CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215650Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality (OPQ) Memorandum

Date	December 2, 2021
NDA	**215650**
Drug Name/Dosage Form/Strength	XACIATO™ (clindamycin phosphate) vaginal gel; 2%
Applicant	Dare Bioscience, Inc.
Subject	**Addendum to OPQ Review # 1**

The purpose of this memorandum is to document a resolution of two outstanding issues listed in the OPQ Review # 1 of NDA 215650 (dated November 14, 2021, in DARRTS):

1. Additional comment included in the CDRH Review.
2. Potential CMC Post-Marketing Commitment (PMC) proposed in the OPQ Review # 1.

Additional CDRH Comment

CDRH was consulted for the NDA regarding the vaginal applicator to be used for the administration of the proposed drug product. The overall information for the vaginal applicator provided in the initial NDA submission and subsequent amendments, was found adequate by the CDRH Reviewer (refer to the CDRH Review dated November 8, 2021, in DARRTS). However, one outstanding minor comment recommending review of the external diameter of the barrel (upon receipt of the applicators), was forwarded to the Applicant via the IR letter dated November 15, 2021. In the amendment dated November 17, 2021, the Applicant agreed to add this additional control for the incoming applicators. The response was found acceptable by the CDRH Reviewer.

Conclusion:

All outstanding Product Quality issues have been satisfactorily resolved and there is no change to the initial recommendation of Approval by the Office of Pharmaceutical Quality (refer to the OPQ Review # 1).

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/s/

DOROTA M MATECKA
12/02/2021 09:50:47 AM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 215650
Assessment # 1

Drug Product Name	XACIATO™* (clindamycin phosphate) vaginal gel
Dosage Form	Gel
Strength	2%
Route of Administration	Vaginal
Rx/OTC Dispensed	Rx
Applicant	Dare Bioscience, Inc.
US agent, if applicable	N/A

**The proposed trade name is under assessment as part of the NDA review*

Submission(s) Assessed	Document Date	Discipline(s) Affected
0001	June 7, 2021	All
0005	June 29, 2021	Drug Product
0011	August 23, 2021	Drug Substance, Process, Device (CDRH)
0015	September 15, 2021	Drug Product (b) (4)
0016	September 30, 2021	Device (CDRH)
0018	October 5, 2021	Drug Product
0019	October 15, 2021	Drug Product
0021	October 20, 2021	Drug Product
0024	November 8, 2021	Device (CDRH)

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rajan Pragani	Paresma Patel
Drug Product	Peter Guerrieri	Dorota Matecka
Manufacturing	Jiao Yang	Steven Frisbee
Microbiology	Renee Marcsisin	Paul Dexter
Labeling	Peter Guerrieri	Dorota Matecka

CDRH	Rebecca Dorsey	Monica Garcia
Environmental Analysis	*Refer to Drug Product Review*	
Laboratory (OTR)	N/A	
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	Clindamycin Phosphate	Adequate	July 23, 2021	*Review by Wei Song*
(b) (4)	III		(b) (4)	N/A*		
(b) (4)	III			N/A*		

**Sufficient information provided in the NDA – refer to Drug Product Review*

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

Document	Application Number	Description
IND	143919	*Development of clindamycin phosphate vaginal gel*

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/ Toxicology	Complete	Adequate (*assessment of the tube extractable/leachable study results*)	*Refer to Drug Product review*	Dr. Kelly
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, clindamycin phosphate vaginal gel, 2%. The manufacturing and testing facilities have been found acceptable and the Overall Manufacturing Inspection Recommendation (OMIR) of "Approve" was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on October 21, 2021. Therefore, this NDA is recommended for **approval** by the Office of Pharmaceutical Quality (OPQ).

The following Post-Marketing Commitment (PMC) *is proposed* to be included in the action letter (refer to the Drug Product Review, below):

PMC Study:

(b) (4)

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

XACIATO™ (clindamycin phosphate) vaginal gel is indicated for the treatment of bacterial vaginosis (BV) in female patients (12 years of age and older). Clindamycin phosphate is a lincosamide antibacterial that has been approved by CDER and marketed for several indications in a variety of dosage forms.

XACIATO™ vaginal gel is a clear, colorless, viscous gel, which contains clindamycin at a concentration of 2%. A single-dose user-filled disposable applicator delivers 5 g of vaginal gel containing 100 mg of clindamycin (present as 119 mg of clindamycin phosphate).

The proposed drug product, XACIATO™ vaginal gel, received Fast Track (FT) and Qualified Infectious Disease Product (QIDP) designations on March 4, 2020 and August 7, 2020, respectively, for the treatment of bacterial vaginosis in women.

Proposed Indication(s) including Intended Patient Population	Treatment of bacterial vaginosis in female patients (12 years of age and older).
Duration of Treatment	The recommended dosage of XACIATO™ vaginal gel is one applicatorful (5 g of vaginal gel containing 100 mg of clindamycin) administered once intravaginally at any time of the day.
Maximum Daily Dose	100 mg of clindamycin
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

Clindamycin is a lincosamide antibacterial that inhibits bacterial protein synthesis at the level of the bacterial ribosome. The drug substance used in the proposed drug product is clindamycin phosphate. The supportive CMC information for the clindamycin phosphate drug substance has been provided via a reference to Type II DMF (b) (4) This DMF has been referenced and was found adequate for other drug products/applications approved by CDER. The most recent review of two latest DMF amendments is dated July 23, 2021 and the DMF status remains adequate. Overall information provided in DMF (b) (4) demonstrates adequate controls of the quality and manufacture of the clindamycin phosphate drug substance including the impurity control strategy which follows the USP monograph for clindamycin phosphate.

Batch analysis data for drug substance batches used in the manufacture of the drug product registration stability batches have been provided by the Applicant in the NDA. Based on the stability information included in the DMF, a retest date of (b) (4) proposed in the NDA for clindamycin phosphate drug substance (b) (4), (b) (4) was found acceptable by the Drug Substance Reviewer.

For further details refer to the Drug Substance Review, below.

Drug Product: Adequate

DARE-BV1 vaginal gel is a thermosetting bioadhesive hydrogel composed of benzyl alcohol, citric acid, poloxamer 407, sodium citrate, xanthan gum, and water, which contains clindamycin (as clindamycin phosphate) at a final concentration of 2%.

The proposed commercial container closure system is a (b) (4) (25 g fill) tube, and the proposed commercial package includes a vaginal applicator to be used for administration of the gel. The recommended dosage of the proposed drug product (clindamycin phosphate vaginal gel) is one applicatorful (5 g of vaginal gel containing 100 mg of clindamycin present as 119 mg of clindamycin phosphate) administered as a single dose intravaginally; thus, the 25 g fill results in unnecessary waste. (b) (4)

(b) (4)

The proposed drug product (clindamycin phosphate vaginal gel) specification includes important quality attributes such as: appearance, identification, assay, related substances, (b) (4), viscosity, pH, minimum fill, within-tube content uniformity, (b) (4) package integrity, antimicrobial preservative effectiveness, and microbial limits. At the FDA recommendation, the acceptance criteria for several quality attributes (e.g., related substances, viscosity, pH, and (b) (4)) were revised to enhance the control of the drug product quality over its lifetime.

The stability information submitted for the drug product in the NDA includes 12 months long term (25°C/60% RH) and 6 months accelerated (40°C/75% RH) stability data for three primary stability batches. All stability testing results conform to the acceptance criteria set in the proposed drug product specification with no major trends other than decrease in viscosity and increase in related impurities at the accelerated storage conditions. Based on the overall stability inforation provided in the

NDA, the proposed 24-month expiration dating for the drug product (to be stored at USP controlled room temperature storage conditions) has been found acceptable by the Drug Product Reviewer.

The Applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of less than 1 ppb. This claim was found acceptable by the Drug Product Reviewer.

For further details refer to the Drug Product Review, below.

Labeling: Adequate

The proposed prescribing information (PI), tube labels, and the carton labeling were found to generally include the necessary information. Several revisions to the applicable to the product quality sections of the PI (Sections 3, 11 and 16) have been recommended by the Labeling Reviewer. That includes a recommendation to add a dosage form and the route of administration to the drug product established name, to state: clindamycin phosphate vaginal gel. Although clindamycin phosphate is an ester and not a salt, the strength for other products containing clindamycin phosphate have historically been expressed in terms of the active moiety, clindamycin. Therefore, the dose for the current drug product will also be expressed in terms of clindamycin and will include an added phrase "present as clindamycin phosphate" in parentheses. Similar revisions have been recommended for the container label and carton labeling (for details refer to the Labeling Review, below).

The above labeling recommendations have been communicated to the OND Project Manager (PM). The labeling review by the NDA review team is currently pending.

Manufacturing: Adequate

The proposed drug product manufacturing process consists of (b) (4) major operations, (b) (4) The Applicant has identified the (b) (4) and proposed the following (b) (4) The proposed (b) (4) cover all the critical quality attributes (COAs) of the drug product affecting (b) (4). For (b) (4) . Overall, the proposed control strategy for the entire manufacturing process to ensure that the drug product meets CQAs has been found adequate by the

Process Reviewer. The overall information provided in the initial NDA submission and the subsequent amendments regarding the proposed manufacturing process and controls have been found adequate by the Process Reviewer.

The drug product, clindamycin phosphate vaginal gel, 2%, will be manufactured by DPT, a Mylan Company located in San Antonio, TX, (b) (4). The DPT facility has a satisfactory history complying with cGMP regulations. The drug substance, clindamycin phosphate, will be manufactured at (b) (4) (b) (4) (b) (4).

All manufacturing facilities have been found acceptable by the OPMA Reviewer based on the review of their previous inspectional history and compliance status. The overall "Approve" recommendation for manufacturing facilities was entered into Panorama on October 21, 2021 (for details refer to the Manufacturing Integrated Assessment, below).

Biopharmaceutics: Choose an item.

N/A

Microbiology: Adequate

The drug product (clindamycin phosphate vaginal gel, 2%) is not required to be sterile. However, it is intended for vaginal administration and adequate microbiological controls are necessary. Therefore, the Product Quality Microbiology Review focused on the assessment of the proposed microbial limits and tests for specified microorganisms. The drug product specification includes the microbiological tests following USP General Chapters <61> <62> and <60>. In addition, the antimicrobial efficacy testing per USP <51> is also part of the drug product specification. The microbiological controls proposed for the drug product were found adequate by the Microbiology Reviewer (refer to the Microbiology Review, below).

CDRH: Adequate

The CDRH review focused on the assessment of the proposed vaginal applicator and condom compatibility studies. Several information requests were conveyed to the Applicant during the NDA review regarding the details of the methods and conditions used in the compatibility testing of condoms with the proposed drug product and quality controls used for the applicators.

Overall information provided in the NDA and subsequent amendments for the proposed vaginal applicator that included materials, dimensions and testing of new and aged applicators was found adequate. Upon further discussion of the product expiration dating, the CDRH Reviewer agreed that the 24-month shelf-life established for clindamycin phosphate vaginal gel could also apply to the vaginal applicator, which is going to be co-packaged with the tube of the gel.

The CDRH Reviewer also concluded that adequate information was provided in the NDA to demonstrate the compatibility of the proposed drug product with natural rubber latex and polyisoprene condoms and to support the labeling claims indicating compatibility with these types of condoms. However, the labeling should also include a statement that the proposed drug product is not compatible with polyurethane condoms. This recommendation has been conveyed to the OND PM.

One remaining minor comment regarding the quality controls used by the Applicant for the in-coming applicators, is listed at the end of the CDRH review; this comment will be conveyed to the Applicant and the response addressed in an addendum to this review. For details, refer to the CDRH Review, below.

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**
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	Formulation Raw materials Process parameters Scale/equipment Site	Low	Adequate long-term stability data for three registration batches; minimal changes over storage at RT	Acceptable	
Content uniformity (within-tube)	Formulation Raw materials Process parameters Scale/equipment Site	Low	Adequate (b) (4) controls (per USP<3>)	Acceptable	
Physical stability	Formulation Raw materials Process parameters Scale/equipment Site	Low	(b) (4)	Acceptable	

pH	Formulation Raw materials Process parameters Scale/equipment Site	Low	Stability results remained within a relatively narrow range	Acceptable	
Viscosity	Formulation Raw materials Process parameters Scale/equipment Site	Low	Acceptance criteria have bee revised to include upper and lower limits; results remain stable on storage at RT	Acceptable	
Microbial limits	Formulation Raw materials Process parameters Scale/equipment Site	Low	Adequate controls have been established in the drug product specification	Acceptable	
Leachables	Formulation Raw materials Process parameters Scale/equipment	Moderate	Extractable and leachable data provided; no significant levels of leachables observed	Acceptable	
Container size (tube fill)	Formulation Container closure system	Moderate	(b) (4)	Acceptable	(b) (4)

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CHAPTER IV: LABELING

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

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	XACIATO™ (clindamycin phosphate) vaginal gel
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
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	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active	N/A	Although the active ingredient clindamycin phosphate is an ester and not a salt, the strength for other products containing the active ingredient have historically been expressed in terms of the active moiety clindamycin. Therefore, the dose is

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		expressed in terms of clindamycin with the added phrase "present as clindamycin phosphate", similar to the equivalency statement in the strength expression for salts.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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)	N/A	The product is packaged with an applicator for administration. The applicator is being reviewed by CDRH. A stepwise procedure for filling the applicator and administering the dose is included in the Patient Information and Instructions for Use (IFU) and was reviewed by DMEPA.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	

Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	Although the active ingredient clindamycin phosphate is an ester and not a salt, the strength for other products containing the active ingredient have historically been expressed in terms of the active moiety clindamycin. Therefore, the dose is expressed in terms of clindamycin with the added phrase "present as clindamycin phosphate" in parentheses.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
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 type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	Although the active ingredient clindamycin phosphate is an ester and not a salt, the strength for other products containing the active ingredient have historically been expressed in terms of the active moiety clindamycin. Therefore, the dose is expressed in terms of clindamycin as follows: "*A single-dose user-filled disposable applicator delivers 5 g of vaginal gel containing 100 mg of clindamycin (present as 119 mg of clindamycin phosphate)*".
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	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	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	Adequate	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	DMEPA request to add the NDC number when available to section 16 has been provided to OND.
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	
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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	N/A	

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	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 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

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

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

In the Patient Information and Instructions for Use, the patient is instructed on how to puncture the tube with the pointed tip on the cap, and not to use if the tube looks like it has been opened before or if the seal is damaged or broken. No other quality information related to the product is provided.

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	N/A	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	N/A	

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

- 25 g tube for this NDA submission

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

(b) (4)

3.2 Carton Labeling

- 25 g tube for this NDA submission

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[5], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	Although the active ingredient clindamycin phosphate is an ester and not a salt, the strength for other products containing the active ingredient have historically been expressed in terms of the active moiety clindamycin. Therefore, it is recommended to add the phrase "present as clindamycin phosphate" to the dosage statement which is expressed in terms of clindamycin. See below for recommended edit.
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	A placeholder for the NDC number is included. DMEPA request to replace the placeholder with the NDC number when available has been provided to OND.
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
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, and these products require a "Not for direct infusion" statement.	N/A	Recommended edit: Add the term "single-dose" and the phrase "present as clindamycin phosphate" to the dosage statement and remove the word (b) (4) to read: "The applicator is filled from the single-dose tube and delivers 5 g of vaginal gel containing 100 mg of clindamycin (present as clindamycin phosphate)."

For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. 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	N/A	
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	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	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *Adequate*

See recommended edits in "ITEMS FOR ADDITIONAL ASSESSMENT."

[5] Established name = [Drug] [Route of Administration] [Dosage Form]

ITEMS FOR ADDITIONAL ASSESSMENT

Requested edits to be conveyed to OND:

In the carton and container labels, add the term “single-dose” and the phrase “present as clindamycin phosphate” to the dosage statement and remove the word [redacted] (b) (4) to read:
“The applicator is filled from the single-dose tube and delivers 5 g of vaginal gel containing 100 mg of clindamycin (present as clindamycin phosphate).”

Overall Assessment and Recommendation:

Recommended edits will be provided to OND.

Primary Labeling Assessor Name and Date: Pete Guerrieri, PhD

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Peter Guerrieri

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Dorota Matecka

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	Treatment of bacterial vaginosis (BV) in adult women
NDA Number	215650
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Proprietary name: Xaciato Established name: DARE – BV1 (clindamycin phosphate vaginal gel 2%)
Route of Administration	Vaginal
Applicant Name	Daré Bioscience Inc.
Therapeutic Classification/ OND Division	Antibacterial OID/DAI
Manufacturing Site	DPT, a Mylan company, 307 E Josephine St., San Antonio, TX 78215
Method of Sterilization	Non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary: **The applicant provided 14 other supporting documents after the original NDA submission in eCTD sequence #0001. Only documents in eCTD sequence #0005 are related to product quality microbiology. In this sequence, the applicant provided a 12 month long-term stability update, which is reviewed in Section P.8.3 below.**

Document(s) Assessed	Date Received
eCTD sequence #0001	**06/07/2021**
eCTD sequence #0005	**06/29/2021**

List Submissions being assessed (table): 06/07/2021, 06/29/2021

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

Remarks: The drug product is administered as a vaginal gel and is therefore not required to be sterile. A sterility assurance review of this NDA was not performed; however, a review of the microbial limits and test for specified microorganisms is necessary.

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

Supporting Documents: N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** A clear, colorless, viscous gel [redacted] and supplied as a 25 g fill in a [redacted] tube with [redacted] applicator that delivers 5 g of intravaginal gel containing 100 mg clindamycin

- **Drug product composition –**

Component	Standard	Function	Amount (g) per dose (5 g)
Clindamycin phosphate	USP	Active	0.119*
Poloxamer 407	NF	[redacted]	[redacted]
Xanthan gum	NF		
Citric acid monohydrate	USP		
Sodium citrate dihydrate	USP		
Benzyl alcohol	NF		
Purified water	USP		
Total	-	-	

The actual amount of clindamycin base in a 5 g dose is 100 mg.

- **Description of container closure system –** The drug product is supplied in the following container closure system:

  - Flexible [redacted] tube with [redacted] seal and [redacted] screw top on one end and a folded crimped end on the other. The tube is supplied by [redacted]
  - [redacted] applicator with plunger for administration [redacted]. The applicator is supplied by [redacted]

Assessment: *Adequate*

[redacted]

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MICROBIOLOGY LIST OF DEFICIENCIES

None

Primary Microbiology Assessor Name and Date: Renee A. Marcsisin, Ph.D., 09/17/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed): CAPT Paul Dexter, MS, 09/17/2021

Renee Marcsisin

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Paul Dexter

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