose, slightly yellowish (b) (4) ophthalmic solution. All the excipients are compendial.

The revised drug product specifications are acceptable and the following quality attributes are included: description, ID, pH, osmolality, assay, impurities, particulate matter, minimum fill volume, antimicrobial effectiveness test, and sterility. 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.

The commercial container closure for the proposed product is a 11 mL multi-dose LDPE bottle with 10 mL fill (commercial presentation) and 3 mL multi-dose LDPE bottle with 1.5 mL fill (physician presentation). The container closure system was demonstrated to be suitable for the proposed drug product and cause no safety concerns.

The applicant has submitted 18 months stability data for the commercial 11 mL (b) (4) and 12 months data for the physician (b) (4) 3 mL at long term (25°C/40%RH) and 6 months at accelerated condition (40°C/25%RH) for three registration batches. All the quality attributes met the specifications, and no obvious trend was observed. The product is stable during the

freeze-thaw and photostability studies. No cautious statement is proposed in the labeling. Therefore, the expiration date of 24 months for the commercial presentation and 18 months for the physician presentation are granted when stored at 15 °C- 25 °C. (b) (4) , we recommend including the following statement in the labeling based on the long term stability studies: "After opening the XDEMVY bottle, it can be used until the expiration date on the bottle."

The storage statement is "Store at 15°C-25°C (59°F-77°F)." 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 (lotilaner ophthalmic solution), 0.25% includes (b) (4) A PAI inspection was performed for the drug product facility ((b) (4)) ending on (b) (4) and was classified as NAI. All the other facilities associated with the application appear acceptable to support the manufacturing of the proposed drug product based on the facilities history. OPMA has issued an overall acceptable recommendation for all the facilities on April 24, 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	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	
pH	Formulation Container closure Process parameters Scale/equipment	L	No trend on stability observed.	L	
Particulate matter	Formulation Container closure Process parameters Scale/equipment	M	Comply with USP <789>	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., May 18, 2023

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Reference ID: 5176584

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	XDEMVY™	On 03/19/22, DMEPA found the proposed proprietary name is conditionally acceptable
Established name(s)	Lotilaner	Adequate
Route(s) of administration	Topical ophthalmic use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Ophthalmic Solution, 2.5 mg/mL Each (b) (4) has 10 mL containing 25 mg lotilaner. Each drop contains (b) (4) mg lotilaner. One drop of XDEMVY in each eye twice daily (approximately 12 hours apart) for 6 weeks	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a	N/A	N/A

scored tablet, state "functionally scored"		
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

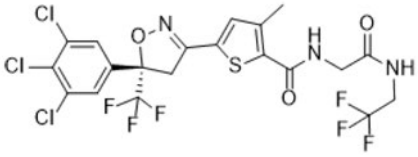
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4) [redacted]	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Solution	Adequate
Strength(s) in metric system	2.5 mg/ mL (0.25%w/v)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	XDEMVY is (b) (4) containing 2.5 mg/mL lotilaner	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary Name Established name(s)	XDEMVY™ Lotilaner	On 03/19/22, DMEPA found the proposed proprietary name is conditionally acceptable.
Dosage form(s) and route(s) of administration	Topical Ophthalmic Solution	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Edetate disodium; Hydroxypropyl methylcellulose (HPMC); Polyoxyl 35 castor oil; Glycerin; Sodium phosphate dibasic; Sodium phosphate monobasic; Water for injection	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	The drug product does not contain alcohol	N/A
Statement of being sterile (if applicable)	This product is sterile	Adequate

Pharmacological/ therapeutic class	(b) (4) .	
Chemical name, structural formula, molecular weight	 Molecular weight: 596.76 g/mol $C_{20}H_{14}Cl_3F_6N_3O_3S$	Adequate
If radioactive, statement of important nuclear characteristics	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	Section 3.2.S.1.2	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	There is no misleading statement on the labels	Adequate

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1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Solution	Adequate
Strength(s) in metric system	2.5 mg/mL (0.25%w/v)	Adequate
Available units (e.g., bottles of 100 tablets)	XDEMVY is supplied as sterile solution in low-density polyethylene (LDPE) (b) (4) bottle (11 mL) with LDPE dropper tip and high-density polyethylene (HDPE) cap.	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.)	Store at 15 °C to 25 °C (59 °F to 77 °F). (b) (4) [redacted] After opening the XDEMVY bottle, it can be used (b) (4) [redacted]. (Note, The samples used for the in-use study were from a batch aged to 10 months only.)	Adequate. Per the SPQA, Dr. ChunChun Zhang, the 18-month long-term stability study should be able to support this statement: "After opening the XDEMVY bottle, it can be used until the expiration date on the bottle." Therefore, the labeling statement is recommended to be consistent to include this statement for all NDAs and ANDAs.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 15 °C to 25 °C (59 °F to 77 °F).	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber	N/A	N/A

latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”		
Include information about child-resistant packaging	N/A	N/A

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

Assessment: There is no other sections of labeling.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Tarsus Pharmaceuticals, Inc. (b) (4) Irvine, CA 92618	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Labeling will be finalized through OND during labeling negotiations with the applicant.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Representative examples of a proposed containers)

Bottle Label (10 mL)

(b) (4)

3 Pages of Draft Labeling have been Withheld in Full as B4(CCI/ TS) Immediately Following this Page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	XDEMVY™	On 03/19/22, DMEPA found the proposed proprietary name is conditionally acceptable.
Dosage strength	2.5 mg/mL (0.25%w/v) multidose (b) (4)	Adequate
Route of administration	Topical	Adequate
Net contents (e.g., tablet count)	2.5 mg/mL (0.25%)	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	Labels contain space for NDC number	Adequate
Lot number and expiration date	Labels contains space for Lot number and expiration date	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 15°C to 25°C (59°F to 77°F).	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use).	N/A	N/A

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	The product does not contain alcohol.	Adequate
Bar code	Labels have space for bar code	Adequate

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Tarsus Pharmaceuticals, Inc., 15440 Laguna Canyon Road, Ste 160, Irvine CA 92618	Adequate
Medication Guide (if applicable)	(b) (4)	Adequate
No text on Ferrule and Cap Overseal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling:

The product labels have all the relevant information in accordance with regulatory requirements from a CMC perspective. Labeling will be finalized through OND during labeling negotiations with the applicant.

ITEMS FOR ADDITIONAL ASSESSMENT

None.

Overall Assessment and Recommendation:

The product labels are acceptable from a CMC perspective. Labeling will be finalized through OND during labeling negotiations with the applicant.

Primary Labeling Assessor Name and Date: Elise Luong, Ph.D., 04/10/23.
Secondary Assessor Name and Date (and Secondary Summary, as needed): ChunChun Zhang, Ph.D., 04/25/2023

Elise Luong

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Chunchun Zhang

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see Chapter VII (Microbiology) of the NDA IQA Guide

Product Information	
NDA Number	217603
Assessment Cycle Number	01
Drug Product Name/ Strength	XDEMVY (Lotilaner) / 0.25%
Route of Administration	Topical Ocular
Applicant Name	Tarsus Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	CDER/OND/OSM/DO
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
eCTD Seq#0001	08/25/2022
eCTD Seq#0004	10/21/2022
eCTD Seq#0009	01/19/2023
eCTD Seq#0011	01/24/2023
eCTD Seq#0013	05/01/2023
eCTD Seq#0014	05/03/2023

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

Remarks: The drug product is a topical ophthalmic indicated for treatment of demodex blepharitis and is a drug-led combination product comprised of a drug constituent and a device constituent (container-closure system or CCS). The drug product is a sterile, preserved, multi-dose ophthalmic solution that is presented in two formats: 10 mL fill volume (commercial presentation) and 1.5 mL fill volume (physician sample presentation). Each filled bottle is placed in a single unit carton. This review includes information requests sent on 01/05/2023, 04/27/2023, and 05/01/2023 as well as responses received on 01/19/2023, 01/24/2023, 05/01/2023, and 05/03/2023.

Concise Description of Outstanding Issues: None identified.

Reference ID: 5176584

Supporting Documents: None.

S DRUG SUBSTANCE

The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance is not reviewed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Section 3.2.P.1, pg. 2/3 in "description-and-composition.pdf"

Lotilaner Ophthalmic Solution, 0.25%, is a drug-led combination product comprised of a drug constituent and a device constituent (container-closure system or CCS). The drug product is a sterile, preserved, multi-dose ophthalmic solution that is presented in two formats: 10 mL fill volume (commercial presentation) and 1.5 mL fill volume (physician sample presentation). Each filled bottle is placed in a single unit carton.

Drug product composition

Component	Quantity (mg/mL)	Function
Lotilaner	2.5	Active Ingredient
Potassium Sorbate, USP	(b) (4)	Preservative
Edetate Disodium, USP		(b) (4)
Hypromellose, USP		
(b) (4)		
Glycerin, USP		
Dibasic Sodium Phosphate (b) (4), USP		
Monobasic Sodium Phosphate (b) (4), USP		
Water for Injection, USP		

Container Closure System

Section 3.2.P.7, pgs. 2-4/15 in "container-closure-system.pdf"

Component	Description	Manufacturer
Bottle (10 mL fill)	11 mL white LDPE bottle, (b) (4)	
Bottle (3 mL fill)	3 mL white LDPE bottle, (b) (4)	(b) (4)
Nozzle (10 mL fill and 3 mL fill)	Natural LDPE dropper, (b) (4)	
Cap (10 mL fill and 3 mL fill)	Tan Brown HDPE Cap, (b) (4)	

Assessment: *Adequate*

The firm provided an adequate description of the drug product's composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Laura Wasil

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/s/

CHUNCHUN N ZHANG
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