

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215650Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 16, 2021

To: Alison Rodgers
Regulatory Project Manager
Division of Anti-Infectives (DAI)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
David Foss, Pharm. D., MPH, BCPS, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)
Drug Name (established name): XACIATO (clindamycin phosphate)

Dosage Form and Route: Vaginal Gel 2%

Application Type/Number: NDA: 215650

Applicant: Daré Bioscience Inc.

1 INTRODUCTION

On June 7, 2021, Daré Bioscience Inc. submitted for the Agency's review:

- an original new drug application (NDA 215650)
- request for priority review
- request for proprietary name review

for DARE-BV1 (clindamycin phosphate) Vaginal Gel 2% indicated for the treatment of bacterial vaginosis in adult women. The proposed proprietary name of XACIATO was conditionally accepted by the FDA based on the correspondence dated September 4, 2020.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infectives (DAI) on June 16, 2021 and June 17, 2021 for DMPP and OPDP respectively to review the Applicant's proposed IFU for XACIATO (clindamycin phosphate) Vaginal Gel 2%.

2 MATERIAL REVIEWED

- Draft XACIATO (clindamycin phosphate) Vaginal Gel 2% IFU received on June 7, 2021 and received by DMPP and OPDP on November 8, 2021.
- Draft XACIATO (clindamycin phosphate) Vaginal Gel 2% Prescribing Information (PI) received on June 7, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 8, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
11/16/2021 02:39:03 PM

DAVID F FOSS
11/16/2021 03:34:52 PM



Food and Drug Administration
Center for Devices and Radiological Health
Office of Product Evaluation and Quality

DATE: November 8, 2021
FROM: Rebecca Dorsey, Biomedical Engineer
CDRH/OHT3/DHT3B/THT3B1
TO: Anh-Thy Ly, Sr. Regulatory Health Project Manager
CDER/OPQ/OPRO/DRBPMI/RBPMB1
RE: NDA 215650: Supporting Document 1
Xaciato (Dare BV1)
Dare Bioscience, Inc.

I. Submission Purpose

The subject combination product is a vaginal gel which has been developed to treat bacterial vaginosis. The gel is contained in a (b) (4) flexible (b) (4) cap with a screw top on one end and a crimped folded edge on the other. A (b) (4) applicator consisting of a barrel and plunger is also provided with the subject product.

CDER is requesting CDRH provide a review of the condom compatibility studies and the evaluation of the vaginal applicator.

Dr. Gunja Pathak previously reviewed this product under IND 143919.

II. Review Summary

This review memo will be limited to the condom compatibility studies and evaluation of the (b) (4) vaginal applicator used to administer the DARE-BV1 gel.

III. Indications for Use

Treatment of bacterial vaginosis (BV) in adult women.

IV. Product Description

DARE-BV1 is a 2% clindamycin gel for vaginal administration. The product is contained in an (b) (4) flexible tube fitted with a screw top cap on one end and a crimped folded edge of the other. The tubes are supplied with a (b) (4) single dose applicator. A single 5-gram dose is filled from the tube into the applicator at the time of administration.

The composition of the gel can be seen in the table below:

Table 1. Composition of the subject product

Table with 6 columns: Component, Standard, Function, Amount per tube, Amount per dose, Amount (%w/w). Rows include Clindamycin Phosphate and Poloxamer 407.

Xanthan Gum	NF	(b) (4)			
Citric Acid Monohydrate	USP	(b) (4)			
Sodium Citrate Dihydrate	USP	(b) (4)			
Benzyl Alcohol	NF	(b) (4)			
Purified Water	USP	(b) (4)			
Total	-	-	25 (b) (4) g	5 (b) (4)	100.00

The container closure system is as follows:

- (b) (4) flexible (b) (4) tube with a screw cap on one end and a crimped folded edge on the other. Each (b) (4) tube is filled with 25 g of gel.
- (b) (4) applicator consisting of a barrel and plunger supplied (b) (4).

The applicator is a (b) (4) vaginal cream applicator made from a clear (b) (4). The (b) (4) applicator has a black mark at the (b) (4) level on the plunger to indicate the amount of gel to be filled into the applicator prior to administration and is supplied (b) (4). The applicator can be seen in **Figure 1** below.



Figure 1. Applicator

Note: Since IND 143919 the sponsor has made changes to the applicator. The applicator is manufactured by the same company (b) (4), but it is made of different materials, has different dimensions, and is no longer pre-filled.

V. Review

Applicator Specifications

The sponsor states that on receipt, the applicators are reviewed against the purchase order and certificate of analysis/conformance supplied with the shipment. The complete manufacturing and controls information is available through (b) (4) drug master file, DMF (b) (4).

Reviewer Comment: I am unable to view DMF (b) (4); therefore, I am unable to review the applicator specifications. On August 12, 2021, I asked the sponsor to provide the applicator's specifications. The sponsor provided the following specifications in their IR response.

Table 2. Applicator Specifications

Parameter	Acceptance Criteria
Material	Barrel and Plunger: (b) (4)
Dimensions	All dimensions shown are in inches and millimeters
Tolerance	As noted on manufacturer's drawings
Manufacturer	(b) (4)
Drawing #	Barrel: (b) (4) Plunger: (b) (4) Barrel and Plunger Assembly: (b) (4)
Packoff	Barrels/plungers to be packed in assembled condition (b) (4)
Case Requirement	(b) (4)
Case Marking	Each case must be accurately marked with the following: A. Description B. (b) (4) Part Number C. (b) (4) Purchase Order Number D. Quantity per case
Pallet/Slip Sheet Load Marking	Each pallet/slip sheet load must be accurately marked with the following: A. Description B. (b) (4) Part Number C. (b) (4) Purchase Order Number D. Quantity per pallet

The following drawings were also provided.





It is still unclear which dimensions are assessed once the sponsor receives the shipment of applicators. Therefore, on 9/23/21, I asked the sponsor to clarify which dimensions are reviewed after receiving the applicators. The sponsor responded on 9/30/21. They stated that the following dimensions are reviewed upon receipt.

Applicator Component	Dimension Reviewed	Specification (inches)
Barrel	Overall Length	(b) (4)
Plunger	Overall Length	(b) (4)

I will recommend that the sponsor also review the external diameter to ensure that the amount of drug product delivered remains consistent between applicators.

Condom Compatibility

The subject product was evaluated to assess its compatibility with condoms using ASTM D7661 “Standard test method for determining compatibility of personal lubricants with natural rubber latex condoms.” Three brands of non-lubricated latex condoms, one brand of polyisoprene condoms, and one brand of polyurethane condoms were tested. Negative control condoms were conditioned but were not exposed to the test gel. Additionally, baseline analyses were performed on the condoms (tested directly from their packages), as well as a positive control group (for the latex and polyisoprene condoms) to validate the lab’s test technique. Mineral oil was used in the positive control group for latex and polyisoprene condoms. A suitable positive control substance for polyurethane was not established. Twenty samples were tested per group, per condom type.

Table 3. Condom Compatibility Results – NRL

		Natural Rubber Latex					
		Trustex		Lifestyles		Trojan ENZ	
		Mean ± SD	% Change	Mean ± SD	% Change	Mean ± SD	% Change
Force at Break (N)	Baseline	(b) (4)					
	Subject Lubricant						
	Mineral Oil						
	Control						

Elongation (%)	Baseline	(b) (4)
	Subject Lubricant	
	Mineral Oil	
	Control	
Airburst Volume (L)	Baseline	
	Subject Lubricant	
	Mineral Oil	
	Control	
Airburst Pressure (kPa)	Baseline	
	Subject Lubricant	
	Mineral Oil	
	Control	

Table 4. Condom Compatibility Results – Synthetic

		Synthetic Condoms			
		Trojan Supra Polyurethane		Lifestyles Polyisoprene	
		Mean ± SD	% Change	Mean ± SD	% Change
Force at Break (N)	Baseline	(b) (4)			
	Subject Lubricant				
	Mineral Oil				
	Control				
Elongation (%)	Baseline				
	Subject Lubricant				
	Mineral Oil				
	Control				
Airburst Volume (L)	Baseline				
	Subject Lubricant				
	Mineral Oil				
	Control				
Airburst Pressure (kPa)	Baseline				
	Subject Lubricant				
	Mineral Oil				
	Control				

Reviewer Comment: The sponsor did not state which version of ASTM D7661 was used to evaluate the compatibility of the subject product with condoms. It is also unclear if the to be marketed product was used for testing. On 8/12/21, I asked the sponsor to provide this information. In addition, the sponsor has included a statement regarding the product's compatibility with condoms in their labeling. However, the sponsor does not clearly state that the subject product is not compatible with polyurethane condoms; therefore, on 8/12/21, I asked the sponsor to clearly state that the product is not compatible with polyurethane condoms. The sponsor responded on 8/23/21, stating that ASTM D7661-18 was followed for testing. This standard is not the currently recognized standard; however, the differences between this standard and the currently recognized standard are only related to removal of lubricant. Therefore, since the condoms used were non-lubricated, it is acceptable that the sponsor followed ASTM D7661-18. The sponsor also stated that the following statement has been added to the patient information: (b) (4)

(b) (4) The sponsor did not state whether the final finished product was tested, and the conditioning methods are not clear in the test report. Therefore, on 9/23/21, I asked the sponsor to clarify whether the final finished product was tested and what methods were used for conditioning the condoms. The sponsor responded on 9/30/21. They clarified that the finished drug product obtained from a manufacturing feasibility lot performed at commercial scale (b) (4), which is

representative of the commercial process, was used as the test article for the condom compatibility study. Although the gel was not transferred to the applicator before testing, it is acceptable to assume the applicator will not affect the gel's compatibility with condoms since the gel will be in the applicator for a short amount of time (b) (4). The sponsor also clarified that the conditioned condoms were conditioned at 40 °C for 60 minutes. Since the sponsor conditioned the condoms according to ASTM D7661-18, the sponsor's response is acceptable.

Applicator Evaluation

The sponsor also provided a test report assessing the minimum force required to fill the BV1 applicator with the BV1 gel product. To determine the minimum force required to transfer the gel from the tube to the applicator, a load cell was placed between the tester's thumb and the tube. The procedure was video recorded to document the time and minimum force needed to transfer the gel from the tube into the applicator, as indicated by the plunger moving. The sponsor states that the minimum force required to move the gel from the tube into the applicator was found to be the most relevant user performance criteria, since it is this force that the user must be able to produce in order to fill the applicator.

Table 5. Applicator Functionality Results

Filling Forces (n=15)				
Force (lbf)	Minimum	Maximum	Average	Standard Deviation
Plunger Movement	(b) (4)			(b) (4)
Full Applicator				
Recorded Maximum Force				

Table 6. Applicator Functionality Results

Filling Forces (n=15)				
	Avg – 3 std	Avg	Avg +3	Standard Deviation
Forces (lbf)	Minimum	Average	Maximum	
Plunger Movement	(b) (4)			(b) (4)
Full Applicator				
Recorded Maximum Force				

Table 7. Applicator time to fill results

Filling Time (n=15)				
	Avg – 3 std	Avg	Avg +3 std	Standard Deviation
Time (minutes:seconds)	Minimum	Average	Maximum	
Time to fill applicator	(b) (4)			(b) (4)

Reviewer Comment: During the review of IND 143919, the previous CDRH reviewer, Gunja Pathak, recommended that the sponsor provide pre-defined acceptance criteria and discuss if the results found were acceptable as they related to the expected clinical use of the subject product. The sponsor did not do that for this study; therefore, it is not clear if the results of the assessment were considered acceptable. On August 12, 2021, I asked the sponsor to provide acceptance criteria and discuss whether the results found were acceptable. In the sponsor's response, they stated that a test with study subjects was used to determine the amount of pinch strength a human can exert. The pinch strength was found to be an average of (b) (4) lbf in the dominant hand and (b) (4) lbf in the non-dominant hand. In the previous

study, as represented in the tables above, the resulting forces were between (b) (4) and (b) (4), which the sponsor notes are below the amount of pinch force measured on human subjects. The sponsor stated that they also conducted a second study to measure the amount of force required to expel the gel from the applicator using a Shimadzu Universal test machine and (b) (4) load cell. The compression force needed to expel the gel was found to be (b) (4) N, which is also below the human pinch strength ((b) (4) N and (b) (4) N). The sponsor states that these results indicate that the gel can be easily administered from the applicator to the patient. The sponsor notes in their test protocol for the original tube and applicator fill force that the minimum force required to move the gel is the most relevant, since this force is needed to be produced by the user in order to fill the applicator. The sponsor did not state the specific acceptance criteria used for assessing the applicator functionality; therefore, on 9/23/21, I asked the sponsor to provide clarification for whether they were using the results from the human study as the acceptance criteria for the functionality study. The sponsor responded on 9/30/21, confirming that the results from the human study were used as acceptance criteria for the functionality study. The acceptance criteria can be seen in the table below.

Table 7. Acceptance criteria for the applicator functionality study

Specification	Acceptance Criteria
Maximum Force	(b) (4) lbf

Since the sponsor has provided an acceptable rationale for the chosen acceptance criteria, the sponsor's response is acceptable.

Stability

The sponsor conducted an in-use stability study to test the finished product after it was held in an applicator to simulate patient use in a worse-case scenario. Samples of the subject product, lot RAH-C, packaged in (b) (4) tubes were used to fill 5-gram applicators. The applicators were then stored at 25°C for 15 hours and tested for clindamycin assay, related to substances, benzyl alcohol content, description, pH, and viscosity.

The sponsor states that the results met the protocol acceptance criteria. The sponsor has concluded that there are no significant differences between the product being held in the applicator and the product in the on-going stability studies of the same lot.

Reviewer Comment: It is unclear if the subject product and the applicator are co-packaged. If they are co-packaged, stability testing should be conducted on the final, to-be marketed product. On 9/23/21, I asked the sponsor to clarify how the product is packaged and whether stability testing was conducted on the full to-be marketed product. The sponsor responded on 9/30/21, clarifying that the applicator was not stored with the gel during the stability studies. They also clarified that the applicator is intended to be provided (b) (4) separate from the tube containing the gel in the secondary packaging carton. The sponsor stated that they will store the applicators with the tubes for the process validation batches and place these lots on stability. They state that the process validation stability protocol will be updated to include parameters to confirm the functionality of the applicators yearly through 3 years of real-time aging and the stability results will be submitted in Annual Reports. Since the applicator is not intended to be co-packaged with the subject gel, it is not necessary for the sponsor to store the applicator with the gel during stability studies. However, to ensure the applicators remain functional throughout the proposed shelf-life, the sponsor should assess the functionality of the applicator after aging. Therefore, on 10/28/21, I asked the sponsor to provide results assessing the functionality of applicators after aging. The sponsor provided the results from applicators that were aged for 18 months and stated that they would provide results of applicators aged 24-months in April 2022, prior to launching the subject product. The results of the 18-month data, as well as 6-month data, can be seen in the table below.

Forces (lbf)	Original 6 months (n=15)		Aged 18 months (n=10)	
	Average	STD	Average	STD
Plunger Movement				(b) (4)
Full applicator				

Recorded Maximum force				(b) (4)

	Barrel Overall Length	Plunger Overall Length
Specification (inches)		(b) (4)
Sample 1		
Sample 2		

The results of the applicator fill force assessment met the acceptance criteria of (b) (4) lbf and the dimensions that the sponsor measured met the specifications. The sponsor's response is acceptable to establish an initial shelf life of 18 months. Once the sponsor submits acceptable results for applicators aged 24 months, the shelf-life can be extended to 24 months.

VI. Recommendation

The sponsor has adequately assessed the applicator for the subject product. However, I have one additional request for the sponsor. Please provide the following comment to the sponsor.

1. In our Information Request dated September 23, 2021, we asked you to clarify which dimensions are reviewed after receiving the applicators. On September 30, 2021, you stated that the overall length of the barrel and the overall length of the plunger are reviewed upon receiving the applicators. To ensure that the gel being delivered to the user from the applicator is consistent between applicators, please also review the external diameter of the barrel upon receipt of the applicator.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Rebecca Dorsey -S 2021.11.08 15:30:05 -05'00'
Assistant Director / Acting Team Lead Sign-Off	Monica D. Garcia -S 2021.11.08 15:32:10 -05'00'

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANH-THY LY
11/08/2021 03:45:36 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: November 5, 2021
Requesting Office or Division: Division of Anti-Infectives (DAI)
Application Type and Number: NDA 215650
Product Name and Strength: Xaciato (clindamycin phosphate) Vaginal Gel, 2%
Applicant/Sponsor Name: Daré Bioscience, Inc. (Daré)
OSE RCM #: 2021-1141-1
DMEPA 1 Safety Evaluator: Deborah Myers, RPh, MBA
DMEPA 1 Team Leader: Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised 25 gram container label and carton labeling received on November 2, 2021 for Xaciato. The Division of Anti-Infectives (DAI) requested that we review the revised 25 gram container label and carton labeling for Xaciato (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations, except for specifying the intended national drug code (NDC) number on the proposed container label and carton labeling. Beyond the Applicant's need to specify the intended NDC number, once assigned, on the proposed container label and carton labeling, we have no additional recommendations at this time.

^a Myers, D. Label and Labeling Review for Xaciato (NDA 215650). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 SEP 30. RCM No.: 2021-1141.

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/s/

DEBORAH E MYERS
11/05/2021 09:29:40 AM

VALERIE S VAUGHAN
11/05/2021 10:00:22 AM

Consult Question:

Please review section 8 of the USPI.

INTRODUCTION AND BACKGROUND

On June 7, 2021, the applicant (Daré Biosciences) submitted a new NDA for DARE-BV1 (clindamycin phosphate) vaginal gel 2%, NDA 215650 for the treatment of bacterial vaginosis in adult women. The Division of Anti-Infectives (DAI) consulted the Division of Pediatric and Maternal Health (DPMH) on July 12, 2021, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Clindamycin was first approved in the United States on February 22, 1970 under the brand name Cleocin HCL capsules, NDA 050162, indicated for the treatment of serious infections caused by susceptible anaerobic bacteria. Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci.
- On March 4, 2020, DARE-BV1 received Fast Track Designation for the treatment of bacterial vaginosis in women, because it is treating a serious or life-threatening disease and is addressing an unmet clinical need (this treatment will offer an alternative single dose regimen for the treatment of bacterial vaginosis). It has also received Qualified Infectious Disease Product (QIDP) designation.
- On September 4, 2020, the proprietary name of Xaciato was conditionally accepted by the FDA.
- On June 7, 2021, the applicant submitted NDA 215650, clindamycin phosphate vaginal gel 2%, for the treatment of bacterial vaginosis in adult women in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The drug relied upon is Clindamycin in 0.9% Sodium Chloride injection, for intravenous use, NDA 208083. Dare Bioscience also proposes to rely upon systemic safety information of Cleocin Vaginal Cream 2%, NDA 050680.
- At the same time of this submission, the applicant also requested a Priority Review.
- On June 7, 2021, DAI consulted DPMH to assist with development of subsections 8.1 and 8.2 of the product's labeling.
- On July 16, 2021, FDA send an Information Request (IR) to the applicant to obtain supplemental information for a review and summary of published literature regarding the use of clindamycin in lactating individuals and in females and males of reproductive potential and pregnancy outcomes from the clinical trials.
- On July 30, 2021, the applicant replied to the IR with a Labeling Supplement Amendment.
- On October 13, 2021, FDA send an Information Request (IR) to obtain the rationale for the timer period selected to contraindicate polyurethane condom use along with the proposed product.
- On October 20, 2021, the applicant responded to the IR.

Drug Characteristics

Clindamycin gel Characteristics¹

Drug Class	antibacterial
Mechanism of action	Clindamycin inhibits bacterial protein synthesis at the level of the bacterial ribosome. The antibiotic binds preferentially to the 50S ribosomal subunit and affects the process of peptide chain initiation. Although clindamycin phosphate is inactive in vitro, in vivo hydrolysis converts this compound to the antibacterially active clindamycin.
Molecular weight	504.96 g/mol
Half-life*	NA
Protein Binding*	NA
Bioavailability*	NA

*DPMH Personal Communication with the Clinical Pharmacology Team on 9/16/21 confirms the systemic absorption of DARE BV1 Vaginal Gel 2% is low but not minimal.

DARE-BV1 is a thermosetting bioadhesive hydrogel containing the phosphate-ester prodrug of clindamycin, clindamycin phosphate. The thermosetting bioadhesive hydrogel contains benzyl alcohol (b) (4), citric acid monohydrate, poloxamer 407, sodium citrate dihydrate, xanthan gum, and water.

The mean C_{max} for vaginal gel is 69.2 ng/mL, while the mean C_{max} for clindamycin oral capsule is 2.5 mcg/mL after a 150 mg oral dose of clindamycin hydrochloride. The C_{max} for vaginal gel is approximately 2.77% of that observed after the administration of a 150 mg oral capsule. Therefore, systemic absorption of Xaciato gel is low. This information was confirmed in discussion with the DAI Clinical Pharmacology Team.

The proposed dosing for DARE-BV1 is a one-time dose of 5 grams of gel containing 100mg of clindamycin phosphate, which is administered into the vagina by an applicator.

Reviewer Comment:

Currently, there are more than 7 approved products indicated for treatment of bacterial vaginosis including orally administered secnidazole and several oral and vaginal formulations of clindamycin phosphate, metronidazole and tinidazole.² Two approved formulations which are administered vaginally also contain benzyl alcohol in their formulation. One approved formulation that contains benzyl alcohol is Cleocin 2% (clindamycin) intravaginal cream, which is indicated for the treatment of pregnant women during the second and third trimester and contains (b) (4) benzyl alcohol.³ Another approved formulation that contains benzyl alcohol is

¹ Based on applicant proposed labeling and discussion with DAI review team (DPMH Personal Communication with DAI Clinical team on 9/15/2021 and Clinical Pharmacology team on 9/16/2021).

² DPMH review of Solosec (secnidazole) by Jane Liedtka, MD on August 23, 2017, NDA 209363, DARRTS Reference ID 4143279

³ PI Cleocin (clindamycin phosphate) Vaginal Cream 2%, NDA 50680. Pfizer. Revised 03/2020. Drugs@FDA. Accessed 12/22/2020

Nuessa (metronidazole 1.3% vaginal gel), NDA 205223,⁴ an intravaginal gel used for the treatment of bacterial vaginosis in adult women and contains (b) (4) or (b) (4) benzyl alcohol per applicator. In a previous discussion with the DAI Clinical Pharmacology team, the team noted that the amount of benzyl alcohol present in the proposed formulation ((b) (4) benzyl alcohol, (b) (4)) is acceptable for use in pregnancy when compared to the other approved products noted above. Neither approved labeling contains any warning regarding the use of benzyl alcohol during pregnancy.

Serious Adverse Effect: The applicant proposes to include C. Difficile associated diarrhea and interaction of clindamycin vaginal gel with polyurethane condoms (weakens condoms).⁵

Current State of the Labeling for the drug relied upon Cleocin Vaginal Cream 2%, NDA 050680

- Although the drug relied upon is Clindamycin in 0.9% Sodium Chloride injection, for intravenous (IV) use, the applicant also proposes to rely upon systemic safety information of Cleocin Vaginal Cream 2%, NDA 050680. Since the current NDA is for a vaginal product, the information in this section includes labeling excerpts from Cleocin Vaginal Cream 2% instead of IV Clindamycin.
- This product was approved on August 11, 1992 and implementation is voluntary for drugs approved prior to June 30, 2001, therefore the approved labeling is not in Physician Labeling Rule (PLR) format or Pregnancy and Lactation Labeling Rule (PLLR) format.
- Cleocin is indicated for the treatment of bacterial vaginosis and can be used to treat non-pregnant women and pregnant women during the second and third trimester.
- There is no boxed warning for this drug.
- There are contraindications for those with history of hypersensitivity to clindamycin, lincomycin, or any of the components of the vaginal cream. Cleocin is also contraindicated in individuals with a history of regional enteritis, ulcerative colitis, or a history of “antibiotic-associated” colitis.
- Serious adverse effect includes C. Difficile associated diarrhea.

Pregnancy

In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters, has not been associated with an increased frequency of congenital abnormalities.

Clindamycin vaginal cream should be used during the first trimester of pregnancy only if clearly needed and the benefits outweigh the risks. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy.

CLEOCIN Vaginal Cream 2% has been studied in pregnant women during the second trimester. In women treated for seven days, abnormal labor was reported

⁴ PI Nuessa (metronidazole 1.3 vaginal gel. Drugs@FDA. Chemo Research SL. Revised 8/3/2018. Drugs@FDA. Accessed 7/16/2021.

⁵ DPMH Personal communication with DAI Clinical Team. 8/18/2021 and 9/16/2021.

in 1.1% of patients who received clindamycin vaginal cream 2% compared with 0.5% of patients who received placebo.

Reproduction studies have been performed in rats and mice using oral and parenteral doses of clindamycin up to 600 mg/kg/day (62 and 25 times, respectively, the maximum human exposure based on body surface area) and have revealed no evidence of harm to the fetus due to clindamycin. Cleft palates were observed in fetuses from one mouse strain treated intraperitoneally with clindamycin at 200 mg/kg/day (about 10 times the recommended dose based on body surface area conversions). Since this effect was not observed in other mouse strains or in other species, the effect may be strain specific.

Nursing Mothers

Limited published data based on breast milk sampling reports that clindamycin appears in human breast milk in the range of less than 0.5 to 3.8 mcg/mL at dosages of 150 mg orally to 600 mg intravenously. It is not known if clindamycin is excreted in human breast milk following the use of vaginally administered clindamycin phosphate.

Clindamycin has the potential to cause adverse effects on the breast-fed infant's gastrointestinal flora. If clindamycin is required by a nursing mother, it is not a reason to discontinue breastfeeding, but an alternate drug may be preferred. Monitor the breast-fed infant for possible adverse effects on the gastrointestinal flora, such as diarrhea, candidiasis (thrush, diaper rash) or rarely, blood in the stool indicating possible antibiotic-associated colitis.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clindamycin and any potential adverse effects on the breast-fed child from clindamycin or from the underlying maternal condition.

-  (b) (4)
- There are no drug-drug interactions with hormonal contraceptives.

PREGNANCY

Bacterial Vaginosis and Pregnancy⁶

Bacterial Vaginosis (BV) is a clinical condition characterized by a shift in vaginal microbiota away from *Lactobacillus* species toward more diverse bacterial species, including facultative anaerobes. The altered microbiome causes a rise in vaginal pH and symptoms that range from none to very bothersome. Future health implications of BV include, but are not limited to, increased susceptibility to other sexually transmitted infections and preterm birth. The diagnosis of BV is usually based on the Amsel criteria⁷, which are simple and useful in an office practice

⁶ Sobel JD. Bacterial vaginosis: Treatment. https://www.uptodate.com/contents/bacterial-vaginosis-treatment?search=BV%20and%20pregnancy&source=search_result&selectedTitle=1~126&usage_type=default&display_rank=1#H3349274846 Accessed 1/7/2021

⁷ Amsel criteria: 1. Thin, white, yellow, homogenous discharge; 2. Clue cells on microscopy; 3. pH of vaginal fluid >4.5; 4. Fishy odor with addition of 10% KOH solution to sample

where microscopy is available. Gram stain of vaginal discharge is the gold standard for diagnosis of BV but is mostly performed in research studies because it requires more time, resources, and expertise than the Amsel criteria.

Pregnant individuals with symptomatic BV should be treated to relieve bothersome symptoms.⁶ Oral treatment is effective and has not been associated with adverse fetal or obstetric effects.

The therapeutic options include:

- Metronidazole 500 mg orally twice daily for seven days
- Metronidazole 250 mg orally three times daily for seven days
- Clindamycin 300 mg orally twice daily for seven days

Previously clinicians avoided the use of metronidazole in the first trimester because it crosses the placenta, and published studies suggested a potential for metronidazole to cause teratogenicity.⁶ However, multiple cross-sectional, case-control and cohort studies of pregnant women have not found any relationship between metronidazole exposure during the first trimester of pregnancy and birth defects, and the Centers for Disease Control and Prevention (CDC) no longer discourages the use of metronidazole in the first trimester.⁸ An additional concern is that the metronidazole is mutagenic in bacteria and carcinogenic in mice, but there is no evidence of harm in humans.

Nonclinical Experience

In animal reproduction studies, no adverse developmental outcomes were observed when XACIATO was vaginally administered to pregnant rats and rabbits during organogenesis at doses approximately equivalent to the recommended human dose. No evidence of any adverse developmental outcomes was observed when oral or subcutaneous doses of clindamycin were administered to pregnant rats and mice during organogenesis at doses 9 to 58 times the recommended human dose based on body surface area comparison.

The reader is referred to the full Pharmacology/Toxicology report by Kelly Brant, Ph.D. and Terry Millar, Ph.D.

Review of Clinical Trials

There were two subjects within the clinical trials who were exposed to DARE-BV1 for the treatment of BV during pregnancy. Both exposures occurred during the first trimester.

- Subject (b) (6) was exposed to the test drug at 5 weeks' gestation. The patient had a history of two spontaneous abortions in the past and terminated this pregnancy at 8 weeks' gestation for unknown reasons.
- Subject (b) (6) was exposed to the test drug at 11⁺¹ weeks' gestation. The patient was taking prenatal vitamins and ginger gummies, and in addition to BV, the patient also had a yeast vaginitis infection. She delivered a healthy baby girl at 39 weeks' gestations via Caesarean section.

Review of Literature

Applicant's Review of Literature

⁸ <https://www.cdc.gov/std/treatment-guidelines/bv.htm>. Accessed 10/12/2021

The applicant performed a literature search of clindamycin use in pregnant females which yielded several articles of clindamycin use during pregnancy. The literature search can be found under a previous submission on December 8, 2020, titled “Type C Meeting Package”⁹ and under the current submission on June 7, 2021, titled “Summary of Clinical Safety.”¹⁰ The applicant discussed the studies^{38,41,42} in more detail in their recent submission titled “response to IR for PLLR formatted labeling” in DocuBridge under 1.2 on July 30, 2021.

The reader is referred to APPENDIX A for a list of articles that discuss the effect of clindamycin in pregnancy.

The applicant concludes:

Overall, safety findings from the adequate and well-controlled clinical studies, including maternal, fetal, and neonatal adverse events, were similar to those reported in the approved labeling of the listed drug, clindamycin in 0.9% sodium chloride injection, for intravenous use.

Reviewer comment:

The applicant conducted a general review of published literature regarding the use of IV, oral and topical clindamycin in pregnancy. Therefore, based on their review of literature, the applicant’s conclusion is reasonable.

DPMH’s Review of Literature

The previous DPMH review of clindamycin, NDA 208083, from February 26, 2017 by Christos Mastroyannis, M.D.,¹¹ was reviewed. The review included the following conclusions:

“[T]here are limited reports of exposure during different trimesters to clindamycin use during pregnancy. No clinical studies have reported findings to inform any potential risk of major congenital malformation or miscarriage.”

The previous DPMH review included the following labeling recommendations:

“In limited published clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of major birth defects... In limited published trials in pregnant women administered clindamycin during the first trimester of pregnancy, there was no difference in the rate of major birth defects reported among in utero exposed infants compared to unexposed infants. From these observational data, it is not possible to draw any conclusions on the rate of specific major birth defects associated with clindamycin. These data cannot definitely establish or exclude any clindamycin-associated risk during pregnancy.”

Reviewer comment: The previous DPMH memo was for IV Clindamycin and for different indications than what the applicant is proposing for this NDA. However, the previous DPMH

⁹ Applicant’s submission on 12/8/2020, “Type C Meeting Package,” page 14-16.

¹⁰ Applicant’s submission on 6/7/2021, DocuBridge Section 2.7.4. “Summary of Clinical Safety,” subsection 5.4 Use in Pregnancy and Lactation, page 19.

¹¹ DPMH review of Clindamycin in 0.9% Sodium Chloride Injection on February 26, 2017, NDA 208083, DARRTS Reference ID 4079753

memo included a general review of published literature regarding the use of IV and oral clindamycin in pregnant patients, including patients with bacterial vaginosis. The 2017 DPMH memo for IV Clindamycin includes a relevant review of published literature that is important for the current NDA.

DPMH conducted an updated search of the published literature in Embase, Pubmed, Micromedex,¹² ReproTox,¹³ TERIS,¹⁴ and Shepard's.¹⁵ Search terms used were “clindamycin” AND “pregnancy,” “clindamycin” AND “pregnancy” AND “fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage.” Three additional articles published since 2017 are summarized below.

- In a population-based case-controlled Canadian study within the Quebec Pregnancy Cohort, there were 8,702 pregnancies that ended in spontaneous abortion and 87,020 controls. Only 34 females in this study filled a prescription for clindamycin. The authors found an association with filling a prescription for clindamycin between the first day of pregnancy and the index date and spontaneous abortion (odds ratio=1.27, 95% CI 0.89–1.81). The risk of miscarriage was similar when pregnancies exposed to clindamycin in this study were compared to those exposed to penicillin (odds ratio= 1.48, 95% CI 1.02–2.14) and cephalosporins (odds ratio=1.42, 95% CI 0.91–2.21).¹⁶ Disease process was not accounted for in this study.
- In a randomized controlled study in Bangladesh, 622 pregnant people between 13 to 19 weeks' gestation with abnormal vaginal flora were randomized to receive either oral clindamycin 300mg twice per day for 5 days or placebo.¹⁷ The incidence of preterm birth was not significantly different between both groups.
- In a population-based case-controlled study based on 15 EUROCAT registries in 13 European countries, 145,936 babies with congenital anomalies (CA) were evaluated. The authors evaluated for an association between congenital anomalies (specifically congenital heart disease (CHD), anencephaly, orofacial clefts, genital and limb reduction anomalies) and first trimester exposure to macrolides (including erythromycin, clarithromycin, azithromycin) (n=307) or lincosamides, included only clindamycin (n=28). This study did not identify an association between clindamycin exposure during the first trimester (compared to unexposed) and musculoskeletal anomalies, ventricular septal defects, atrial septal defects, and atrioventricular septal defects. The authors identified an association between use of clindamycin in the first trimester and hydrocephalus aOR 6.63, 95% CI (1.46, 30.18); however, there were only 3 exposed cases and the authors noted that this finding needs confirmation in an

¹² Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 7/19/2021.

¹³ ReproTox Website: www.Reprottox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 7/19/2021.

¹⁴ TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 7/19/2021.

¹⁵ 2020 Shepard's: A Catalog of Teratogenic Agent. Accessed 7/19/2021.

¹⁶ Muanda, F.T.; Sheehy, O. and Berard, A.: Use of antibiotics during pregnancy and risk of spontaneous abortion. CMAJ 189(17):E625-E633, 2017b.

¹⁷ Lee A.C., Mullany L.C., Quaiyum M., Mitra D.K., Labrique A., Christian P., Ahmed P., Uddin J., Rafiqullah I., DasGupta S., Rahman M., Koumans E.H., Ahmed S., Saha S.K., Baqui A.H. Effect of population-based antenatal screening and treatment of genitourinary tract infections on birth outcomes in Sylhet, Bangladesh (MIST): a cluster-randomised clinical trial. The Lancet Global Health 2019 7:1 (e148-e159)

independent dataset.¹⁸

According to American College of Obstetrics and Gynecologists (ACOG), clindamycin is indicated for use during labor for the prevention of group B streptococcal infection in neonates if the mother has a high risk of anaphylaxis from penicillin and the GBS isolate is known to be susceptible to clindamycin.¹⁹

Micromedex¹² states clindamycin crosses the placenta and “available evidence is inconclusive or is inadequate for determining fetal risk when used in pregnant [females] or [females] of childbearing potential.” There are no adequate and well-controlled studies of clindamycin use in pregnant females during the first trimester. Micromedex gives Pregnancy Rating: “Fetal risk cannot be ruled out.”

ReproTox¹³ states “based on experimental animal studies, clindamycin therapy during pregnancy is not expected to increase the risk of congenital anomalies.” There are several studies in humans of clindamycin use in pregnancy. Clindamycin pharmacokinetics do not appear to change during human pregnancy.^{20,21} Three publications cited by ReproTox that were not previously mentioned are described below.

- A study reported no malformations among 16 children born to females treated with clindamycin and amoxicillin during the first trimester.²²
- Congenital anomalies were observed in two (3%) of 66 infants whose mothers were treated with a combination of quinine (10 mg salt/kg every 8 hours) and clindamycin (5 mg/kg every 8 hours) for seven days for acute uncomplicated falciparum malaria in the second or third trimester of pregnancy. No increase in malformations were observed among the infant exposed to clindamycin and quinine for malaria in the second or third trimester of pregnancy.²³
- The frequency of congenital anomalies was no greater than expected among the infants of 104 women treated with clindamycin in the second or third trimester of pregnancy as part of a controlled trial of therapy to prevent low birth weight.²⁴

¹⁸ Leke, AZ et al. Macrolide and lincosamide antibiotic exposure in the first trimester of pregnancy and risk of congenital anomaly: A European case-control study, *Reproductive Toxicology*. 2021(100):101-108.

¹⁹ ACOG Committee Opinion No. 797, February 2020. <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/02/prevention-of-group-b-streptococcal-early-onset-disease-in-newborns>

²⁰ Weinstein AJ et al: Placental transfer of clindamycin and gentamicin in term pregnancy. *Am J Obstet Gynecol* 124:688-91, 1976.

²¹ Philipson A et al: Erythromycin and clindamycin absorption and elimination in pregnant women. *Clin Pharmacol Ther* 19:68-77, 1976.

²² Ou M-C, Pang C-C, Chen F-M et al: Antibiotic treatment for threatened abortion during the early first trimester in women with previous spontaneous abortion. *Acta Obstet Gynecol Scand* 80:753-756, 2001.

²³ McGready R, Cho T, Samuel et al: Randomized comparison of quinine- clindamycin versus artesunate in the treatment of falciparum malaria in pregnancy. *Trans R Soc Trop Med Hyg* 95:651-656, 2001.

²⁴ McCormack WM, Rosner B, Lee Y-H, Munoz A, Charles D, Kass EH: Effect on birth weight of erythromycin treatment of pregnant women. *Obstet Gynecol* 69(2):202-207, 1987

Shepard¹⁴ references the studies described in APPENDIX A and the studies noted above.

TERIS¹⁵ notes the quality and quantity of the data on which risk estimate is based on are limited, although small risk cannot be excluded, a high risk of congenital anomalies is unlikely. The systemic absorption of clindamycin is about 5% from vaginal preparations and less from topical preparations applied to the skin.

Reviewer comment:

Overall, the published literature did not identify an association between clindamycin use during the pregnancy and an increased risk of major congenital malformations (MCM), miscarriage, or adverse maternal and fetal outcomes. There were three observational studies on first trimester clindamycin use and MCMs^{44,45,18}(see Appendix A). Although one population based study found an association between clindamycin (route of administration was not specified) use during pregnancy and an elevated risk of musculoskeletal system malformations (aOR1.67, 95% CI (1.12-2.48), n=29) and ventricular/atrial septal defect (aOR 1.81, 95% CI (1.04-3.16), n=13), this was an exploratory finding and was not duplicated in other studies⁴⁵ Clindamycin does not decrease the risk of preterm birth in pregnant people with BV.^{48,50,54,56,57,58,59} One study suggests utilization of vaginal clindamycin during 26 to 32 weeks' gestation increases the rate of preterm deliveries and neonatal infectious morbidity in those mothers with history of preterm birth without BV compared to placebo.⁵⁹ The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION

Nonclinical Experience

Administration of XACIATO to female rats at 2 mg clindamycin/day (approx. 5 mg/kg/day) from gestational day 6 up to lactation day 21 via the vaginal route had no adverse effect to the pregnant/lactating animals or their offspring. No clindamycin was detected in plasma samples from offspring collected on postnatal day 4 or postnatal day 21. There were no dedicated animal lactation studies that were conducted.

The reader is referred to the full Pharmacology/Toxicology report by Kelly Brant, Ph.D. and Terry Millar, Ph.D.

Review of Literature

Applicant's Review of Literature

The applicant conducted a search of published literature and found no relevant clinical studies regarding use of clindamycin during lactation.

DPMH's Review of Literature

The previous DPMH review of clindamycin from February 26, 2017 by Christos Mastroyannis, M.D.,²⁵ concluded the following:

“Clindamycin is present in breast milk in small amounts. As such, it has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora. If oral or intravenous

²⁵ DPMH review of Clindamycin in 0.9% Sodium Chloride Injection on February 26, 2017, NDA 208083, DARRTS Reference ID 4079753

clindamycin is required by a breastfeeding woman, it is not a reason to discontinue breastfeeding, but an alternate drug may be preferred. The American Academy of Pediatrics classified clindamycin as compatible with breastfeeding.”

DPMH conducted an updated search of published literature in PubMed and Embase using the search terms “clindamycin” AND “lactation” and “clindamycin” AND “breastfeeding.”

- There are no new articles on the use of clindamycin during lactation.

Micromedex,¹¹ ReproTox,¹² and LactMed²⁶ note that clindamycin is present in human milk following oral and parenteral administration.

LactMed notes the following in the table below.

Table 1. Clindamycin milk level in breastfeeding²⁷

Author/Year/Location	Timing	Route of Administration	Subjects	Milk level
Matsuda S, et al. ²⁸ 1969, Japan*		150mg orally	2	1.3 mg/L 4 hours after dosing
Smith JA, et al. ²⁹ 1975, Canada	Not stated	600mg IV q6h followed by 300mg orally q 6 hours	2	Present in milk [†]
Stéen B, et al. ³⁰ 1982, Sweden	Within 2 weeks pp	150 mg orally TID (1 weeks into treatment)	5	Mean peak: 1.2 mg/L (range <0.5 mg/L to 3.1 mg/L) 6 hours after last dose [†]
Matsuda S. et al. ³¹ 1984, Japan		150mg orally (single dose)	2	0.3-1.2 mg/L between 1 and 6 hours after dose. Peak at 2 and 4 hours after dose.
Zhang Y, et al. ³² 1997, China	1 month pp	600mg IV (single dose)	15	Mean level 1.03 mg/L 2 hours after dose.

*The reported result is cited from LactMed, this reviewer was unable to locate the actual article.

[†] The reported result cited from LactMed is inconsistent with the article. LactMed reports milk peak was 2.65 mg/L 3.5 hours after an IV dose and 3.1 mg/L 30 min after an oral dose. This reviewer found inconsistency in the letter cited. The letter states the levels measured were clindamycin blood concentrations. However, the authors noted that

²⁶ <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The lactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Access 3/13/21.

²⁷ Reviewer’s table, created from studies from LactMed, accessed 7/22/2021, the effect on the breastfeeding infants were not reported in any of the articles listed in this table.

²⁸ Matsuda S, Mori S, Azuma S. Clinical evaluation of clindamycin in gynecology-obstetrics. *Chemotherapy (Tokyo)*. 1969; 17:899–900.

²⁹ Smith JA, Morgan JR, Rachlis AR, et al. Clindamycin in human breast milk. *Can Med Assoc J* 1975; 112:806. Letter. PMID: 20312646.

³⁰ Steén B, Rane A. Clindamycin passage into human milk. *Br J Clin Pharmacol*. 1982; 13:661–4.

³¹ Matsuda S. Transfer of antibiotics into maternal milk. *Biol Res Pregnancy Perinatol*. 1984; 5:57–60.

³² Zhang Y, Zhang Q, Xu Z. *Zhonghua Fu Chan Ke Za Zhi*. 1997; 32:288–92. [Tissue and body fluid distribution of antibacterial agents in pregnant and lactating women]

the milk from mothers that received clindamycin showed antimicrobial properties on bacterial inhibition test, while the controls did not.

‡ The authors found a correlation between milk and plasma AUC levels. Drug transfer to milk is inversely dependent on plasma protein binding. Individual variations were significant

Clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora. Bloody stools in a 5-day-old breastfed infant were possibly caused by maternal clindamycin use (600mg intravenously every 6 hours and gentamicin 80mg intravenously).³³ Micromedex advises monitoring breastfed infants exposed to clindamycin for possible adverse effects, such as diarrhea, candidiasis, or bloody stools.

LactMed²⁶ notes that vaginal application is unlikely to cause infant side effects. Hales³⁴ states that about 5% of vaginal clindamycin is absorbed into the maternal circulation.³⁵ Both Hales³⁴ and Brigg's³⁶ categorized clindamycin as breastfeeding compatible.

The American Academy of Pediatrics considers clindamycin to be compatible with breastfeeding.³⁷

The World Health Organization recommends avoiding clindamycin while nursing.³⁸

Reviewer comment:

Clindamycin is present in human milk when administered orally and intravenously. Because the systemic concentration following intravaginal administration of clindamycin is low, transfer of clindamycin into breastmilk is likely to be low. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Long term studies in animals to evaluate carcinogenic potential have not been performed with XACIATO, or the active ingredient, clindamycin phosphate. The genotoxic potential of clindamycin has been evaluated in a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative.

Fertility studies in rats treated vaginally with 2 mg/day clindamycin phosphate (0.1g/day XACIATO) or orally with 300 mg/kg/day (approximately equivalent to and 29-times the MRHD based on BSA comparisons, respectively) revealed no effects on fertility or mating ability.

³³ Mann CF: Clindamycin and breast-feeding. Pediatrics 66:1030-1, 1980.

³⁴ Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.

³⁵ Pharmaceutical manufacturer prescribing information, 2010.

³⁶ Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 3/13/21.

³⁷ Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human breast milk. Pediatrics 108:776-89, 2001.

³⁸ Anon: Breastfeeding and Maternal Medication. World Health Organization, Geneva, Switzerland, 2002.

The reader is referred to the full Pharmacology/Toxicology report by Kelly Brant, Ph.D. and Terry Millar, Ph.D. on September 17, 2020.

Review of Literature

Applicant's Review of Literature

The applicant conducted a search of published literature and found no relevant clinical studies regarding the use of clindamycin and fertility.

DPMH's review of literature

The previous DPMH review of clindamycin from February 26, 2017 by Christos Mastroyannis, M.D.,³⁹ did not find any reports of adverse effects of clindamycin on the fertility of females and males of reproductive potential in the published literature.

DPMH conducted an updated search of published literature using Embase, Pubmed, Micromedex,⁴⁰ ReproTox,⁴¹ and TERIS.⁴² Search terms used were "clindamycin" AND "reproduction," "clindamycin" AND "infertility," and "clindamycin" AND "contraception."

- No articles of clindamycin adversely affecting fertility were found.

ReproTox⁴¹ notes that product labeling indicated that no adverse effects on fertility or mating were observed in rats treated orally at up to 300 mg/kg/day, the equivalent of 31 times the human dose on body surface area basis.⁴³

Reviewer comment:

There is no published literature on clindamycin adversely affecting human fertility. Animal fertility studies did not show any adverse effects of clindamycin on fertility.

In discussion with CDRH, DAI Clinical Team and the DAI Clinical Pharmacology Team, it was noted that there is a potential interaction between intravaginal clindamycin with polyurethane condoms, which may render polyurethane condoms less effective. Based on concentration of clindamycin in the vagina (which drops on day 3 following clindamycin gel administration in majority of the patients, but some had measurable levels on day 4 and day 6 following clindamycin gel administration), the DAI Clinical Team agrees with not using polyurethane condoms during XACIATO gel use and for 7 days after the completion of treatment. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

³⁹ DPMH review of Clindamycin in 0.9% Sodium Chloride Injection on February 26, 2017, NDA 208083, DARRTS Reference ID 4079753

⁴⁰ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 7/20/21.

⁴¹ Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 7/20/21.

⁴² Teris database, Truven Health Analytics, Micromedex Solutions, Accessed 7/20/21.

⁴³ Pharmacia and Upjohn Company LLC. 2019. Cleocin product label. Available at <https://dailymed-nlm-nih.gov/fda/idm.oclc.org/dailymed/drugInfo.cfm?setid=d952e542-d040-42ec-b40e-198195bfe8d0>

DISCUSSION AND CONCLUSIONS

Pregnancy

Available data from published literature, observational studies and randomized controlled trials, over decades of use with clindamycin during pregnancy have not identified a consistent increased risk of major birth defects, miscarriage, or other adverse maternal and fetal outcomes. There were three published studies that evaluated the use of clindamycin during the first trimester of pregnancy. Of the three studies, one study demonstrated an elevated risk of musculoskeletal system malformations and ventricular/atrial septal defect; however, the authors noted that this was an exploratory finding, and this finding was not duplicated in other studies. Most of the reported exposures to clindamycin occurred during the second and third trimesters of the pregnancy.

Additionally, based on DPMH discussion with the DAI Clinical Pharmacology Team, the Clinical Pharmacology Team confirmed that systemic exposure of XACIATO Vaginal Gel 2% is low. In premenopausal women (mean C_{max} of 11.3 ng/mL and AUC₀₋₂₄ of 188 h*ng/mL) is relatively low compared to IV injection (14.1 µg/mL and AUC_{24h} = 104 µg·h/m). The Clinical Pharmacology Team and DPMH agreed to include the following statement in subsection 8.1, Risk Summary: “Based on the low systemic absorption of XACIATO gel, maternal use is not likely to result in significant fetal exposure to the drug.”

The listed drug relied upon for this submission is Cleocin Vaginal Cream 2%, NDA 050680, which is indicated for the treatment of bacterial vaginosis and can be used to treat non-pregnant women and pregnant women during the second and third trimester. Vaginal clindamycin has been widely used for treatment of BV during all trimesters of pregnancy, including the first trimester.⁸ DPMH agrees with the DAI Clinical Team that the indication for XACIATO gel should include the treatment of bacterial vaginosis in female patients (12 years of age and older) without specific reference to pregnancy trimester. When a drug is approved in female patients, the drug is also approved to treat pregnant patients. Based on the information noted above from the review of literature and based on discussion with the DAI Clinical Pharmacology Team, DPMH updated subsection 8.1 of XACIATO gel labeling.

No new safety concerns were identified in this updated clindamycin review. DPMH does not recommend a postmarketing pregnancy study at the current time.

Lactation

Clindamycin is present in human milk following oral and parenteral administration. Because systemic concentration following intravaginal administration of clindamycin is relatively low compared to IV clindamycin injection; transfer of XACIATO gel into breastmilk is likely to be low. Although labeling for the listed drug relied upon, Cleocin Vaginal Gel 2%, includes information regarding a case report of bloody diarrhea in a breastfed infant whose mother was exposed to IV clindamycin, this adverse effect is unlikely with intravaginal administration of XACIATO gel, which has low systemic absorption; therefore, this information will not be included in subsection 8.2 of XACIATO gel labeling. Subsection 8.2 will be updated to include language about low systemic absorption. There are no data on the effect of clindamycin on milk production.

Since systemic absorption of XACIATO gel is likely to be low and since there are no new safety concerns identified in this review regarding clindamycin use in lactation, DPMH does not recommend a postmarketing lactation study at the current time.

Females and Males of Reproductive Potential

There is no evidence in the literature to suggest that clindamycin use adversely affects male or female fertility. An animal fertility study did not show any adverse effects on fertility. There is anticipated drug-to-drug interaction between clindamycin with hormonal contraceptives. There is a potential interaction between intravaginal clindamycin with polyurethane condoms, which may render polyurethane condoms less effective. Based on discussion with the DAI Clinical Team, DPMH agrees with not using polyurethane condoms during XACIATO gel use and for 7 days after treatment. This information should be included under Warnings and Precautions and Patient Counseling Information. DPMH recommends omitting subsection 8.3 of the labeling.

LABELING RECOMMENDATIONS



(b) (4)

APPEARS THIS WAY IN ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WENJIE SUN
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MIRIAM C DINATALE
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LYNNE P YAO
11/02/2021 07:08:39 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: 10/29/2021

To: Mukil Natarajan, M.D.
Division of Anti-Infectives (DAI)

Alison Rodgers, Regulatory Project Manager, (DAI)

Abimbola Adebawale, Associate Director for Labeling, (DAI)

From: Melissa Khashei, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for Xaciato (clindamycin phosphate vaginal gel 2%)

NDA: 215650

In response to DAI's consult request dated June 23, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI)/Medication Guide/Instructions for Use (IFU), and carton and container labeling for the original NDA/BLA submission for Xaciato.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAI on October 21, 2021, and are provided below.

OPDP comments on the proposed PPI/Medication Guide/IFU will be sent under separate cover, either as a combined OPDP and Division of Medical Policy Programs (DMPP) review or a separate OPDP review.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAI on October 21, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or Melissa.Khashei@fda.hhs.gov.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MELISSA KHASHEI
10/29/2021 02:03:38 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 15, 2021

TO: File

THROUGH:

FROM: Alison Rodgers

SUBJECT: CDRH Review

APPLICATION/DRUG: NDA 215650/Xaciatto

Attached is the CDRH review of the Biocompatibility Protocol for NDA 215650.



Food and Drug Administration
Center for Devices and Radiological Health
Office of Product Evaluation and Quality

DATE: October 7, 2021
FROM: Rebecca Dorsey, Biomedical Engineer
CDRH/OHT3/DHT3B/THT3B1
TO: Alison Rodgers, Regulatory Health Project Manager
CDER/OND/ORO/DROID
RE: NDA 215650: Supporting Document 1
Xaciato (Dare BV1)
Dare Bioscience, Inc.

I. Submission Purpose

The subject combination product is a vaginal gel which has been developed to treat bacterial vaginosis. The gel is contained in a (b) (4) flexible (b) (4) tube with a screw top on one end and a crimped folded edge on the other. A (b) (4) applicator consisting of a barrel and plunger is also provided with the subject product.

CDER is requesting CDRH provide a review of the assays with the applicator. This includes the following test reports: (b) (4) MTT Cytotoxicity Test, (b) (4): ISO Guinea Pig Maximization Sensitization Test, and (b) (4): ISO Vaginal Irritation Study in Rabbits.

Dr. Gunja Pathak previously reviewed this product under IND 143919.

II. Review Summary

This review memo will be limited to the biocompatibility studies provided to support the safety of the (b) (4) vaginal applicator used to administer the DARE-BV1 gel.

III. Indications for Use

Treatment of bacterial vaginosis (BV) in adult women.

IV. Product Description

DARE-BV1 is a 2% clindamycin gel for vaginal administration. The product is contained in an (b) (4) flexible tube fitted with a screw top cap on one end and a crimped folded edge of the other. The tubes are supplied with a (b) (4) single dose applicator. A single 5-gram dose is filled from the tube into the applicator at the time of administration.

The container closure system is as follows:

- (b) (4) flexible (b) (4) tube with a screw cap on one end and a crimped folded edge on the other. Each (b) (4) tube is filled with 25 grams of gel.
- (b) (4) applicator consisting of a barrel and plunger (b) (4).

The applicator is a (b) (4) vaginal cream applicator (b) (4) (b) (4). The (b) (4) applicator has a black mark (b) (4) on the plunger to

indicate the amount of gel to be filled into the applicator prior to administration (b) (4)
(b) (4). The applicator can be seen in the figure below.



The applicator in this submission is not the same as the applicator that was reviewed under IND 143919. Under IND 143919, the applicator was prefilled. In this submission the sponsor has changed the packaging of the subject product. The gel is contained in an (b) (4) tube and is transferred to the applicator at the time of application. The applicators are produced by the same manufacturer, (b) (4) however, they are made of different materials and have different dimensions.

V. Review

Per the CDRH Guidance Document *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"*, the proposed applicator is a surface device that contacts both the skin and mucosal membranes for a limited (<24 hours) contact duration. Therefore, the sponsor should assess the cytotoxicity, sensitization, and irritation potential of the subject applicator.

The sponsor provided results of cytotoxicity, sensitization, and vaginal irritation testing on the subject applicator. Dr. Gunja Pathak previously reviewed the biocompatibility test reports for the applicator under IND 143919 and found them to be acceptable. Since the applicator was changed, the sponsor reconducted the biocompatibility studies on the current applicator. However, the same test protocols were followed, and the results were only slightly different, but were still acceptable. The table below provides an assessment of the testing conducted.

Biocompatibility Information Red = Inadequate or Unanswered Yellow = Focal Point			
There is/are 1 tissue contacting products/components/materials.			
Material compositions described?: Yes			
Device has Special Considerations?: No			
Table of Materials and Rationales			
Component	Material	Type of Contact	Identical Material & Rationale
Vaginal Applicator	(b) (4)	Direct	No, No Rationale
Rationale			
Rationale: No rationale provided.			
Biocompatibility Material 1:			
Test Component/Material: Vaginal Applicator / (b) (4)			
Potential for Repeat Exposure?: No			
Type of Tissue Contact: Surface Device: Mucosal Membrane			
Duration of Contact: < 24 hours			
Cytotoxicity Testing Red = Inadequate or Unanswered Yellow = Focal Point			
Cytotoxicity testing conducted: Extraction Method (MEM Elution)			
Test Article: (b) (4) vaginal applicator			
Extraction Conditions	Methods	Results	Conclusion and Recommendation
Extraction Method: 3 cm ² /ml (>0.5mm thick) Extraction Vehicles: Culture medium with 5-10% serum Extraction Conditions: 37 °C for 24 hr Sample Modified?: No Study Controls: All Extract Appearance is acceptable?: Yes Storage Conditions: Used by 24 hrs post-extraction	Test System: L-929 Mouse fibroblasts (monolayer) Assessment Times: Required: 37°C for 48 hr minimum Proper Scale Used: Yes Deviations?: No	Cell Abnormalities: No Scores in controls as expected: Yes	Cytotoxic Potential: Non-cytotoxic (Grade 0) Recommendation: Acceptable
Comments: (b) (4)			
Sensitization Testing Red = Inadequate or Unanswered Yellow = Focal Point			
Sensitization testing conducted: Yes, Guinea Pig Maximization Test (GPMT)			
Test Article: (b) (4) vaginal applicator			
Extraction Conditions	Methods	Results	Conclusion and Recommendation
Extraction Ratio: 3 cm ² /ml (>0.5mm thick) Extraction Vehicle: Both	Test System: ≥ 10 Test & ≥ 5 Control Males &/or Females (nulliparous, not pregnant) Proper Injections Given?: Yes	Normal & No Deaths?: Normal appearance, no deaths Polar extract score < 1.0?: Yes	Sensitizing Potential: Non-Sensitizer Recommendation: Acceptable

Biocompatibility Information		Red = Inadequate or Unanswered	Yellow = Focal Point
Extraction Conditions: 50 °C for 72 hr Sample was adjusted?: No Positive Control: Historical control <3 months from the time of test The Positive Control is: DNCB (0.05-0.5%) The Negative Control is: Extraction vehicles without test material only Extract Appearance is acceptable?: Yes Storage Conditions: Used by 24 hrs post-extraction	Proper Procedure on Day 6?: Yes Proper Procedure on Day 7?: Yes Proper Procedure after 14 Days?: Yes Assessment Times after Challenge: 24 and 48 hours Deviations?: No	Non-Polar extract score < 1.0?: Yes Positive Control ≥ 1.0?: Yes	
Comments: (b) (4)			
Irritation Testing		Red = Inadequate or Unanswered	Yellow = Focal Point
Irritation testing conducted: Yes, Mucosal Irritation Test			
Comments: See below for summary of the mucosal irritation test. (b) (4)			

MTT Cytotoxicity Test (3.2.P.2)

The test article, (b) (4) vaginal applicator, was evaluated for potential cytotoxic effects. This study was conducted following the guidelines of ISO 10993-5, *Biological evaluation of medical devices – Part 5: Tests for in vitro cytotoxicity*. A single preparation of the test article was extracted in single strength minimum essential medium (1X MEM) at 37 °C for 24 hours. A negative control, reagent control, and two positive controls were similarly prepared. Following extraction, the test article and each of two positive control extracts were diluted to obtain solutions of approximate concentrations of 50%, 25%, and 12.5%. Triplicate monolayers of L-929 mouse fibroblast cells were dosed with the full strength (100%) and diluted extracts and incubated at 37 °C (humidified) in the presence of 5% CO₂ for 24-26 hours. Following incubation, the culture medium was replaced with a 1 mg/mL MTT solution and incubated for an additional 2 hours. Following this step, the MTT solution was replaced with isopropanol. The percent viability for the test article was determined from the reagent control. A decrease in the number of living cells results in a decrease in the metabolic activity in the sample. This decrease directly correlates to the amount of blue-violet formazan formed, as monitored by the optical density at 570 nm.

The 1X MEM test extract showed no cytotoxic potential to L-929 mouse fibroblast cells at 100% or any dilution.

Guinea Pig Maximization Test (3.2.P.2)

The test article, (b) (4) vaginal applicator, was evaluated for the potential to cause delayed dermal contact sensitization in a guinea pig maximization test. This study was conducted based on the requirements of ISO 10993-10, *Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization*. The test article was extracted in 0.9% sodium chloride USP and sesame oil, NF. Each extract was intradermally injected and occlusively patched to ten test guinea pigs (per extract). The extraction vehicle was similarly injected and occlusively patched to five control guinea pigs (per vehicle). Following a recovery period, the test and control animals received a challenge patch of the appropriate test article extract and the vehicle control. All sites were scored for dermal reactions at 24 and 48 hours after patch removal.

The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was not considered a sensitizer in the guinea pig maximization test.

Vaginal Irritation Study in Rabbits (3.2.P.2)

The test article, (b) (4) vaginal applicator, was evaluated for the potential to cause irritation to vaginal tissue in rabbits. This study was conducted in accordance with the requirements of ISO 10993-

10, *Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization*. The test article was extracted in 0.9% sodium chloride USP solution (SC) and sesame oil, NF (SO). Three animals per extract each received a daily 1 mL intravaginal administration of the appropriate test article extract for 5 consecutive days. Three additional animals per extract vehicle were similarly treated with SC or SO to serve as the control condition. The animals were euthanized the day following the last treatment, each vagina was removed, and evaluated macroscopically and microscopically.

The SC test article extract was considered a nonirritant to vaginal tissue of the rabbit. The SO test article extract was considered a nonirritant to vaginal tissue of the rabbit.

VI. Recommendation

The sponsor has adequately assessed the necessary biocompatibility endpoints for the applicator.

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Assistant Director / Acting Team Lead Sign-Off	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALISON K RODGERS
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 30, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 215650
Product Name and Strength:	Xaciato (clindamycin phosphate) Vaginal Gel, 2%
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Daré Bioscience, Inc (Daré)
FDA Received Date:	June 7, 2021 and August 30, 2021
OSE RCM #:	2021-1141
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for Xaciato (clindamycin phosphate) Vaginal Gel, the Division of Anti-Infectives (DAI) requested that we review the proposed Xaciato prescribing information (PI), patient package insert (PPI), and Instructions for Use (IFU), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

(b) (4)

1.1 REGULATORY HISTORY

NDA 215650 is a 505(b)(2) NDA and the reference products are Cleocin Vaginal Cream 2% (NDA 050680) and Clindamycin in 0.9% Sodium Chloride injection (NDA 208083).

On June 7, 2021, Daré included their

(b) (4)

According to Daré, "Currently, application of the product by the patient requires dispensing only 5 g of the 25 g fill into a vaginal applicator for single unit dosing of the product. Note, the remainder of the material in the (b) (4) tube is discarded and results in waste of product."

(b) (4)

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A

(b) (4)

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Label and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), patient package insert (PPI) and Instructions for Use (IFU), container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Daré Bioscience, Inc.

4 RECOMMENDATIONS FOR DIVISION OF ANTI-INFECTIVES (DAI)

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The package type term is missing throughout the prescribing information, as well as on the container label and carton labeling.	Omission of an appropriate package type term can result in the remaining contents being “saved” for future use resulting in deteriorated drug product medication errors.	We defer to Office of Pharmaceutical Quality (OPQ) to determine the appropriate package type term (e.g., single use) to be incorporated throughout the prescribing information (e.g., Sections 3 and 16), container label, and carton labeling.
Highlights of Prescribing Information			
Full Prescribing Information – Section 2 <i>Dosage and Administration</i>			

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	As currently presented, subsection 2.1 <i>Recommend Dosage</i> states (b) (4) does not include information regarding the dosage strength.	To avoid medication errors involving strength confusion, the product strength designation should be consistent across all elements of the labeling (e.g., container, carton, and prescribing information).	Revise the current statement to include the strength (i.e., 5 g of vaginal gel contains approximately 100 mg of clindamycin). For example, “The recommended dosage of XACIATO is a single applicator containing 5 g of XACIATO gel (5 g contains 100 mg of clindamycin) administered once intravaginally at any time of the day.”
2.	We note the inclusion of (b) (4) (b) (4) (b) (4) within the PI could lead to use error. Additionally, as the PI is intended for use by healthcare providers (HCPs) we are curious if the proposed (b) (4) is necessary. We discussed our concerns with the DAI review team and determined that (b) (4) could be omitted from the PI. Therefore, we recommend deleting (b) (4) from the PI and instead including a statement in Section 2 to refer to the Instructions for Use for instructions to prepare and administer this product.		
Full Prescribing Information – Section 3 <i>Dosage Forms and Strengths</i>			
1.	As currently presented, the appropriate information to facilitate identification of the dosage form is not included.	A description of identifying characteristics is required by 21 CFR 201.57(c)(4)(ii) and can be used to help mitigate the risk of administering deteriorated or contaminated drug for this product.	We recommend that the description of identifying characteristics of the dosage form, such as color (e.g., colorless) and clarity (e.g., clear) and any other identifying characteristics (e.g., viscous), be added in accordance with 21 CFR 201.57(c)(4)(ii) (i.e., as stated in Section 11,

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			<i>Description, "clear, colorless, viscous gel").</i>
Full Prescribing Information – Section 16 <i>How Supplied/Storage and Handling</i>			
1.	As currently presented, the National Drug Code (NDC) is not included.	To facilitate identification of the dosage form, the NDC number is required per 21 CFR 201.57(c)(17)(iii).	Once assigned and in accordance with 21 CFR 201.57(c)(17)(iii), add the NDC number to the How Supplied section.
2.	As currently presented, the appropriate information to facilitate identification of the "vaginal gel" dosage form is not included.	A description of identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57(c)(17)(iii).	We recommend that the description of identifying characteristics to facilitate identification of the "vaginal gel" dosage form, such as color (e.g., clear, colorless, viscous gel) or other identifying characteristics, be added in accordance with 21 CFR 201.57(c)(17)(iii).

5 RECOMMENDATIONS FOR DARÉ BIOSCIENCE, INC

Table 3. Identified Issues and Recommendations for Daré Bioscience, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling (25 gram)			
1.	As currently presented, the package type term is not included.	If an appropriate package type term is not included, patients might attempt to save the remaining contents of the tube for future use resulting in use of deteriorated drug product medication errors.	Add the appropriate package type term as determined by OPQ. Additionally, we recommend that the package type term be followed by the statement "Discard Unused Portion."

Table 3. Identified Issues and Recommendations for Daré Bioscience, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	As currently presented, the storage statement "Store at 20-25°C (68-77°F); excursions permitted to 15-30° (59-86°F)..." included on the proposed container label and carton labeling lacks the degree symbol (°) and units of measurement (Centigrade and Fahrenheit) following the first numbers in the temperature ranges. Additionally, this storage statement on the proposed container label and carton labeling does not align with the storage statement "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)..." in the proposed prescribing information (PI).	The lower temperatures in the ranges may be overlooked. Additionally, when a hyphen is included in a range instead of the word "to," the hyphen can be overlooked.	To provide clarity and consistency with the storage statement as presented in the proposed PI, add the degree and Centigrade symbols (°C) following the numbers "20" and "15," and the degree and Fahrenheit symbols (°F) following the numbers "68" and "59" within the storage statement. Additionally, we also recommend replacing the hyphen with its intended meaning "to." For example, "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)..."
3.	As currently presented, the National Drug Code (NDC) is denoted by a placeholder (NDC XXXX-XXXX-XX) on both the proposed container label and carton labeling.		Once assigned, replace the current placeholders (NDC XXXXX-XXXX-XX) with the intended NDCs on the container label and carton labeling and submit for our review. Additionally, in accordance with 21 CFR 201.57(c)(17)(iii), you will need to be add your intended NDC to Section 16,

Table 3. Identified Issues and Recommendations for Daré Bioscience, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			<i>How Supplied /Storage and Handling of the Prescribing Information.</i>
Container Label (25 gram)			
1.	As currently presented, the route of administration statement "FOR INTRAVAGINAL USE ONLY. Not for Ophthalmic, Dermal, or Oral Use." is not included on the principal display panel of the container (PDP) label.	The route of administration statement is considered to be "critical information." For more information see the draft guidance for industry, " <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> ". ^b To avoid medication errors involving wrong route of administration, the route of administration statement should be prominently displayed on the PDP.	To increase the prominence, we recommend that you relocate the route of administration statement "FOR INTRAVAGINAL USE ONLY. Not for Ophthalmic, Dermal, or Oral Use." to the PDP.
2.	The format for the human-readable expiration date is not defined.	Clearly defining the human-readable expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the human-readable expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only

^b When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

Table 3. Identified Issues and Recommendations for Daré Bioscience, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Carton Labeling (25 gram)			
1.	As currently presented, the terminology within the recommended dosage statement (i.e.,  ^{(b) (4)} is inconsistent with the terminology in the Prescribing Information."	The recommended dosage statement terminology should be consistent across the labeling to mitigate risk of confusion.	To ensure consistency with the Prescribing Information, we recommend revising the current dosage statement,  ^{(b) (4)} to instead state "Dosage: One single-dose 5 g applicatorful. See prescribing information. Administration: See Instructions for Use."
2.	As currently presented, the intended location for the lot number and expiration date is not provided on the	The lot number statement is required on the carton labeling per 21 CFR 201.10(i)(1) and the product expiration date is	Identify the intended location of the lot number statement and expiration date. When determining this placement, please ensure that there are no other numbers located in close

Table 3. Identified Issues and Recommendations for Daré Bioscience, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	proposed carton labeling that was submitted.	also required on the carton labeling per 21 CFR 201.17.	proximity to the lot number/expiration date that can be mistaken as the lot number/expiration date. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use for the expiration date. We recommend that the human-readable expiration date on the container labels and carton labeling include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
3.	As currently presented, the intended location of the human-readable and machine-readable (2D	The Drug Supply Chain Security Act (DSCSA) requires manufacturers and re-packagers, respectively,	We recommend that you review the guidance to determine if the product identifier requirements apply

Table 3. Identified Issues and Recommendations for Daré Bioscience, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	data matrix barcode) product identifier on the smallest saleable unit (usually the carton) is not provided.	to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	to your product’s labeling. See <i>Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers</i> (July 2021). ^c Additionally, we recommend you ensure there is sufficient white space between the linear barcode and 2-D matrix barcode to allow barcode scanners the ability to correctly read each barcode.

(b) (4)

(D) (4)

^c Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers>.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Xaciato that Daré Bioscience, Inc submitted on June 7, 2021.

Table 4. Relevant Product Information for Xaciato	
Initial Approval Date	N/A
Active Ingredient	clindamycin phosphate
Indication	treatment of bacterial vaginosis in adult women
Route of Administration	intravaginal
Dosage Form	vaginal gel
Strength	2%
Dose and Frequency	A single applicator containing 5 g of gel administered once intravaginally at any time of the day.
How Supplied	Supplied in a carton containing one 25-gram tube of gel and one vaginal applicator. One single-dose, user-filled disposable applicator delivers approximately 5 grams of gel containing approximately 100 mg clindamycin.
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [USP Controlled Room temperature].
Container Closure	Flexible (b) (4) tube with (b) (4) seal and screw top on one end and a folded crimped end on the other. (b) (4) applicator with plunger for administration (b) (4) (b) (4)

APPENDIX F. LABEL AND LABELING

F.1 List of Label and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Xaciato labels and labeling submitted by Daré Bioscience, Inc.

- Container labels received on June 7, 2021
 - 25 g tube for this NDA submission
 - [REDACTED] (b) (4)
- Carton labeling received on June 7, 2021
 - 25 g tube for this NDA submission
 - [REDACTED] (b) (4)
- Patient Package Insert (PPI) and Instructions for Use (IFU), received on June 7, 2021, available from: <\\CDSESUB1\evsprod\nda215650\0001\m1\us\114-labeling\draft\labeling\patient-information-word.docx>.
- Prescribing Information (PI) received on August 30, 2021
 - Draft labeling available at the following link: <\\CDSESUB1\evsprod\nda215650\0013\m1\us\114-labeling\draft\labeling\bv1-draft-pi-aug-2021-word.docx>.
 - Annotated draft labeling available at the following link: <\\CDSESUB1\evsprod\nda215650\0013\m1\us\114-labeling\draft\annotated\draft-annotated-labeling-word.docx>.

^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

F.2 Label and Labeling Images

Container label

- 25 g tube for this NDA submission



(b) (4)



(b) (4)

Carton labeling

- 25 g tube for this NDA submission



(b) (4)



(b) (4)

(b) (4)



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/s/

DEBORAH E MYERS
09/30/2021 11:55:04 AM

VALERIE S VAUGHAN
09/30/2021 03:57:29 PM

Clinical Inspection Summary

Date	23 September 2021
From	Cheryl Grandinetti, PharmD Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Alison Rodgers, RPM Mukil Natarajan, MD, Medical Reviewer Hiwot Hiruy, MD, PhD, Medical Team Leader Division of Anti-Infectives (DAI)
NDA #	215650
Applicant	Dare Bioscience, Inc.
Drug	Clindamycin phosphate vaginal gel 2% (DARE-BV1)
NME	No
Proposed Indication	For the treatment of bacterial vaginosis in female patients, aged 12 years and older
Consultation Request Date	30 June 2021
Summary Goal Date	11 October 2021
Action Goal Date	7 December 2021
PDUFA Date	7 December 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Routine PDUFA inspections were conducted for two clinical investigators, Drs. Nicholson-Uhl and Perez, in support of this application (NDA 215650). The two inspections covered one clinical study, DARE-BV1-001. Overall, the study appears to have been conducted adequately, and the data generated by these two sites appear acceptable in support of the respective indication.

During the inspections, the primary efficacy endpoint source data for clinical cure (i.e., investigator assessment of vaginal discharge, 10% KOH whiff test, and clue cell percentage) were verified against the sponsor's data line listings for 30 out of 40 subjects randomized at these two sites. No discrepancies were noted. Although certified copies of the Nugent scores used to determine the supportive secondary efficacy endpoint of bacteriological cure were not available at the clinical investigator sites, these certified copies were submitted to the NDA and subsequently verified by this reviewer against the sponsor's data line listings for all 40 randomized subjects at the two sites. No discrepancies were noted.

II. BACKGROUND

NDA 215650 was submitted in support of the use of Xaciatto (DARE-BV1) for the treatment of bacterial vaginosis in female patients, aged 12 and older. A key study supporting the application was the following:

DARE-BV1-001, “A Phase 3, Double-Blind, Placebo-Controlled, Randomized Study of DARE-BV1 in the Treatment of Bacterial Vaginosis”

This was a multicenter, randomized, double-blind, placebo-controlled study of a single dose of DARE-BV1 (clindamycin phosphate vaginal gel, 2%) compared to a single dose of placebo vaginal gel (hydroxyethylcellulose [HEC] Universal Placebo Gel) for the treatment of bacterial vaginosis (BV). The primary objective was to assess the efficacy of DARE-BV1 for the treatment of BV in postmenarchal females, based on the proportion of patients demonstrating clinical cure when assessed once between Day 21 to 30 post-administration.

- **Subjects:** A total of 307 subjects were enrolled and randomized and 290 completed the study (204 were randomized to DARE-BV1 and 103 were randomized to placebo)
- **Sites:** 35 sites in the United States (U.S.)
- **Study initiation and completion dates:** 9 July 2020 (first patient, first visit) to 12 November 2020 (last patient contact)
- **Database Lock Date:** 24 November 2020
- **Study Unblinding Date:** 25 November 2020

Patients were evaluated at 3 time points in the study:

- Day 1 Screening/Randomization Visit
- Day 7 to 14 Interim Assessment Visit
- Day 21 to 30 Test of Cure (TOC) Visit

Patients who discontinued prematurely from the study received a safety follow-up telephone call between Day 21 to 30. The total study duration was up to approximately 1 month for each individual patient. At the Screening/Randomization visit (Day 1), eligible patients were randomized in a 2:1 ratio via an Interactive Response Technology (IRT) system to one of the following treatment groups:

- DARE- BV1 (clindamycin phosphate vaginal gel), 2%, 5 grams QD × 1 day
- Placebo vaginal gel (Universal HEC Placebo Gel), 5 grams, QD × 1 day

Study drug was to be applied intravaginally within 1 day of randomization. At both the Interim Assessment Visit (Day 7- 14) and TOC Visit (Day 21 – 30), the investigator performed gynecological examinations and collected specimens for the following tests:

- Saline wet mount to assess clue cell percentage
- 10% KOH “whiff test,” vaginal pH
- Gram stain for Nugent Scoring
- Blood chemistry, hematology, urinalysis, and urine pregnancy test

The signs and symptoms of bacterial vaginosis including color, odor, and consistency of vaginal discharge, vulvovaginal itching, and irritation were also evaluated at Visit 1 (Screening/Randomization), Visit 2 (Interim Assessment), and Visit 3 (TOC).

The primary efficacy endpoint was the proportion of patients with clinical cure at the TOC visit (Day 21 to 30). Clinical cure was defined as:

- Resolution of abnormal vaginal discharge associated with BV as determined by the investigator
- Negative 10% KOH whiff test (data line listing 16.2.6.1.1 positive or negative)
- Clue cells < 20% of the total epithelial cells in the saline wet mount

The supportive secondary efficacy endpoints are bacteriological cure and therapeutic cure.

- The bacteriological cure was defined as Nugent's score <4 (via gram stain central laboratory analysis)
- Therapeutic cure is defined as having achieved clinical cure and bacteriological cure.

Procedure for Nugent's score: The clinical sites collected and shipped vaginal swab samples (i.e., primary and back-up slides prepared from vaginal swabs) to the Central Laboratory, (b) (4) for evaluation and determination of Nugent scores. Each slide was evaluated by a primary reader and a secondary reader, who was blinded to the primary reader's results. For Nugent scores that were within two points, the first reading was recorded. For Nugent scores that differed by more than two points, a third reader was used to evaluate the slide independently. The result of the reader that was within two points of the third reader was reported.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, and prior inspectional history.

III. RESULTS (by site):

1. Scott Nicholson-Uhl, MD

Site # 125

4700 Wichers Drive, Suite 200

Marrero, LA 70072

PDUFA Inspection Dates: 19 to 23 July 2021

At this site for Protocol DARE-BV1-001, 23 subjects were screened, 20 were randomized, and 18 subjects completed the study. One subject discontinued early due to moving to another state before the TOC visit, and one subject was lost to follow-up before the TOC visit.

A full audit of the study records for 23 screened subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments;

IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other source records related to clinical cure (i.e., primary efficacy endpoint); adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

There was no evidence of under-reporting of adverse events. The source records documenting the clinical cure criteria (i.e., investigator assessment of vaginal discharge, 10% KOH whiff test, and clue cell percentage) were reviewed and verified against the sponsor's data line listings for 20 randomized subjects. No discrepancies were noted when comparing the source records against the sponsor's data line listings.

Reviewer's comment: *In a 12 July 2021 response to an IR, the sponsor submitted certified copies of the Nugent Score test results from the central laboratory (b) (4) (b) (4) to the NDA. Nugent scores were used in the assessment of bacteriological cure (i.e., supportive secondary efficacy endpoint). Certified copies of the Nugent score results from both the primary and secondary readers were reviewed and verified against the sponsor's data listings for the 20 randomized subjects. No discrepancies were noted, and Nugent scores were recorded and reported as pre-specified in the DARE-BV1-001 Microbiology Protocol.*

2. Brandon Perez, MD

Site #125

4720 South I-10 Service Road, Suite 201

Metairie, LA 70001

PDUFA Inspection Dates: 16 to 20 August 2021

At this site for Protocol DARE-BV1-001, 40 subjects were screened, 20 were randomized, and 19 subjects completed the study. One subject was lost to follow-up after the Screening/Randomization Visit.

A full audit of the study records for 11 of the 20 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and source records related to clinical cure (i.e., primary efficacy endpoint); adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

There was no evidence of under-reporting of adverse events. The source records documenting the clinical cure criteria (i.e., investigator assessment of vaginal discharge, 10% KOH whiff test, and clue cell percentage) were reviewed and verified against the sponsor's data line listings for 10 of the 20 randomized subjects. No discrepancies were noted when comparing the source records against the sponsor's data line listings.

Reviewer's comment: *In a 12 July 2021 response to an IR, the sponsor submitted certified copies of the Nugent Score test results from the central laboratory (b) (4) (b) (4) to the NDA. Nugent scores were used in the assessment of bacteriological cure (i.e., supportive secondary efficacy endpoint). Certified copies of the Nugent score results from both the primary and secondary readers were reviewed and verified against the sponsor's data listings for the 20 randomized subjects. No discrepancies were noted and Nugent scores were recorded and reported as pre-specified in the DARE-BV1-001 Microbiology Protocol.*

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/s/

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