CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216632Orig1s000

OTHER REVIEW(S)

Division of Dermatology and Dentistry
Associate Director for Labeling Review of the
Prescribing Information

Product Title	CABTREO® (clindamycin phosphate, adapalene, and benzoyl peroxide) topical gel
Applicant	Bausch Health US, LLC
Application/Supplement Number	NDA 216632
Type of Application/Submission[1]	New NDA
Regulatory Pathway	505(b)(2)
Is Proposed Labeling in "Old" Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	Y
Proposed Indication	CABTREO is a combination of clindamycin phosphate (a lincosamide antibacterial), adapalene (a retinoid) and benzoyl peroxide indicated for the topical treatment of acne vulgaris in patients (b) (4) years of age and older.
Approved Indication	CABTREO is a combination of clindamycin phosphate (a lincosamide antibacterial), adapalene (a retinoid), and benzoyl peroxide indicated for the topical treatment of acne vulgaris in adult and pediatric patients 12 years of age and older.
Date FDA Received Application	December 22, 2022
Review Classification (Priority/Standard)	Standard
Action Goal Date	October 22, 2023
Review Date	October 18, 2023
Reviewer	Matthew White

INTRODUCTION

New NDA 216632 for CABTREO (clindamycin phosphate, adapalene, and benzoyl peroxide) topical gel was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

The Applicant is relying on the Agency's finding of safety and effectiveness for Epiduo Forte (adapalene, benzoyl peroxide) gel, 0.3%/2.5% as the listed drug. The Applicant has ownership and right of reference to Acanya (clindamycin, benzoyl peroxide) gel, 1.2%/2.5%, (NDA 050819) and Onexton (clindamycin, benzyl peroxide) gel, 1.2%/3.75% (NDA 050819) as well as Benzaclin (clindamycin phosphate, benzyl peroxide) gel, 1.2%/5% (NDA 050756).

LABELING HISTORY

Listed Drug:
EPIDUO FORTE was first approved on July 15, 2015. The most recent revision to the label was approved under supplement 008 on April 27, 2022. EPIDUO FORTE, is a combination of adapalene, a retinoid, and benzoyl peroxide and is indicated for the topical treatment of acne vulgaris in adults and pediatric patients 12 years of age and older.

Drugs the Applicant has Ownership of and Right of Reference:
ACANYA was first approved on October 12, 2008. The most recent revision to the label was approved under supplement 024 on February 21, 2020. ACANYA Gel is a combination of clindamycin phosphate (a lincosamide antibacterial) and benzoyl peroxide indicated for the topical treatment of acne vulgaris in patients 12 years or older.

ONEXTON was first approved on November 24, 2014, under NDA 50818 Supplement 012. ONEXTON Gel is a combination of clindamycin phosphate (a lincosamide antibacterial) and benzoyl peroxide indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

Benzaclin was first approved on December 21, 2000. The most recent revision to the label was approved under supplement 037 on June 17, 2010. The label is not currently in compliance with Physician Labeling Rule (PLR) [including the Pregnancy and Lactation Labeling Rule (PLLR)] requirements. BenzaClin topical gel is indicated for the topical treatment of acne vulgaris.

New NDA - 505(b)(2) - CABTREO (clindamycin phosphate/adapalene/ benzoyl peroxide) gel

The Applicant submitted their proposed United States Prescribing Information (USPI), Patient Package Insert (PPI), Instructions for Use (IFU), and Carton and Container labeling with the original NDA on December 22, 2022. The Applicant submitted a revised sample tube on April 21, 2023.

The Agency's proposed edits to the USPI, PPI, IFU, and Carton and Container labeling were conveyed to the Applicant on September 28, 2023. The Applicant's response was received October 5, 2023. Additional Agency edits to the USPI, PPI, and IFU were conveyed to the Applicant on October 16, 2023. The Applicant's response was received October 17, 2023.

REVIEW

This review describes the updates implemented to the prescribing information (PI), received on March 27, 2023, to help ensure that it:

- Is compliant with Physician Labeling Rule (PLR) [including the Pregnancy and Lactation Labeling Rule (PLLR)] requirements,[2]

[2] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(a) and (e) and 201.80.

- Is consistent with labeling guidance recommendations[3] and with CDER labeling policies, as appropriate,
- Conveys the essential scientific information needed for safe and effective use of the drug,
- Is clinically meaningful and scientifically accurate,
- Is a useful communication tool for health care practitioners, and
- Is consistent with other PI with the same active moiety, drug class, or similar indication, as appropriate

The following groups contributed to the review of the label:

- Division of Dermatology and Dentistry: Tatiana Oussova, MD, MPH (Deputy Director for Safety), Gordana Diglisic, MD (Associate Director for Therapeutic Review), Mary Kim, MD and Amy Woitach, DO, MS (Clinical), John Dougherty, PhD and Barbara Hill, PhD (Nonclinical)
- Division of Biometrics III: Katherine Meaker, MS, Kathy Fritsch, PhD, and Mohamed Alosh, PhD
- Division of Inflammation and Immune Pharmacology: Soo Hyeon Shin, PharmD, PhD and Chinmay Shukla, PhD
- Division of Pediatrics and Maternal Health: Kristie Baisden, DO, Tamara Johnson, MD, MS, and Lynne P. Yao, MD
- Division of Medication Error Prevention and Analysis 1: Corwin Howard, PharmD, and Madhuri Patel, PharmD
- Office of Prescription Drug Promotion: Elvy Varghese and Jim Dvorsky
- Division of Medical Policy Programs: Susan Redwood, MPH, BSN, RN, Barbara Fuller, RN, MSN, and LaShawn Griffiths, MSHS-PH, BSN, RN

The attached PI shows differences between the Applicant's proposes PI, submitted on February 22, 2022, and the agreed upon PI received on October 17, 2023. The PI includes comments conveyed between the Agency and the Applicant during labeling discussions.

This review includes a high-level summary of the rationale for major changes to the PI as compared with the applicant's draft PI (see the table below).

Full Prescribing Information Sections[1]	**Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)[2]**
1 INDICATIONS AND USAGE	• The nonproprietary names and strengths were removed from the indication statement in accordance with the recommendations of the draft guidance for industry: *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*. (July 2018) (when final, this guidance will represent FDA's current thinking on this topic). • The term "children" was changed to "pediatric patients" in accordance with the recommendations of the guidance for industry:

[3] See *Prescription Drug Labeling Resources* website for PLR labeling guidances. When final, guidances represent the FDA's current thinking on a topic. Applicants can use an alternative approach if it satisfies statutory and regulatory requirements.

	Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling (March 2019). • The age group in the indication statement was change from (b) (4) years of age and older to 12 years of age and older per Clinical's recommendation.
2 DOSAGE AND ADMINISTRATION	• The Applicant's proposal was based on the information included in the listed drug label (Epiduo Forte) and the Onexton gel label. • Reworded instructions for clarity and concision. Reordered instructions so that dosage and administration instructions appear first followed by administration information intended for risk mitigation. • Added "Avoid…areas of broken, eczematous, or sunburned skin *[see Warnings and Precautions (5.3)]"*. Avoiding these areas during administration of CABTREO is a mitigation strategy included under subsection 5.3 Skin Irritation and Allergic Contact Dermatitis.
4 CONTRAINDICATIONS	• The Applicant's proposal was based on the information included in the listed drug label and the Onexton gel label. • Formatted in accordance with the recommendations of the guidance for industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011). • Removed (b) (4) . A cross reference was added to Warnings and Precautions (5.1). Subsection 5.1 Hypersensitivity includes a description of the hypersensitivity reactions reported in in postmarketing use with clindamycin phosphate/benzoyl peroxide.

5 WARNINGS AND PRECAUTIONS	5.1 Hypersensitivity • A warning and precaution for hypersensitivity was added. This is consistent with the PI for the listed drug. The Warning and Precaution includes a succinct description of the adverse reactions reported with use of clindamycin phosphate, benzoyl peroxide, and adapalene. It also includes steps to take to prevent, mitigate, monitor for or manage the AR for consistency with the listed drug and in accordance with the recommendations of the guidance for industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format (October 2011).* 5.2 Colitis • The Applicant's proposal (b) (4) • Removed (b) (4) from the Warning and Precaution per Clinical's recommendation. 5.3 Photosensitivity • The Applicant's proposal was based on the information included in the listed drug label (b) (4) • Changed the name of the subsection from (b) (4) to "Photosensitivity". This is consistent with the listed drug label and also describes the clinically significant AR or risk in accordance with the guidance for industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format (October 2011).* • The Warning and Precaution includes a succinct description of the adverse reactions and also includes steps to take to prevent, mitigate, monitor for or manage the AR in accordance with the aforementioned guidance for industry. • The information about weather extremes was moved under 5.4 Skin Irritation and Allergic Contact Dermatitis as this is a more appropriate location for the information. 5.4 Skin Irritation and Allergic Contact Dermatitis • The Applicant's proposal (b) (4) • Changed the list of adverse reactions from those that may occur to those that have been reported with use of CABTREO. • Added a statement to describe the AR rates of CABTREO compared with vehicle in accordance with the guidance for industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format (October*

	2011) • The information about weather extremes was moved from under 5.3 to 5.4 as this is a more appropriate location for the information. • Added instructions to avoid use of "waxing" for consistency with the listed drug label. • Modified the language concerning concomitant use of other potentially irritating topical products for consistency with the Acanya label.
6 ADVERSE REACTIONS	The Applicant's proposal was based on the information included in the Onexton gel label. Added the following clinically significant ARs at the beginning of the ADVERSE REACTIONS Section between Section 6 and subsection 6.1 in accordance with the guidance for industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format.* These ARs have been reported with use of clindamycin. phosphate, benzoyl peroxide, and adapalene: • Hypersensitivity Skin Infections • Skin Irritation and Allergic Contact Dermatitis <u>6.1 Clinical Trials Experience</u> • Studies were named in accordance with the February 2017 MPC recommendations. • The number of pediatric and adult subjects in clinical trials and the route of drug administration was included in the trial description in accordance with the guidance for industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*. • Removed baseline demographics and added a cross-reference to section 14 because the demographics are generally the same and the description of the baseline demographics are included the CLINICAL STUDIES section (page 41 of the Labeling Review Tool). • Modified the title of Table 1 and Table 2 per the recommendations on page 73 of the Labeling Review Tool. • A column with maximum severity during treatment course was added to Table 2 and the order the information is presented in Table 2 was changed per Clinical's recommendation. <u>6.2 Postmarketing Experience</u> • The Applicant's proposal was based on the information included in the listed drug label and the Onexton gel label. • Removed the statement, (b) (4)

	[redacted] (b) (4) This is not a recommended statement in the guidance for industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format.* • Separated the adverse reactions identified during post-approval use of products containing clindamycin phosphate, adapalene, and benzoyl peroxide as the active ingredients under two subheadings: Immune system disorders and Local adverse reactions in accordance with current labeling practices. • Added two additional subheadings (Gastrointestinal Disorders and Bacterial Infections) to reflect all adverse reactions identified postmarketing for products containing clindamycin phosphate, adapalene, and benzoyl peroxide as active ingredients.
7 DRUG INTERACTIONS	• The Applicant's proposal [redacted] (b) (4) • [redacted] (b) (4)
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	<u>8.1 Pregnancy and 8.2 Lactation</u> • The Applicant's proposal was based on the information included the listed drug label and the Onexton gel label. • Changes to these sections were based on the recommendations of the Nonclinical review team and the Division of Pediatrics and Maternal Health (DPMH). <u>8.4 Pediatric Use</u> • The pediatric use statement was modified and a summary of the basis for approval was added according to the recommendations in the guidance for industry: *Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling (March 2019)*. <u>8.5 Geriatric Use</u> • The geriatric use statement was modified to reflect that no geriatric subjects were included in clinical trials with CABTREO.
12 CLINICAL PHARMACOLOGY	<u>12.1 Mechanism of Action</u> • The Applicant's proposal was based on the information included in the listed drug label and the Onexton gel label. <u>12.2 Pharmacodynamics</u> • Subsection 12.2 was added and includes the following statement as recommended in the guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2016)*:

	○ "Pharmacodynamics of CABTREO unknown." 12.3 Pharmacokinetics • The Applicant's proposal was based on the information included in the listed drug label and the Onexton gel label. • Changes to section made per Clinical Pharmacology's recommendations. • The Drug Interaction information for erythromycin (b) (4) subsection 12.3 per Clinical Pharmacology's recommendation and current labeling best practices. (b) (4) 12.4 Microbiology • The Applicant's proposal was based on the information included in the Onexton gel label.
13 NONCLINICAL TOXICOLOGY	• The Applicant's proposal was based on the information included in the listed drug label and the Onexton gel label. • Changes were made to section 13 per the recommendations of the Nonclinical review team.
14 CLINICAL STUDIES	• Information was reordered so that the trial description is presented first, followed by demographic information, endpoints, and efficacy results. • Additional demographic information for race, ethnicity, and age was added. • Added the disclaimer, "While subjects aged 10 to less than 12 years were included in these trials, CABTREO is not approved for use in patients less than 12 years of age." CABTREO is approved for use in patients 12 years and age and older and this section must not include any information that implies or suggests indications or uses or dosing regimens not stated in the INDICATIONS AND USAGE or DOSAGE AND ADMINISTRATION sections.
17 PATIENT COUNSELING INFORMATION	• The Applicant's proposal was based on the information included in the listed drug label and the Onexton gel label. • Formatted the information and added subheadings per current labeling best practices. • Added instructions to avoid areas of broken, eczematous, or sunburned skin when applying CABTREO and instructions to wash hands after application. These instructions are included in the Dosage and Administration section. • Removed (b) (4)

	[redacted] (b) (4). This is concept is not discussed elsewhere in the label. Additionally, these are general instructions that would be considered a standard component of any provider-patient discussion (e.g., use as directed) that are not included in section 17. • Colitis was added because CABTREO is contraindicated in patients with a history of colitis and is a Warning and Precaution (5.2). Colitis is a risk for which a patient may need to do something actionable (Discontinue CABTREO if diarrhea occurs). • Photosensitivity and skin irritation and contact dermatitis information was updated in accordance with changes made to the information in the Warnings and Precautions section. • Included a discussion of the risks of a drug in during lactation if the information concerns an important risk per the guidance for industry: *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products –Content and Format* (December 2014).
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	<u>3 Dosage Forms and Strengths</u> • Presented the information in accordance with the recommendations on page 34 of the Labeling Review Tool. <u>11 Description</u> • Presented the information in accordance with the recommendations on pages 60 and 61 of the Labeling Review Tool. Grouped the established pharmaceutical classes of the APIs together. <u>16 How Supplied/Storage and Handling</u> • Presented the information in accordance with pages 74 and 75 of the Labeling Review Tool. • Removed the statements [redacted] (b) (4) These statements are not applicable to special handling and storage conditions for the HCP.

[1] The product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved. The finalized PI was compared to the currently approved PI and the Applicant's draft PI).

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/s/

MATTHEW E WHITE
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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:	October 12, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 216632
Product Name, Dosage Form, and Strength:	Cabtreo (clindamycin phosphate, benzoyl peroxide, and adapalene) topical gel, 1.2%/ 0.15%/ 3.1%
Applicant/Sponsor Name:	Bausch Health US, LLC
TTT ID #:	2022-3156-1
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on October 5, 2023 for Cabtreo. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Cabtreo (Appendix A) to determine if it is 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

We note the Applicant has the dosage form listed as (b) (4) instead of 'topical gel'. We defer to the Division of Dermatology and Dentistry (DDD) to determine the final dosage form and ensure the dosage form is consistent throughout the labels and labeling. The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Howard, C. Label and Labeling Review for Cabtreo (NDA 216632). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAY 19. TTT ID No.: 2022-3156.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 5, 2023

Container labels

(b) (4)

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MADHURI R PATEL
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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:	September 6, 2023
To:	Dawn Williams, BSN Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Elvy Varghese. PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	CABTREO (clindamycin phosphate, adapalene and benzoyl peroxide)
Dosage Form and Route:	topical gel
Application Type/Number:	NDA 216632
Applicant:	Bausch Health US, LLC

1 INTRODUCTION

On December 22, 2022, Bausch Health US, LLC submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 216632 for CABTREO (clindamycin phosphate, adapalene and benzoyl peroxide) topical gel with a proposed indication for the treatment of acne vulgaris. The referenced listed drugs (RLD) used for the basis of this 505(b)(2) submission include:

- EPIDUO FORTE (adapalene/benzoyl peroxide) Gel, NDA 207917
- ACANYA (clindamycin phosphate and benzoyl peroxide) Gel, NDA 050819
- ONEXTON (clindamycin phosphate and benzoyl peroxide) Gel, NDA 050819
- BENZACLIN (clindamycin phosphate and benzoyl peroxide) Gel, NDA 050756

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Dermatology and Dentistry (DDD) on February 22, 2023, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for CABTREO (clindamycin phosphate, adapalene and benzoyl peroxide) topical gel.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft CABTREO (clindamycin phosphate, adapalene and benzoyl peroxide) topical gel PPI and IFU received on December 22, 2022, and received by DMPP and OPDP on August 30, 2023.
- Draft CABTREO (clindamycin phosphate, adapalene and benzoyl peroxide) topical gel Prescribing Information (PI) received on December 22, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 30, 2023.
- Approved EPIDUO FORTE (NDA 207917) labeling dated April 27, 2022.
- Approved ACANYA (NDA 050819) labeling dated February 21, 2020.
- Approved ONEXTON (NDA 050819) labeling dated November 24, 2014.
- Approved BENZACLIN (NDA 050756) labeling dated March 02, 2011.

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 APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are 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 PPI and IFU are 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 PPI and IFU.

Please let us know if you have any questions.

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/s/

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09/06/2023 10:45:48 AM

BARBARA A FULLER
09/06/2023 10:49:48 AM

LASHAWN M GRIFFITHS
09/06/2023 11:11:18 AM

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

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

Memorandum

Date: September 6, 2023

To: Dawn Williams, Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)

Mary E. Kim, Clinical Reviewer, DDD

From: Elvy Varghese, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for CABTREO™ (clindamycin phosphate, adapalene, and benzoyl peroxide) topical gel

NDA: 216632

Background: In response to DDD's consult request dated February 22, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for CABTREO™ (clindamycin phosphate, adapalene, and benzoyl peroxide) topical gel [Cabtreo].

PI/PPI/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 30, 2023 and our comments are provided below.

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

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on August 30, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at Elvy.Varghese@fda.hhs.gov.

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/s/

ELVY M VARGHESE
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urology, and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health PLLR Labeling Memorandum

Date: August 9, 2023 **Date consulted:** February 17, 2023

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
DPMH

Lynne P. Yao, MD, OND, Division Director
DPMH

To: Mary Kim, MD, Clinical Reviewer
Division of Dermatology and Dentistry

Drug: Cabtreo (clindamycin phosphate/adapalene/benzoyl peroxide gel, 1.2%/0.15%/3.1%), for topical use

NDA: 216632

Applicant: Bausch Health US, LLC

Subject: Pregnancy and Lactation Labeling

Proposed Indication: the topical treatment of acne vulgaris in patients (b) (4) years of age and older

Materials Reviewed:

- DPMH PLLR Review of Epiduo Forte (adapalene and benzoyl peroxide gel, 0.3%/2.5%)/NDA 207917, Differin (adapalene lotion, 0.1%)/NDA 22502, Differin (adapalene gel, 0.3%)/NDA 21753 by Carrie Ceresa, PharmD, MPH, dated 1/4/22, DARRTs Reference ID: 4914644.
- DPMH PLLR Review of Epsolay (benzoyl peroxide cream, 5%)/NDA 214510 by Jane Liedtka, MD, dated 1/27/21, DARRTs Reference ID: 4914644.

- DPMH PLLR Review of DARE-BV1 (clindamycin phosphate vaginal gel 2%)/NDA 215650, by Wenjie Sun, MD, dated 11/1/21, DARRTs Reference ID: 4881885.
- DPMH PLLR Review of Onexton (clindamycin phosphate and benzoyl peroxide gel, 1.2%/3.75%)/NDA 050819 and Acanya (clindamycin phosphate and benzoyl peroxide gel, 1.2%/2.5%)/NDA 050819, by Christos Mastroyannis, MD, dated 11/22/2019, DARRTs Reference ID: 4524401.

Consult Question: "DDD requests DPMH input on the PLLR labeling"

INTRODUCTION

On December 22, 2023, the applicant, Bausch Health IS, LCC, submitted a new drug application (NDA 216632) for Cabtreo (clindamycin phosphate/adapalene/benzoyl peroxide gel, 1.2%/0.15%/3.1%), for topical use, via the 505(b)(2) regulatory pathway. On February 17, 2023, the Division of Dermatology and Dentistry consulted the Division of Pediatric and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy, Lactation, and Females of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- The proposed indication for Cabtreo (clindamycin phosphate/adapalene/benzoyl peroxide gel, 1.2%/0.15%/3.1%) NDA 216632 is for the topical treatment of acne vulgaris in patient (b) (4) years of age and older. Cabtreo is a novel triple combination product for acne vulgaris.
- The applicant is relying on the Agency's finding of safety and effectiveness for Epiduo Forte (adapalene/benzoyl peroxide gel, 0.3%/2.5%) as the listed drug relied upon. The applicant has ownership and right of reference to Acanya (clindamycin/benzoyl peroxide 1.2%/2.5%, gel)/NDA 050819 and Onexton (clindamycin/benzyl peroxide 1.2%/3.75% gel)/NDA 050819 as well as Benzaclin (clindamycin phosphate/benzyl peroxide 1.2%/5%, gel)/NDA 050756.
- On February 28, 2023, the Agency sent the applicant an information request (IR) included in the Filing Communication Letter to provide a review and summary of available information regarding use of the active components of Cabtreo in pregnant, lactating, and females and males of reproductive potential.
- On May 17, 2023, the applicant submitted the IR response to support proposed PLLR labeling.

Drug Characteristics[1]

- *Mechanism of action*:
  - Clindamycin: lincosamide antibacterial
  - Adapalene: retinoid
  - Benzoyl Peroxide: oxidizing agent with bactericidal and keratolytic effects
- *Dosage forms and strengths*: gel, 1.2% clindamycin phosphate/0.15% adapalene/3.1% benzoyl peroxide.

[1] Cabtreo (NDA 216632) proposed package insert.

- *Dosage and administration*: apply a thin layer to the affected areas once daily. Avoid the eyes, mouth, paranasal creases, and mucous membranes. Not for oral, ophthalmic, or intravaginal use.
- *Molecular weight*:
    - Clindamycin phosphate: 504.97 Daltons
    - Adapalene: 412.52 Daltons
    - Benzoyl Peroxide: 242.23 Daltons
- *Warnings and Precautions*: colitis; ultraviolet light and environmental exposure; skin irritation.
- *Adverse reactions*: application site reactions; pain, dryness, irritation, exfoliation, and erythema.

Current State of the Labeling[2,3]

Epiduo Forte (adapalene/benzoyl peroxide 0.3%/2.5%), the listed drug relied upon, currently approved labeling is in the Physician Labeling Rule (PLR) format and was converted to PLLR format in 2022. The applicant's proposed labeling for Cabtreo references the PLLR approved labeling for Epiduo Forte as follows:

> ***8.1 Pregnancy*:**
> Risk Summary
> Available pharmacovigilance data with Epiduo Forte use in pregnant women are insufficient to establish a drug- associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with the combination gel.
>
> *Adapalene gel, 0.3%*
> Available data from clinical trials with adapalene gel 0.3% use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of adapalene to pregnant rats and rabbits during organogenesis at dose exposures 41 and 81 times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 2 g resulted in fetal skeletal and visceral malformations *(see Data).*
>
> *Benzoyl peroxide gel, 2.5%*
> The systemic exposure of benzoyl peroxide is unknown. Based on published literature, benzoyl peroxide is rapidly metabolized to benzoic acid (an endogenous substance), which is eliminated in the urine. Hence, maternal use is not expected to result in fetal exposure of the drug.

[2] Epiduo Forte NDA 207917 currently approved labeling from 4/27/22. Drugs@FDA
[3] Onexton NDA 050819 currently approved labeling from 2/21/20. Drugs@FDA

Data

Animal Data

No malformations were observed in rats treated with oral adapalene doses of 0.15 to 5.0 mg/kg/day, up to 8 times the MRHD of 2 grams of Epiduo Forte based on a mg/m^2 comparison. However, malformations were observed in rats and rabbits when treated with oral doses of ≥ 25 mg/kg/day adapalene (41 and 81 times the MRHD, respectively, based on a mg/m2 comparison). Findings included cleft palate, microphthalmia, encephalocele, and skeletal abnormalities in rats and umbilical hernia, exophthalmos, and kidney and skeletal abnormalities in rabbits.

Dermal adapalene embryofetal development studies in rats and rabbits at doses up to 6.0 mg/kg/day (9.7 and 19.5 times the MRHD, respectively, based on a mg/m2 comparison) exhibited no fetotoxicity and only minimal increases in skeletal variations (supernumerary ribs in both species and delayed ossification in rabbits).

8.2 Lactation:

Risk Summary

Adapalene gel, 0.3%

There are no data on the presence of adapalene topical gel or its metabolite in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, adapalene is present in rat milk with oral administration of the drug. When a drug is present in animal milk, it is likely that the drug will be present in human milk. It is possible that topical administration of large amounts of adapalene could result in sufficient systemic absorption to produce detectable quantities in human milk *(see Clinical Considerations).*

Benzoyl peroxide gel, 2.5%

The systemic exposure of benzoyl peroxide is unknown. Based on the published literature, benzoyl peroxide is rapidly metabolized to benzoic acid (an endogenous substance), which is eliminated in the urine. Any amount of benzoyl peroxide excreted into human milk by a nursing mother would be expected to be rapidly metabolized by tissue and stomach esterases. There are no data on the presence of benzoyl peroxide in human milk, its effects on the breastfed infant or its effects on milk production.

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

Clinical Considerations

To minimize potential exposure to the breastfed infant via breastmilk, use Epiduo Forte on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply Epiduo Forte directly to the nipple and areola to avoid direct infant exposure.

The applicant's proposed labeling for Cabtreo also references the PLLR approved labeling for Onexton as follows:

8.1 Pregnancy:

Risk Summary

There are no available data on Onexton Gel use in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. The limited published data on use of clindamycin in pregnant women with exposure during the first trimester are insufficient to inform a drug-associated risk of pregnancy-related adverse outcomes *(see Data)*. 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 animal reproduction studies, clindamycin did not cause malformations or embryo-fetal development toxicity in pregnant rats and mice when administered during the period of organogenesis at systemic doses up to 240 times the maximum recommended human dose (MRHD) of 2.5 g Onexton Gel, based on body surface area (BSA) comparisons (*see Data*).

Data

Human Data

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. These data cannot definitely establish or exclude any clindamycin-associated risk during pregnancy.

Animal Data

Animal reproductive/developmental toxicity studies have not been conducted with Onexton Gel or benzoyl peroxide. Developmental toxicity studies of clindamycin performed in pregnant rats and mice administered during the period of organogenesis at oral doses of up to 600 mg/kg/day (240 and 120 times the MRHD for, respectively, based on BSA comparisons) or subcutaneous doses of up to 200 mg/kg/day (80 and 40 times the MRHD for clindamycin, respectively, based on BSA comparisons) revealed no malformations or embryo-fetal development toxicity.

8.2 Lactation:

There are no data on the presence of clindamycin or benzoyl peroxide in human milk, the effects on the breastfed child, or the effects on milk production following topical administration. However, clindamycin has been reported to be present in breast milk in small amounts following oral and parenteral administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Onexton Gel and any

potential adverse effects on the breastfed child from Onexton Gel or from the underlying maternal condition.

Clinical Considerations
If used during lactation and ACANYA Gel is applied to the chest, care should be taken to avoid accidental ingestion by the infant.

DATA REVIEW
PREGNANCY
Nonclinical Experience
Animal reproduction studies have not been conducted with Cabtreo.

Clinical Experience
Clinical Trials
Pregnant women were excluded from clinical trials with Cabtreo. At the time of pregnancy detection, study drug was discontinued. As of the 120-day Safety Update, the applicant reported the following positive pregnancy tests in patients exposed to study drug and outcomes:

- **Study V01-126A-201 (2 subjects)**
  - Subject (b) (6) lost to follow-up
  - Subject elective abortion (no report of congenital anomalies)

- **Study V01-126A-202 (3 subjects)**
  - Subject (b) (6) normal livebirth C-section
  - Subject ongoing pregnancy
  - Subject lost to follow-up

- **Study V01-126A-301 (1 subject)**
  - Subject (b) (6): lost to follow-up

Reviewer's Comment
The trimester of study drug exposure in these pregnancy cases is not clear because last menstrual period, estimated gestational age, and estimated due date information were not provided in the case reports. Further, only 2/6 pregnancy outcomes were available (1 livebirth and 1 elective abortion) whereas the majority of pregnancy exposure cases were lost to follow up. Overall, the available data from clinical trials are insufficient to evaluate for a drug-associated risk of birth defects, miscarriage, or adverse maternal or fetal outcomes.

Published Literature
Applicant's Review of the Published Literature
The applicant performed a literature search in Embase on the use of clindamycin phosphate and benzoyl peroxide and adapalene in pregnant women (see submission of Safety Information Amendment for search details). A total of 12 articles were identified, of which only 3 review articles were found by the applicant to be relevant only to the

individual components of Cabtreo.[4,5,6] One additional article was identified that provided general pregnancy safety recommendations as described below.[7] However, the applicant noted that none of the reviewed articles provides specific information regarding the combination of clindamycin phosphate, adapalene, and benzoyl peroxide for topical use during pregnancy.

- A review article, which describes that clindamycin is compatible with pregnancy and has not been shown to increase the risk of malformation. Benzoyl peroxide is absorbed by the skin and metabolized to benzoic acid, which is a food additive, present in the normal diet. The safety data regarding adapalene are limited.[7]

DPMH's Review of the Published Literature
Clinical experience data on the use of clindamycin in pregnancy was previously reviewed by DPMH in 2019.[8] DPMH concluded the following:

> *Clindamycin*
> 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. The limited published data on systemic clindamycin in pregnant women with exposure during the first trimester are insufficient to inform a drug associated risk of pregnancy-related adverse outcomes.

Clinical experience data on use of adapalene and benzoyl peroxide in pregnancy was previously reviewed by DPMH in 2022.[9] DPMH concluded the following:

> *Adapalene*
> Retinoids, such as adapalene, are vitamin A derivatives that are FDA-approved and commonly prescribed to treat acne. Although teratogenic effects, including cleft palate, microphthalmia, encephalocele, and skeletal abnormalities in rats; and umbilical hernia, exophthalmos, and kidney and skeletal abnormalities, are observed in animals treated with oral adapalene at high dose multiples, no teratogenic effects are observed when rats and rabbits are treated topically.

[4] Pugashetti R, et al. Treatment of acne vulgaris in pregnant patients. Dermatologic Therapy (2013) 26:4 (302-311).
[5] Cuddy L, et al. Assessment and recommended treatment options for acne. Prescriber (2014) 25:19 (19-26).
[6] Thielitz A, et al. Topical retinoids in acne-An evidence-based overview. Journal of German Society of Dermatology (2008) 6:12 (1023-1031).
[7] Murase JE, et al. Safety of dermatologic medications in pregnancy and lactation: Part 1. Pregnancy. Journal of the American Academy of Dermatology (2014) 70:401.e1-e14.
[8] DPMH PLLR Review of Onexton (clindamycin phosphate and benzoyl peroxide gel, 1.2%/2.5%)/NDA 050819 and Acanya (clindamycin phosphate and benzoyl peroxide gel, 1.2%/2.5%)/NDA 050819, by Christos Mastroyannis, MD, dated 11/22/2019, DARRTs Reference ID: 4524401.
[9] DPMH PLLR Review of Epiduo Forte (adapalene and benzoyl peroxide gel, 0.3%/2.5%)/NDA 207917, Differin (adapalene lotion, 0.1%)/NDA 22502, Differin (adapalene gel, 0.3%)/NDA 21753 by Carrie Ceresa, PharmD, MPH, dated 1/4/22, DARRTs Reference ID: 4914644.

The findings from available case reports found in the applicant's pharmacovigilance database and in published literature with use of topical retinoids, including adapalene exposure, have not identified a specific pattern of birth defects or an association with retinoid-related embryopathy.

Benzoyl Peroxide
Due to the low systemic exposure noted in the literature discussing the metabolism of benzoyl peroxide in skin, maternal use of benzyl peroxide is not expected to result in fetal exposure to the drug.

This Reviewer performed a focused literature search in PubMed, Embase, Micromedex[10], TERIS[11], Reprotox[12], and Briggs[13] to find any relevant articles published since the most recent DPMH PLLR Reviews described above. Search terms included: "Cabtreo" or "IDP-126 gel" or "topical clindamycin phosphate and adapalene and benzoyl peroxide" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," OR "miscarriage." No relevant articles were identified.

Reviewer's Comment
Overall, there is no available published literature regarding the combination of topical clindamycin phosphate, adapalene, and benzoyl peroxide. Therefore, it is unknown whether the combination of these three drugs in a single product (Cabtreo) would pose any greater risk than the use of any of these drugs in isolation.

LACTATION
Nonclinical Experience
Animal lactation studies have not been conducted with Cabtreo.

Clinical Experience
Clinical Trials
Lactating women were excluded from clinical trials with Cabtreo. No lactation cases have been reported.

Published Literature
Applicant's Review of the Published Literature
The applicant performed a cumulative literature search in Embase on the use of clindamycin phosphate and benzoyl peroxide and adapalene in lactating women (see submission of Safety Information Amendment for search details). The applicant identified 1 review article as briefly summarized below.[14] However, the applicant noted that no articles were identified that provide specific safety information regarding the

[10]Truven Health Analytics information, http://www.micromedexsolutions.com Accessed 7/6/2023.
[11]TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 7/6/2023.
[12]Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 7/6/2023.
[13] Briggs GG, et al. Drugs in Pregnancy and Lactation: A Reference Guide , 9th Ed. 2011.
[14] Butler DC, et al. Safety of dermatologic medications in pregnancy and lactation Part II. Lactation. Journal of the American Academy of Dermatology (2014) 70:417.e1-e10.

combination of clindamycin phosphate, adapalene, and benzoyl peroxide for topical use during lactation.

- A review article which notes clindamycin reaches breast milk in small concentrations and is deemed safe for lactation by the American Academy of Pediatrics (AAP). There is no information on adapalene or benzoyl peroxide in this publication.[14]

DPMH's Review of the Published Literature
Clinical experience data on the use of clindamycin in lactation was previously reviewed by DPMH in 2019.[8] DPMH concluded the following:

> *Clindamycin*
> There are no data on the presence of clindamycin in human milk, the effects on the breastfed infant, or the effects on milk production following topical administration. However, clindamycin has been reported to be present in breast milk in small amounts following oral and parental administration.

Clinical experience data on use of adapalene and benzoyl peroxide in lactation was previously reviewed by DPMH in 2022.[9] DPMH concluded the following:

> *Adapalene*
> There is no information regarding the presence of topical adapalene in human milk. In animal studies, adapalene is present in rat milk with oral or intravenous administration of the drug. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Therefore, it is possible that topical administration of large amounts of adapalene could result in sufficient systemic absorption to produce detectable quantities in human milk. Similar to the approach used for other topical retinoids, PLLR labeling should include information on minimizing the potential exposure to the breastfed infant via breastmilk and using the product on the smallest area of skin and for the shortest duration possible while breastfeeding. Additional, labeling should include information about avoiding placing the product directly to the nipple and areola to avoid direct infant exposure.
>
> *Benzoyl Peroxide*
> Due to the low systemic exposure noted in literature discussing the metabolism of benzoyl peroxide in skin, breastfeeding is not expected to result in the exposure of the nursing child to clinically relevant amounts of benzoyl peroxide. There are no data on the presence of benzyl peroxide in human milk, the effects on the breastfed child, or the effects on milk production.

This Reviewer performed a focused search in *Medications and Mother's Milk*[15], Micromedex[10] Reprotox[12], PubMed, and Embase to find any relevant articles published since the most recent DPMH PLLR reviews. Search terms included: "Cabtreo" or "IDP-126 gel" or "topical clindamycin phosphate and adapalene and benzoyl peroxide" AND "lactation" OR "breastfeeding." No relevant articles were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Animal fertility studies have not been performed with Cabtreo.

Published Literature

Applicant's Review of the Published Literature

The applicant performed a cumulative literature search in Embase on the use of clindamycin phosphate and benzoyl peroxide and adapalene and effects on fertility (see submission of Safety Information Amendment for search details). The applicant did not identify any relevant articles.

DPMH's Review of the Published Literature

Clinical experience data on the use of clindamycin and effects on fertility was previously reviewed by DPMH in 2019.[8] DPMH concluded the following:

> *Clindamycin*
> There is no human data regarding clindamycin and effects on fertility in females and males of reproductive potential. Animal studies with oral clindamycin revealed no effects on fertility or mating ability.

Clinical experience data on use of adapalene and benzoyl peroxide and effects on fertility was previously reviewed by DPMH in 2022.[9] DPMH concluded the following:

> *Adapalene*
> There are no human or animal data on the effects of adapalene on fertility to to inform a potential clinical risk.
>
> *Benzoyl Peroxide*
> There are no human or animal data on the effects of benzoyl peroxide on fertility To inform a potential clinical risk.

This Reviewer performed a focused search in PubMed, Embase, and Reprotox[12] to find any relevant articles published since the most recent DPMH PLLR reviews. Search terms included: "Cabtreo" or "IDP-126 gel" or "topical clindamycin phosphate and adapalene and benzoyl peroxide" AND "fertility," "contraception," "oral contraceptives," OR "infertility." No relevant articles were identified.

[15] Hale, Thomas (2017) Medications and Mother's Milk. Amarillo, Texas. Hale Publishing.

DISCUSSION/CONCLUSIONS

Pregnancy

Pregnant women were excluded from Cabtreo clinical trials. Six pregnancy exposures were reported during the clinical development program; however, only two pregnancy outcomes were available for review (1 livebirth and 1 elective abortion) as the majority pregnancy cases were lost to follow-up. Overall, the available data from clinical trials are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes with Cabtreo use during pregnancy. No new potential safety concerns were identified in this review, thus DPMH does not recommend issuing any postmarketing requirements for a pregnancy safety study.

Lactation

Clinical lactation studies have not been performed with Cabtreo and lactating women were excluded from clinical trials during the development program. Therefore, DPMH recommends Cabtreo subsection 8.2 labeling that is consistent with currently approved PLLR labeling for Epiduo Forte, the listed drug relied upon, and Onexton, for which the applicant has right of reference. No new potential safety concerns were identified in this review, thus DPMH does not recommend issuing any postmarketing requirements for a lactations study.

Fertility

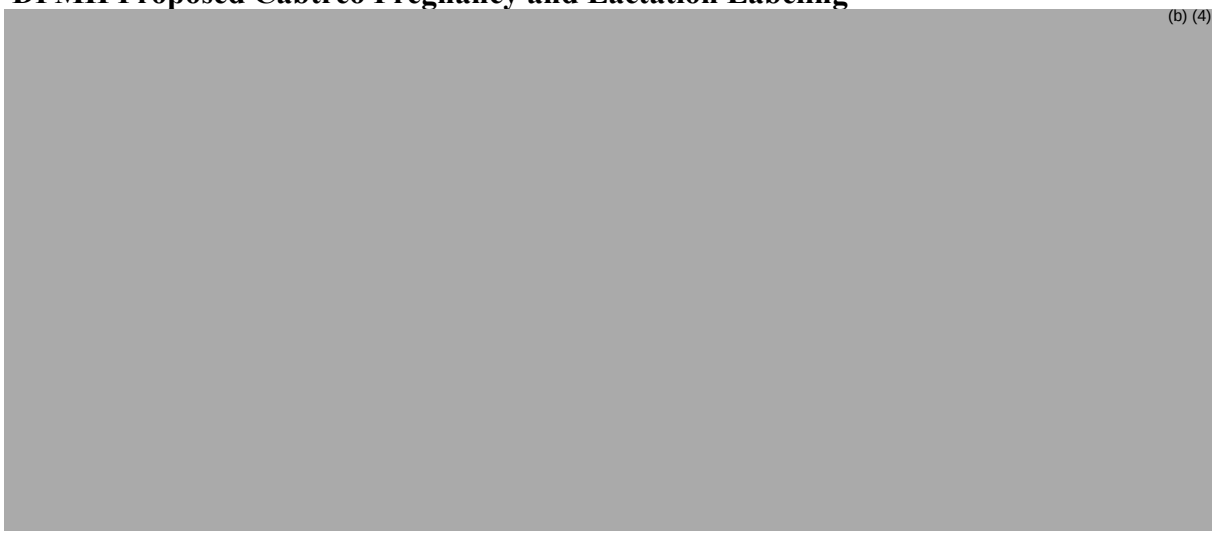
DPMH recommends omitting subsection 8.3 of Cabtreo labeling. DPMH did not identify any data to suggest Cabtreo use would have an adverse effect on fertility. Pregnancy testing and contraception headings will not be included.

LABELING RECOMMENDATIONS

DPMH proposed labeling recommendations for subsections 8.1, 8.2, and section 17 in Cabtreo labeling for compliance with the PLLR (see below). DPMH discussed the labeling recommendations below with DDD on July 25, 2023 and August 15, 2023. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Cabtreo Pregnancy and Lactation Labeling

(b) (4)



2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KRISTIE W BAISDEN
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08/10/2023 04:18:22 PM

LYNNE P YAO
08/18/2023 02:06:45 PM

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:	May 19, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 216632
Product Name, Dosage Form, and Strength:	Cabtreo (clindamycin phosphate, benzoyl peroxide, and adapalene) topical gel, 1.2% / 0.15% / 3.1%
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bausch Health US, LLC
FDA Received Date:	December 22, 2022, and April 21, 2023
TTT ID #:	2022-3156
DMEPA 1 Safety Evaluator:	Corwin Howard, PharmD, RPh
DMEPA 1 Acting Team Leader:	Madhuri Patel, PharmD

1. REASON FOR REVIEW

As part of the approval process for Cabtreo (clindamycin phosphate, benzoyl peroxide, and adapalene) topical gel, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Cabtreo Prescribing Information (PI), Patient Packet Insert (PPI), Instructions for Use (IFU), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

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
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels 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 Packet Insert (PPI), Instructions for Use (IFU), container labels 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 Bausch Health US, LLC.

4. RECOMMEDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

Table 2. Identified Issues and Recommendations for Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information, Patient Package Insert, Instructions for Use – General Issues			
1.	The storage information post dispensing is unclear/inconsistent between the PI, PPI, IFU, container labels, and carton labeling.	Not including information regarding discarding 10 weeks after dispensing may result in the risk of the storage information being overlooked and lead to deteriorated drug medication errors.	We recommend revising the storage information in the PI, PPI, and IFU for consistency with the container labels and carton labeling. For example: • Revising the How Supplied Section of the PI as follows: Revise (b) (4) to "After Dispensing:" and add "Discard unused portion 10 weeks after date of dispensing." • Revising the storage information in the PPI and IFU from "Throw away (discard) CABTREO that has passed the expiration date." to "Throw away (discard) CABTREO 10 weeks after date of dispensing."

5. RECOMMENDATIONS FOR BAUSCH HEALTH US, LLC

Table 3. Identified Issues and Recommendations for Bausch Health US, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s)			
1.	The storage information is separated on different panels/areas.	Relocating storage information to one panel will minimize confusion	For the commercial sizes, relocate the following statements near each other:

Table 3. Identified Issues and Recommendations for Bausch Health US, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		from incomplete information and minimize the risk for deteriorated drug medication errors.	• "Use by date handwritten on your label or within 10 weeks of dispensing date." • "Store at room temperature at or below…" • See crimp for lot number and expiration date. • "Use by:" [box] Additionally, consider adding "___/____/____" inside the box and unbolding the statement "Store at room temperature at or below…"
Carton Labeling			
1.	The storage information is separated on different panels.	Relocating storage information to one panel will minimize confusion from incomplete information and minimize the risk for deteriorated drug medication errors.	Relocate the following statements near each other: • "Use by date handwritten on your label or within 10 weeks of dispensing date." • "Store at room temperature (b) (4) • "Use by:" [box] Additionally, consider adding "___/____/____" inside the box and unbolding the statement "Store at room temperature (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Error! Reference source not found. presents relevant product information for Cabtreo that Bausch Health US, LLC submitted on December 22, 2022, and the listed drug (LD).

Table 4. Relevant Product Information for Cabtreo and the Listed Drug		
Product Name	Cabtreo	Epiduo Forte[a]
Initial Approval Date	N/A	July 15, 2015
Active Ingredient	clindamycin phosphate, benzoyl peroxide, and adapalene	adapalene and benzoyl peroxide
Indication	topical treatment of acne vulgaris in patients (b) (4) years of age and older.	topical treatment of acne vulgaris in adults and pediatric patients 12 years of age and older.
Route of Administration	topical	topical
Dosage Form	topical gel	topical gel
Strength	1.2% / 0.15% / 3.1%	0.3% / 2.5%
Dose and Frequency	Apply a thin layer to the affected areas once daily. Avoid the eyes, mouth, paranasal creases, and mucous membranes.	Apply a thin layer of EPIDUO FORTE to affected areas of the face and/or trunk once daily after washing. • Use a pea-sized amount for each area of the face (e.g., forehead, chin, each cheek).
How Supplied	(clindamycin phosphate/ adapalene/benzoyl peroxide) Gel, 1.2%/0.15%/3.1% is a white to off-white, opaque, smooth gel supplied as follows: 20 g tube (NDC 0187-0006-20) 50 g tube (NDC 0187-0006-50) 20 g pump (NDC 0187-0006-10) 50 g pump (NDC 0187-0006-25)	EPIDUO FORTE (adapalene and benzoyl peroxide) topical gel 0.3% / 2.5% is white to very pale yellow in color and opaque in appearance, and is supplied as follows: 15 gram pump NDC 0299-5906-15 30 gram pump NDC 0299-5906-30 45 gram pump NDC 0299-5906-45

[a] Epiduo Forte [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2023 May 19. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207917Orig1s004s008lbl.pdf

		60 gram pump NDC 0299-5906-60 70 gram pump NDC 0299-5906-70
Storage	Store at room temperature at or below 25°C (77°F). (b) (4) Keep away from heat. Store pump upright. (b) (4)	Store at controlled room temperature 20 – 25˚C (68 – 77˚F) with excursions permitted to 15˚ – 30˚C (59˚ – 86˚F) [see USP controlled room temperature]. Keep away from heat. Protect from light. Keep out of reach of children.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Cabtreo labels and labeling submitted by Bausch Health US, LLC.

- Container label(s) received on December 22, 2023
- Carton labeling received on December 22, 2023
- Professional Sample Carton Labeling received on April 21, 2023
- Instructions for Use received on December 22, 2023, available from \\CDSESUB1\EVSPROD\nda216632\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions.pdf
- Prescribing Information (Image not shown) received on December 22, 2023, available from \\CDSESUB1\EVSPROD\nda216632\0001\m1\us\114-labeling\draft\annotated\annotated-draft-labeling-text.pdf
- Patient Prescribing Information (Image not shown) received on December 22, 2023, available from \\CDSESUB1\EVSPROD\nda216632\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-patient-pi.pdf

F.2 Label and Labeling Images

Container label(s)

20 g Tube

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[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CORWIN D HOWARD
05/19/2023 11:06:55 AM

MADHURI R PATEL
05/22/2023 09:26:22 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 21, 2023

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead Cardiac Safety IRT, DCN

To: Dawn Williams, RPM
DDD

Subject: QT Consult to NDA216632 (SDN 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 2/22/2023 regarding the sponsor's QT related question. We reviewed the following materials:

- Sponsor's Request for TQT waiver (NDA216632 / SDN001);
- Sponsor's Summary of Clinical Pharmacology studies (NDA216632 / SDN001);
- Sponsor's Proposed Labeling (NDA216632 / SDN001);
- Clinical Pharmacology and Biopharmaceutics Review for NDA207917; and
- Highlights of clinical pharmacology and cardiac safety (NDA216632 / SDN001).

1 Responses for the Sponsor

Consult from the Review Division: In this Original NDA 505(b)(2) submission, the applicant has submitted a TQT waiver request. We are requesting your evaluation and recommendation of this request.

IRT's response: Systemic exposure to adapalene and clindamycin after multiple dose treatment with IDP-126 Gel is in the sub nanomolar range and has similar (or lower exposures) to the exposures with other marketed acne vulgaris products containing adapalene and clindamycin. If the review division concurs with the applicant that the other marketed acne vulgaris products have no QT prolongation risk, then a TQT study for IDP-126 Gel is not necessary.

2 Internal Comments for the Division

- *None*

3 BACKGROUND

3.1 Product Information

The sponsor has developed IDP-126 Gel for the treatment of acne vulgaris (acne) in patients (b) (4) years of age and older. IDP-126 Gel is a novel fixed-dose combination product containing clindamycin phosphate, benzoyl peroxide (BPO), and adapalene (1.2%/3.1%/0.15%). Qualitatively, the IDP-126 Gel formulation has the same excipient and active ingredient composition as ACANYA® (clindamycin phosphate 1.2%/BPO 2.5%) Gel, with the only difference being the addition of the synthetic retinoid, adapalene.

Acne vulgaris (acne) is a very common disorder of sebaceous follicles that is most prevalent among teenagers, usually triggered by the increase in androgen production occurring at puberty. The pathogenesis is complex and appears to involve 4 primary features: stimulation of sebum gland activity, bacterial proliferation (especially Cutibacterium acnes), abnormal follicular hyperkeratinization and resultant obstruction of the sebaceous follicles, and the release of inflammatory mediators. Both clindamycin phosphate (an antibiotic) and BPO (an antimicrobial) decrease Cutibacterium acnes proliferation by independent mechanisms; BPO is also keratolytic; and adapalene additionally regulates keratinization.

The recommended therapeutic dose regimen is topical application of a thin layer of IDP-126 Gel to the affected areas once daily.

The clinical pharmacokinetics of clindamycin, and adapalene after topical application of IDP-26 Gel is summarized in the summary of clinical pharmacology studies and in the table of highlights clinical pharmacology and cardiac safety. In brief, the clinical pharmacokinetics of IDP-126 Gel was investigated in a maximal use study (V01-126A-501) in which 2.5 g (the maximal use dose) of the study drugs (IDP-126 Gel or reference listed drug EPIDUO FORTE Gel) was applied to the face, neck, upper chest, upper back, and shoulders once daily, at approximately the same time each morning (between 6 and 10 AM), for 28 days. The mean plasma adapalene concentrations at all time points on Days 1-2, Days 14-15, and Days 28-29 were < 0.20 ng/mL (0.485 nM), regardless of age or assigned study drug (IDP-126 Gel or EPIDUO FORTE Gel) were higher for IDP-126 Gel compared to IDP-126 Gel. Similarly, despite 3-fold accumulation between day 1-28, the mean plasma concentrations of clindamycin were < 5 ng/mL (0.99 nM) at all collection time points regardless of age.

Reviewer's comments: *Findings from the maximal use study indicates that systemic exposure to adapalene and clindamycin after topical application of IDP-126 Gel and IDP-126 Gel are in the sub nanomolar range and therefore meet the criteria for waiving the TQT study.*

3.2 Sponsor's position related to the question

The sponsor is requesting for waiver of the requirement to conduct a TQT study for IDP-126 Gel. The sponsor presents the following arguments to support the request:

1. IDP-126 Gel contains the same active ingredients as those contained in products marketed in the US for more than 25 years without cardiovascular safety concerns.
2. Nonclinical studies indicates that adapalene, clindamycin and benzoic acid do not block hERG channels and invivo treatment with enhanced formulation (Twice the composition of IDP-126 Gel) does not cause ECG abnormalities.
3. The maximal use study did not indicate any adverse cardiovascular outcomes.
4. The maximal use study indicates that exposure to adapalene following IDP-126 Gel application is lower than that from reference listed EPIDUO FORTE Gel.

Combination products containing various concentrations and pairings of adapalene, clindamycin phosphate, and BPO have been marketed in the US for more than 25 years, and no cardiovascular safety concerns have been associated with any of the topical uses in humans. A systematic search of publicly-available databases, including the FDA Postmarket Drug Safety Information for Patients and Providers, AERS, QT Drugs, and PubMed did not reveal any concerns for increased risk of cardiac events with adapalene or clindamycin phosphate; BPO is not absorbed systemically and is therefore not an API of concern.

Qualitatively, the IDP-126 Gel formulation has the same excipient and active ingredient composition as ACANYA Gel, with the only difference being the addition of the synthetic retinoid, adapalene. As a pharmacological class, retinoids have been marketed for decades and have an established record of safety, with no association to QT interval prolongation or cardiac events of interest.

In the 3-month repeated dose dermal toxicity study, the daily human equivalent doses of the APIs applied to minipigs were approximately 2.5- to 25-fold higher than the maximum amount intended for application to patients with acne. There were no test article related ECG abnormalities following treatment with the IDP-126 Gel test articles, including an enhanced formulation that contained the active ingredients at concentrations that were 2-fold higher than the final to-be-marketed formulation. Safety margins for adapalene and clindamycin based on systemic exposure (AUC) at the nonclinical NOAEL are 72 and 4, respectively, when considering the clinical exposure for patients with acne who are 9 years of age and older.

The IDP-126 Gel clinical program included bridging studies to allow for reliance on the FDA's previous finding of safety for the LD, EPIDUO FORTE Gel. Overall, in the maximal use PK study, greater exposure to adapalene was observed for EPIDUO FORTE Gel relative to IDP-126 Gel; systemic exposures of clindamycin were relatively low for IDP-126 Gel in this study.

Given the totality of the nonclinical and clinical evidence and supported by human safety information available in public databases and literature reports related to the active ingredients in the combination product, there is a lack of concern for QT interval prolongation with IDP-126 Gel therapy in patients with acne who would be expected to use IDP-126 Gel once approved. Based on the feedback provided by the FDA during development, these data support a waiver for a clinical TQT study for IDP-126 Gel.

3.3 Nonclinical Cardiac Safety

Refer to table of clinical pharmacology highlights and cardiac safety.

Reviewer's Comment: *hERG safety margin for adapalene should be > 6000 (assuming 100% unbound exposure, IC50 > 3µM, maximal use Cmax = 0.2 ng/mL and MW = 412.5). hERG safety margin for clindamycin should be >1009 (assuming 100% unbound exposure, IC50 > 10µM, maximal use Cmax = 5 ng/mL and MW = 504.97). hERG safety margin for benzoic acid is unknown since its systemic exposure after maximal use was not determined.*

3.4 Clinical Cardiac Safety

Refer to table of clinical pharmacology highlights and cardiac safety.

3.5 Summary results of prior QTc assessments

NA

3.6 Relevant details of planned Phase 3 study

NA

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

ELIFORD N KITABI
04/21/2023 03:02:54 PM

CHRISTINE E GARNETT
04/21/2023 03:05:41 PM