CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217469Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 217469
Assessment # 1

Drug Product Name	Vevye (cyclosporine ophthalmic solution)
Dosage Form	Solution
Strength	0.1%
Route of Administration	Topical ophthalmic
Rx/OTC Dispensed	Rx
Applicant	Novaliq GmbH
US agent, if applicable	Strategic Drug Development Services, LLC

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Aug 8, 2022	All disciplines
Quality Amendment	Oct 14, 2022	Drug substance
Quality Amendment	Dec 19, 2022	Drug product
Quality Amendment	Feb 1, 2023	Manufacturing process
Quality Amendment	Mar 10, 2023	Quality microbiology
Quality Amendment	Mar 22, 2023	Drug product
Quality Amendment	Apr 24, 2023	Quality microbiology

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Jing Li	Sithamalli Chandramouli
Drug Product	Milton Sloan	Chunchun Zhang
Manufacturing	Laurie Nelson	Sateesh Sathigari
Microbiology	Yarery Smith	Yeissa ChabrierRosello
Biopharmaceutics	NA	
Regulatory Business Process Manager	Shazma Aftab	
Application Technical Lead	Chunchun Zhang	
Laboratory (OTR)	NA	

Environmental	Milton Sloan	Chunchun Zhang

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	7/20/2022	
	III			NA		

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

Document	Application Number	Description
IND	128163	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics		NA		
Pharmacology/Toxicology		Adequate	3/7/2023	Erin Ruhland
CDRH		NA	8/16/2022	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 multi-dose vials are considered low risk and CDRH confirmed that a CDRH consult is not necessary on 8/16/2022.

The compliance status of the drug product manufacturing facility, Alliance Medical Products, Inc. (FEI: 2027189, Irvine, CA) was determined acceptable based on the most recent inspection performed ending May 5, 2023. Therefore, OPMA issued an overall recommendation of "Approval" on May 8, 2023. Therefore, NDA 217469 is recommended 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

The drug product cyclosporine ophthalmic solution, 0.1% is a non-aqueous, sterile, preservative-free solution stored in 5 mL natural polypropylene (PP) multi-dose vials with 2 mL fill volume.

Proposed Indication(s) including Intended Patient Population	For Treatment of dry eyes; each drop is (b) (4) (b) (4)
Duration of Treatment	(b) (4)
Maximum Daily Dose	
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance cyclosporine is a white to almost white powder. CMC information is referenced in DMF (b) (4) which was found adequate on 7/20/2022.

Drug Product: Adequate

Cyclosporine ophthalmic solution, 0.1% is a sterile, non-aqueous, preservative-free, clear and colorless solution. The composition contains a novel excipient perfluorobutylpentane (F4H5), and (b) (4) ethanol. The CMC information for F4H5 is provided and found adequate.

The revised drug product specifications are acceptable and include the following quality attributes: appearance, identification, visible particles, particulate matter (sub-visible), fill volume, (b) (4), cyclosporine assay, related impurities and sterility. All the analytical methods are adequately validated. Evaluation of the risk assessment of the elemental impurities showed low risk. Extractable/leachable studies were performed; three leachable impurities (b) (4) (b) (4) are detected and are monitored as part of the drug product specification.

Cyclosporine ophthalmic solution, 0.1% is packaged in a 5 mL PP multi-dose vial with 2 mL fill volume. The container closure system was demonstrated to be suitable for the proposed drug product and cause no safety concerns.

The applicant has submitted three primary stability batches (two batches were used in the phase 3 studies) for 12 months in the inverted orientation at long term 25°C/60%RH and 6 months at accelerated condition 40°C/75% RH. All the quality attributes met the specifications. The applicant conducted 4 weeks in-use stability study, however there is no concern from quality microbiology perspective and we recommend the product can be used through the expiration date. Additionally, the bottle should be always kept tightly closed and not stored neither in a refrigerator nor freezer. Therefore, the expiration date of 18 months for commercial products is granted when stored at 15 °C to 25 °C.

The storage statement is “After first opening the tamper ring of the cap remains on the bottle neck. Retain the cap and keep the bottle tightly closed when not in use. Store at 15°C to 25°C (59°F to 77°F). Do not freeze or refrigerate. BRANDNAME (Cyclosporine ophthalmic solution 0.1%) can be used until the expiration date after first opening of the bottle.” 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 includes (b) (4)

(b) (4) Several process related deficiencies are found acceptable. The drug product facility was inspected in May 2023 and was found acceptable. All the other manufacturing sites are acceptable based on the inspection history and manufacturing capability. Therefore, OPMA issued an overall recommendation of "Approval" on May 8, 2023.

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		L	
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment	H		L	

Leachables	• Formulation • Container closure	H	(b) (4)	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

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 11, 2023

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CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

Environmental

4.1. Requested approval

Novaliq GmbH is filing a NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for its product CyclASol® (0.10% of the active moiety cyclosporine A (w/v) dissolved in a vehicle comprising (b) (4)% w/w anhydrous ethanol in perfluorobutylpentane (F4H5)). The product is marketed as solution packaged in multi-dose and preservative free polypropylene bottles. An Environmental Assessment (EA) has been submitted pursuant to 21 CFR Part 25.

4.2. Need for action

CyclASol® is an anti-inflammatory and immune-modulating drug for the treatment of dry eye disease. This NDA requests an approval for ocular use.

4.3. Locations of use

Patients with dry eye disease will use CyclASol® in their homes, in clinics and in hospitals throughout the USA.

4.4. Disposal sites

Hospitals, pharmacies and clinics will dispose of empty or partially empty packages of drug product according to their internal established standard operating procedures of waste treatment. In the home, empty or partially empty containers will typically be disposed of by the community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of the unused drug may potentially be disposed of directly into the sewer system.

6. Environmental Issues

As described in the Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications, the Expected Introduction Concentration (EIC) of an active moiety into the aquatic environment may be calculated as follows:

EIC-Aquatic (ppb) = A x B x C x D

where:
A = kg/yr produced for direct use (as active moiety)
B = 1/1.214 x 10^{11} liters per day entering POTWs [1996 Needs Survey, Report to Congress]
C = 1 year/365 days per year
D = 10^{9} µg/kg (conversion factor)

The EIC-Aquatic of the active moiety cyclosporine A has been calculated for the peak production year estimate. An estimate of drug substance production requirements for the peak year (b) (4) is presented in the Confidential Appendix 11.2.1. The estimate was made until (b) (4) as a worst-case approach. The calculated EIC-Aquatic for the active moiety cyclosporine A is provided in the Confidential Appendix 11.1.

The active moiety cyclosporine A is brought to the market using perfluorobutylpentane (F4H5) as novel excipient. Even though no EA is required for novel excipients it is presented in the Confidential Appendices 11.1.1 and 11.1.3 for completeness.

The applicant is confident that the actual EIC will not exceed the estimated EIC by an order of magnitude for the active moiety and the novel excipient.

According to 21 CFR Part 25.31(b), action on a New Drug Application is categorically excluded from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb).

Since the EIC for active moiety cyclosporine A was estimated to be below 1 ppb (refer to Confidential Appendix 11.1.2), cyclosporine A qualifies for categorical exclusion and no Environmental Assessment was prepared. The same applies for the novel excipient perfluorobutylpentane (refer to Confidential Appendix 11.1.3).

7. Mitigation Measures

Based on the information provided in Section 6 it can be concluded that no adverse environmental effects have been identified for the use of CyclASol® within the United States. Therefore, no mitigating measures are needed.

8. Alternatives to the Proposed Action

No alternatives to the proposed action are proposed since no adverse environmental effects have been identified for the use of CyclASol® within the United States.

9. List of Preparers

(b) (4)

Degree in Biology. Over eight year's professional experience in Environmental Hazard and Risk Assessment for industrial chemicals, biocides and pharmaceuticals.

10. References

FDA (1998): Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (FDA, July 1998, CMC 6, Revision 1).

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Assessment: ***Adequate***
The EIC is well below 1 ppb.

Primary Environmental Assessor Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div3/Branch 6

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Chunchun Zhang, Ph.D.,
Quality Assessment Lead,
OPQ/ONDP/Div3/Branch 6

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

(b) (4)

[redacted]

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	Yes	See DMEPA review
Established name(s)	Yes	
Route(s) of administration	Yes	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other	N/A	

package terms include pharmacy bulk package and imaging bulk package.		

1.2 FULL PRESCRIBING INFORMATION

(b) (4)

[redacted]

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

[redacted]

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	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	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	No	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
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	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Yes	Anhydrous- absolute
Statement of being sterile (if applicable)	Yes	
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	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	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	N/A	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	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	

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.)	Yes	Do not freeze or refrigerate. BRANDNAME can be used until the expiration date on the bottle (b) (4) (b) (4) (b) (4) Further consideration for this proposed edit is being discussed and will be resolved during labeling negotiations.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant	N/A	

has a warning such as “Do not eat.”		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	
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 latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	
Include information about child-resistant packaging	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.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Rx only
Manufactured for Novaliq GmbH by:
Alliance Medical Products, Inc. (DBA Siegfried Irvine), 9342 Jeronimo Road, Irvine, CA 92618 (USA)
Distributed by:
Novaliq GmbH, Heidelberg, Germany

Part number/revision date

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	Yes	

2.0 PATIENT LABELING

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

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Copy/paste or refer to a representative example of a proposed container)

(b) (4)

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes	
Dosage strength	Yes	
Route of administration	Yes	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	Yes	
"Rx only" displayed on the principal display	Yes	
NDC number	Yes	
Lot number and expiration date	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Yes	
Bar code	Yes	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	
Medication Guide (if applicable)	Yes	
No text on Ferrule and Cap overseal	No	
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	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: *{Adequate/Inadequate}*

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

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date:
Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div3/Branch 6

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Chunchun Zhang, Ph.D.,

Quality Assessment Lead,
OPQ/ONDP/Div3/Branch 6

APPEARS THIS WAY ON ORIGINAL

Milton Sloan

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Chunchun Zhang

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	217469
Assessment Cycle Number	01
Drug Product Name/ Strength	VEVYE (cyclosporine ophthalmic solution)/0.1 %
Route of Administration	Topical Ophthalmic
Applicant Name	Novaliq GmbH
Therapeutic Classification/ OND Division	Anti-inflammatory and Immunomodulator/Division of Ophthalmology
Manufacturing Site	Alliance Medical Products, Inc., Irvine, CA
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: The drug product is (b) (4)

List Submissions Being Assessed (table):

Document(s) Assessed (Seq. #)	Date Received
Original submission (001)	08/08/2022
Amendment (009)	02/01/2023
Amendment (0010)	03/10/2023
Amendment (0013)	04/24/2023
Amendment (0014)	04/25/2023

Remarks:

- The subject drug product is a fast-acting topical anti-inflammatory and immunomodulatory product indicated for the treatment of the signs and symptoms of dry eye disease. The applicant states that the drug product is a multidose, non-aqueous sterile formulation, free of preservatives.
- The submission in Seq. 009 contains the response to IRs issued by the CMC reviewer; however, some information from the referenced submission is also relevant to the sterility assurance of the drug product and it is included in this review as applicable. The submissions in Seq. 0010, 0013, and 0014 contain responses to IRs issued by this reviewer. There have been additional submissions to the application apart to the ones referenced above; however, those submission do not contain information relevant to the sterility assurance of the drug product.

Concise Description of Outstanding Issues: N/A

Supporting Documents: None

S DRUG SUBSTANCE

The information pertinent to the manufacturing of the drug substance was not included in this review as the manufacturing of the drug product [redacted]

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Drug product composition –**

	Function	Quantity per unit (mg/2 mL)	Quantity per mL (mg)
Cyclosporine	API	2.00	1.0
Perfluorobutylpentane	[redacted]		
Ethanol			

- **Drug product description –**

The drug product is a non-aqueous, clear, colorless, non-preserved, multi-dose ophthalmic sterile solution designed to be used as a topical eye drop.

- **Description of container closure system –**

Configuration	Component	Description	Manufacturer	Product #
0.1 % Solution	Bottle	5 mL polypropylene (PP) round plastic bottle	[redacted]	
	Dropper	[redacted] polyethylene dropper		
	Cap	Screw cap [redacted] polyethylene		

P.2 PHARMACEUTICAL DEVELOPMENT
P.2.5 MICROBIOLOGICAL ATTRIBUTES

[redacted]

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(b) (4)

MICROBIOLOGY LIST OF DEFICIENCIES: N/A

Primary Microbiology Assessor Name and Date: Yarery Smith, Ph.D., 05/03/2023

Secondary Assessor Name and Date (and Secondary Summary, as needed): Yeissa Chabrier-Rosello, Ph.D. 05/03/2023

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Yeissa Chabrier Rosello

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Yarery Smith

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