CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209354Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
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:	March 13, 2019
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 209354
Product Name and Strength:	Duobrii (halobetasol propionate and tazarotene) lotion, 0.01%/0.045%
Applicant/Sponsor Name:	Bausch Health Americas, Inc.
FDA Received Date:	February 11, 2019
OSE RCM #:	2017-1709-2
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

Division of Dermatology and Dental Products (DDDP) requested that we review the revised container labels and carton labeling for Duobrii (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 revised container labels and carton labeling for Duobrii are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Patel, M. Label and Labeling Review for Duobrii (halobetasol propionate and tazarotene) (NDA 209354). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JAN 28. RCM No.: 2017-1709-1.

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/s/

MADHURI R PATEL
03/14/2019 07:45:26 AM

SEVAN H KOLEJIAN
03/14/2019 08:50:20 AM

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:	February 19, 2019
To:	Kendall Marcus, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	DUOBRII (halobetasol propionate and tazarotene)
Dosage Form and Route:	Lotion, for topical use
Application Type/Number:	NDA 209354
Applicant:	Dow Pharmaceutical Sciences, Inc.

1 INTRODUCTION

On August 15, 2018, Dow Pharmaceutical Sciences, Inc., submitted for the Agency's review a Class 2 Resubmission for a 505 (b)(2) New Drug Application (NDA) 209354 for DUOBRII (halobetasol propionate and tarzarotene) lotion. The purpose of this resubmission is to address deficiencies identified in the Complete Response (CR) letter issued by the Agency on June 15, 2018.

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 Dermatology and Dental Products (DDDP) on September 13, 2018 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for DUOBRII (halobetasol propionate and tarzarotene) lotion, for topical use.

2 MATERIAL REVIEWED

- Draft DUOBRII (halobetasol propionate and tarzarotene) lotion PPI received on August 15, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 12, 2019.
- Draft DUOBRII (halobetasol propionate and tarzarotene) lotion Prescribing Information (PI) received on August 15, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 12, 2019.

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.

In our collaborative review of the PPI we:

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

- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI 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 PPI 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 PPI.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
02/19/2019 11:08:06 AM

LAURIE J BUONACCORSI
02/19/2019 11:10:14 AM

SHAWNA L HUTCHINS
02/19/2019 11:17:25 AM

LASHAWN M GRIFFITHS
02/19/2019 01:04:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date of Consult Request:	September 6, 2017
From:	Jane Liedtka, MD, Medical Officer (MO) Division of Pediatric and Maternal Health (DPMH)
To:	Nancy Xu, MD, Associated Director for Labeling (ADL) Division of Dermatology and Dental Products (DDDP)
NDA Number:	209354
Drug:	Halobetasol and tazarotene lotion, 0.01%/0.045%
Applicant:	Dow Pharmaceutical Sciences, Inc.
Indication:	a combination of halobetasol propionate and tazarotene indicated for the topical treatment of plaque psoriasis.

DDDP submitted a consult request to the DPMH on September 6, 2017, asking for assistance with the review of labeling language for the pregnancy and lactation sections for the above referenced NDA. The submission was given a Complete Response on June 15, 2018 and the DPMH consult was categorized as ongoing. On August 28, 2018, the submission was resubmitted. DPMH participated in a labeling meeting with DDDP on February 12, 2019 and proposed labeling recommendations for the above referenced NDA.

DPMH- Maternal Health, has no further comments at this time, thus, this memorandum will close out the consult request.

DPMH Maternal Health MO Reviewer- Jane Liedtka, MD
DPMH Maternal Health Team Leader- Miriam Dinatale, DO
DPMH Division Director- Lynne Yao, MD
DPMH RPM- Lori Gorski

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/s/

JANE E LIEDTKA
02/15/2019 10:29:55 AM

MIRIAM C DINATALE
02/19/2019 04:54:57 PM

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

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

Memorandum

Date: February 14, 2019

To: Hamid Tabatabai/Clinical Reviewer, M.D.
Division of Dermatology and Dental Products (DDDP)

Barbara Gould, Regulatory Project Manager, (DDDP)

Nancy Xu, Associate Director for Labeling, (DDDP)

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045%

NDA: 209354

In response to DDDP's consult request dated September 13, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% (Duobrii).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDDP on February 12, 2019, and are provided below.

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

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 11, 2019, and we have no comments.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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/s/

LAURIE J BUONACCORSI
02/14/2019 11:40:29 AM

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

REVIEW DEFERRAL MEMORANDUM

Date:	June 18, 2018
To:	Kendall Marcus, MD Director **Select Division Name**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN 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)**
Subject:	Review Deferred: Patient Package Insert (PPI)
Drug Name (established name):	DUOBRII (halobetasol propionate and tazarotene)
Dosage Form and Route:	Lotion, 0.01%/0.045%, for topical use
Application Type/Number:	NDA 209354
Applicant:	Dow Pharmaceutical Sciences, Inc., c/o Valeant Pharmaceuticals North America, LLC.

1 INTRODUCTION

On August 18, 2017, Dow Pharmaceutical Sciences, Inc., c/o Valeant Pharmaceuticals North America, LLC., submitted for the Agency's review a 505(b)2 New Drug Application (NDA) 209354 for DUOBRII (halobetasol propionate and tazarotene), Lotion, 0.01%/0.045%, for topical use. The proposed indication is for the treatment of plaque psoriasis.

On September 11, 2017, the Division of Dermatology and Dental Products (DDDP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for DUOBRII (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045%, for topical use.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI for DUOBRII (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045%, for topical use.

2 CONCLUSIONS

Due to outstanding nonclinical deficiencies, DDDP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SUSAN W REDWOOD
06/18/2018

BARBARA A FULLER
06/18/2018

Clinical Inspection Summary

Date	March 16, 2018
From	Bei Yu, Ph.D., Reviewer Janice Pohlman, M.D., M.P.H., Team Leader Susan D. Thompson, M.D., Team Leader for Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Strother Dixon, Regulatory Project Manager Hamid Tabatabai, M.D., Clinical Reviewer Snezana Trajkovic, M.D., Clinical Team Leader Division of Dermatology and Dental Products (DDDP)
NDA #	209354
Applicant	Dow Pharmaceutical Sciences, a Division of Valeant Pharmaceuticals North America LLC
Drug	IDP-118 Lotion (Halobetasol Propionate and Tazarotene)
NME	No
Review Priority	Standard Review
Proposed Indication	Plaque Psoriasis
Consultation Request Date	November 3, 2017
Summary Goal Date	March 30, 2018
Action Goal Date	June 4, 2018
PDUFA Date	June 18, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Bagel, DuBois, and Simmons were inspected in support of NDA 209354. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites and as reported by the sponsor to the NDA appear acceptable in support of the respective indication.

The final classification of the inspections of these clinical investigators was No Action Indicated (NAI).

II. BACKGROUND

The Applicant submitted this NDA to support the use of IDP-118 lotion, a combination product with halobetasol propionate (HP) 0.01% w/w and tazarotene 0.045% w/w for the treatment of adults with (b) (4) plaque psoriasis. Inspections were requested for the following two identical protocols in support of this application:

Protocols V01-118A-301 and **V01-118A-302**, entitled "A Phase 3, Multicenter, Double-Blind, Randomized, Vehicle Controlled Clinical Study to Assess the Safety and Efficacy of IDP-118 in the Treatment of Plaque Psoriasis".
Study 301 was conducted at 16 clinical sites in the U.S. between August 2015 and November 2016. A total of 203 subjects were enrolled. Study 302 was conducted at 16 clinical sites in the U.S. between August 2015 and October 2016. A total of 215 subjects were enrolled.

The two identical studies were randomized, double-blind, parallel-group, multicenter studies designed to assess the safety and efficacy of IDP-118 Lotion in comparison with its vehicle for treatment of adults with moderate-to-severe plaque psoriasis. Eligible subjects were randomized to one of the two study drug groups in a 2:1 ratio (IDP-118 [HP 0.01%, Taz 0.045%] Lotion: IDP-118 Vehicle Lotion). The assigned study drug was applied topically to the affected area once daily for 8 weeks.

The primary efficacy endpoint was the percent of subjects with treatment success at Week 8, defined as at least a 2-grade improvement from Baseline in Investigator's Global Assessment IGA score and an IGA score equating to "Clear" or "Almost Clear".

Rationale for Site Selection:
All the sites were selected for inspection mainly due to a high site efficacy effect and the fact that these clinical investigators had no prior history of good clinical practice (GCP) inspections.

III. RESULTS (by site):

Site #/ Name of CI/ Address	**Protocol # / # of Subjects Enrolled**	**Inspection Dates**	**Classification**
Site #201 **Jerry Bagel, M.D.** 59 One Mile Road, Suite B East Windsor, NJ 08520	V01-118A-302 Subjects: 18	3, 5, 8 - 11 Jan 2018	NAI
Site #104 **Janet DuBois, M.D.** 8140 N. Mopac, Bldg 3, Suite 120 Austin, TX 78759	V01-118A-301 Subjects: 21	16 - 19 Jan 2018	NAI
Site #101 **Reginold Simmons, M.D,** 4257 West Kennedy Blvd. Tampa, FL 33609	V01-118A-301 Subjects: 21	2 - 4 Jan 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

Clinical Investigator Sites

1. Jerry Bagel, M.D.

At this site for Protocol V01-118A-302, a total of 21 subjects were screened and 18 subjects were enrolled, 17 of whom completed the study. The informed consent forms for all 21 screened subjects were reviewed to ensure that subjects were properly consented.

The records for all 18 enrolled subjects were reviewed. These included, but were not limited to, IRB approvals, source documents, training records, record retention, protocol deviation, delegation log, and test article accountability log. The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection.

2. Janet DuBois, M.D.

At this site for Protocol V01-118A-301, 39 subjects were screened and 21 subjects were enrolled, 18 of whom completed the study.

The records for all 21 enrolled subjects were reviewed. These included, but were not limited to, the informed consent forms, study records, patient histories, drug accountability, lab results, concomitant medications, and sponsor correspondence. The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection.

3. Reginold Simmons, M.D.

At this site for Protocol V01-118A-301, 49 subjects were screened and 21 subjects were enrolled, 19 of whom completed the study. The informed consent forms for all 49 screened subjects were reviewed to ensure that subjects were properly consented.

The records reviewed included, but were not limited to, source and case report forms for all enrolled subjects, IRB correspondence, adverse event reporting, monitoring visits, and drug accountability. The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

The Clinical Study Report submitted in the NDA indicated that Dr. Susan Barker was the principal investigator (PI). During the conduct of the inspection it was learned that following the retirement of Dr. Barker in August 2016, Dr. Simmons transitioned from the role of a sub-investigator for this study to PI. All subjects had been enrolled and active study procedures had been completed by the time of transition. Dr. Barker had served as a consultant until the study was closed.

A Form FDA 483 was not issued at the conclusion of the inspection.

{See appended electronic signature page}

Bei Yu, Ph.D.
Pharmacologist
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D., Team Leader for
Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. / NDA 209354
DDDP /Medical Team Leader/ Snezana Trajkovic
DDDP /Project Manager/ Strother Dixon
DDDP/MO/ Hamid Tabatabai
OSI/DCCE/ Division Director/ Ni Khin
OSI/DCCE/Branch Chief/ Kassa Ayalew
OSI/DCCE/Team Leader/Janice Pohlman
OSI/DCCE/GCP Reviewer/Bei Yu
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague

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/s/

BEI YU
03/16/2018

JANICE K POHLMAN
03/16/2018

SUSAN D THOMPSON
03/16/2018

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

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

Memorandum

Date: February 16, 2018

To: Strother Dixon, Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Jina Kwak, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 209354
OPDP labeling comments on Halobetasol and Tazarotene Lotion, 0.01%/0.045%

This memo is in response to DDDP labeling consult request dated September 6, 2017. Due to a lack of a clinical bridge and other issues, DDDP plans to issue a Complete Response letter. Therefore, OPDP defers comments on the proposed labeling at this time and request that DDDP submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Jina Kwak at (301) 796-4809 or jina.kwak@fda.hhs.gov

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/s/

JINA KWAK
02/16/2018

LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
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:	February 16, 2018
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 209354
Product Name and Strength:	Duobrii (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045%
Product Type:	Multi-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Dow Pharmaceutical Sciences Inc. c/o Valeant Pharmaceuticals North America, LLC
FDA Received Date:	January 8, 2018
OSE RCM #:	2017-1709
DMEPA Safety Evaluator:	Carlos M Mena-Grillasca, BSPharm
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container labels, carton labeling, and Prescribing Information (PI), for Duobrii (halobetasol propionate and tazarotene) lotion (NDA 209354), in response to a consult from the Division of Dermatology and Dental Products (DDDP). The Applicant submitted NDA 209354, a 505(b)(2) application, on August 18, 2017.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing to market Duobrii in 45 g, 60 g, and 100 g tubes. We note the reference products (i.e. Ultravate cream and Tazorac cream) are available in 30 g, 50 g, 60 g, and 2 X 50 g tubes; therefore, we find the proposed tube sizes adequate.

We reviewed the container labels and carton labeling and noted that the established name is not at least ½ the size of the proprietary name and does not meet 21 CFR 201.10(g)(2) taking into consideration the condensed font used for the presentation of the established name. In order to prevent medication errors, we recommend including the statement 'Not for oral, ophthalmic or intravaginal use' on the container and carton labeling. Finally, the 3 g container label is a small label and the information is crowded and difficult to read. Per 21 CFR 201.10(i) small labels are only required to bear the proprietary name, established name, strength, lot number, expiration date, and name of manufacturer. Therefore, we provide recommendations to improve the small 3 g container label.

4 CONCLUSION & RECOMMENDATIONS

We find the proposed packaging configuration acceptable. We recommend the following label and labeling revision be implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DOW PHARMACEUTICAL SCIENCES, INC. C/O VALEANT PHARMACEUTICALS NORTH AMERICA, LLC

A. General Recommendations (All labels and labeling)
    a. Revise the presentation of the established name to ensure that it is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). By choosing a condensed font size for the presentation of the established name, we find is not commensurate in size to the proprietary name.
    b. Add the statement 'Not for oral, ophthalmic or intravaginal use' in bold font above the usual dosage statement. (This recommendation is not applicable to the 3 g container label)
    c. Use bold font for the storage statement 'Store at 20 to 25˚C (68 to 77˚F)'.

B. Container Label (3 g sample only)
    a. This is a small label and the information presented on the back panel is crowded and in small font, making it difficult to read. Therefore, revise the back panel to include only the following information, and allowing blank space between each statement for clarity:

Usual Dosage: Apply a thin layer to the affected areas once daily.

Keep out of reach of children.

Store at 20 to 25˚C (68 to 77˚F)

Mfg. for: Dow Pharmaceutical Sciences, a division of Valeant Pharmaceutical North America LLC, Bridgewater, NJ 08807 USA

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Duobrii received on January 8, 2018 from Dow Pharmaceutical Sciences, and the Listed Drugs (LD)

Table 2. Relevant Product Information for Duobrii and the Listed Drug

Product Name	**Duobrii**	**Ultravate Cream** **Tazorac Cream**
Initial Approval Date	n/a	Ultravate– 12/27/1990 Tazorac– 9/29/2000
Active Ingredient	Halobetasol propionate and tazarotene	Ultravate– halobetasol propionate Tazorac - tazarotene
Indication	Topical treatment of plaque psoriasis	Ultravate - relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses Tazorac – treatment of plaque psoriasis and acne vulgaris
Route of Administration	Topical	Topical
Dosage Form	lotion	cream
Strength	0.01%/0.045%	Ultravate cream – 0.05% Tazorac cream – 0.05% and 0.%
Dose and Frequency	Apply a thin film to the affected areas once daily	Ultravate – Apply a thin layer to the affected areas once or twice daily Tazorac – apply a thin layer to the affected area once daily in the evening
How Supplied	45 g, 60 g, 100 g tubes	Ultravate – 50 g, 2 x 50 g tubes Tazorac – 30 g, 60 g tubes
Storage	20 to 25˚C (68 to 77˚F)	Ultravate - 15 to 30˚C (59 to 86˚F) Tazorac - 20 to 25˚C (68 to 77˚F)
Container Closure	n/a	n/a

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 15, 2018, we searched DMEPA's previous reviews using the terms, Duobrii. Our search did not identify any relevant label and labeling reviews.

APPENDIX C. HUMAN FACTORS STUDY

N/A

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F. OTHER SOURCES

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Duobrii labels and labeling submitted by Dow Pharmaceutical Sciences Inc.

- Container labels and Carton labeling received on January 8, 2018
- Instructions for Use received on January 8, 2018 (image not shown)
- Medication Guide received on January 8, 2018 (image not shown)
- Prescribing Information received on January 8, 2018 (image not shown)

G.2 Label and Labeling Images

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

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/s/

CARLOS M MENA-GRILLASCA
02/16/2018

SARAH K VEE
02/16/2018

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: February 15, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Strother Dixon, RPM
DDDP

Subject: QT-IRT Consult to NDA 209354

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 10/20/2017 regarding the sponsor's TQT waiver request. The QT-IRT reviewed the following materials:

- Sponsor's briefing material;
- Previous advice letter from DDDP under IND 111218 dated 04/22/2016 in DARRTS (http://mercado.fda.gov/search/resources/panorama/documentum/DARRTS/090140af803e2075?includeRequestSystem=true); and
- Highlights of clinical pharmacology and cardiac safety.

1. QT-IRT Response to the Division

A TQT study is not required for IDP-118 lotion (fixed combination drug product containing halobetasol propionate (0.01%) and tazarotene (0.045%)). Our conclusion is based on the following rationale:

- Previously, the Agency had indicated to the sponsor that, "a waiver of thorough QT trial would be reasonable if the results from the maximal use PK trial confirm that the systemic exposure of halobetasol propionate, tazarotene and tazarotenic acid following IDP-118 lotion treatment under maximal use conditions is low and less than or similar to

those following treatment with listed drugs Tazorac cream, 0.1% and Ultravate cream, 0.05%." In the sponsor's maximal use PK study in patients, the steady state C_{max} for halobetasol propionate was higher by 1.5-fold (87.2/58.2 pg/mL), for tazarotenic acid was higher by ~1.6-fold (471/286 pg/mL on Day 14 and 525/340 pg/mL on Day 28) and for tazarotene was higher by 1.1- to 3.1-fold (31.6/10.2 pg/mL on Day 14 and 24.1/22.3 pg/mL on Day 28) for IDP-118 lotion compared to the corresponding listed drugs (Ultravate cream (0.05%) and Tazorac cream (0.1%)).

- However, there is sub-nanomolar systemic exposure (C_{max}) of halobetasol propionate and tazarotene and ~1.6 nM systemic exposure of tazarotenic acid with IDP-118 lotion. The preclinical data suggested a safety margin of at least 4-orders of magnitude over observed C_{max} in patients for all these moieties for hERG inhibition (IC_{50} for halobetasol propionate, tazarotenic acid and tazarotene are >10 μM, >10 μM and 5.7 μM respectively). Furthermore, tazarotene and tazarotenic acid are highly bound to human plasma proteins (>90%) which further increases the safety margin corresponding to the free drug concentration in plasma for these moieties towards hERG inhibition. Also, no large QTc outliers (QTcF > 500 ms or ΔQTcF ≥ 60 ms) or higher mean changes in QTc compared to vehicle control were seen in ECG assessments in Phase 3 study for IDP-118. Postmarketing experience of 25 years for halobetasol propionate and 18 years for tazarotene did not identify significant cardiovascular adverse effects with topical use. Thus, the totality of evidence suggests minimal risk for QTc prolongation for IDP-118 lotion despite the findings of higher exposures compared to listed drugs in the maximal use PK study.

2. BACKGROUND

Product Information

IDP-118 Lotion is a fixed combination drug product containing halobetasol propionate (0.01%) and tazarotene (0.045%). Both halobetasol propionate and tazarotene are approved as monotherapies for psoriasis, Ultravate Cream (0.05%) and Tazorac Cream (0.05%/0.1%), respectively. These drugs belong to established pharmacological classes; halobetasol propionate is a corticosteroid, while tazarotene is a retinoid.

IDP-118 Lotion is indicated for topical treatment of plaque psoriasis in patients 18 years of age and older. The clinical program included bridging clinical studies in order to rely on the Agency's previous finding of safety for the listed drugs (LD) Ultravate (0.05% halobetasol propionate) Cream and Tazorac (0.05% tazarotene) Cream.

Sponsor's position related to the question

The Sponsor is requesting a waiver for conducting a Thorough QT/QTc (TQT) study with IDP-118 Lotion. The waiver request was initially submitted to the IND (Sequence 0053, 02Feb2016). This updated waiver request document incorporates human exposure data from the maximum use clinical study with IDP-118 Lotion as well as electrocardiogram (ECG) data from one of the IDP-118 Lotion Phase 3 studies.

Following topical dermal administration of IDP-118 Lotion in psoriasis patients, drug-related systemic exposure was low and comparable to that of the listed drugs Ultravate Cream (0.05%

halobetasol propionate) and Tazorac Cream (0.05% tazarotene). There was no apparent effect of IDP-118 Lotion administration on QT interval duration compared to baseline and to vehicle based on ECG measurements. Based on the wealth of safety data from the extensive marketing experience with the active ingredients, and low human systemic exposure with high safety factors to nonclinical data resulting from IDP-118 Lotion administration, there is a lack of concern for QT interval prolongation with the halobetasol propionate and tazarotene combination in IDP-118 Lotion.

In Vitro hERG Inhibition

The potential for halobetasol propionate, tazarotene and tazarotenic acid to inhibit IKr was evaluated in an in vitro patch clamp test at near physiological temperature using HEK293 human embryonic kidney cells expressing hERG (Study V01-118A-608). Test articles were tested individually and in combination at concentrations up to 10 µM (Table 3). The top concentration was selected to provide an exposure multiple of approximately 4 orders of magnitude higher than the anticipated human plasma exposure with IDP-118 Lotion. The cisapride positive control performed as expected, thereby validating the assay sensitivity.

Tazarotene inhibited hERG current with an IC50 of 5.7 µM. Tazarotenic acid and halobetasol propionate inhibited hERG current minimally at the high dose, with IC50 >10 µM. Dosing of tazarotene and halobetasol propionate in combination at 1 µM produced 20.9% inhibition, and can be mostly attributed to tazarotene which produced 20.1% inhibition alone (Table 3). Tazarotenic acid and halobetasol propionate, which are the two entities likely to be found in plasma after treatment with IDP-118 Lotion, only produced minimal hERG inhibition in combination at 1 µM, i.e. 4.2% inhibition.

Table 3. Summary of In Vitro hERG Inhibition Results

Concentration (µM)			% Inhibition (Mean ± SD)	n
Halobetasol Propionate	Tazarotene	Tazarotenic Acid		
1	-	-	0.6±0.3	3
10	-	-	16.9±2.0	4
-	0.3[a]	-	5.6±0.7	3
-	1[a]	-	20.1±2.0	3
-	3[a]	-	41.6±0.6	3
-	10[a]	-	59±1.0	4
-	-	1	1.9±1.1	3
-	-	10	9.8±0.6	3
1	1	-	20.9±0.8	3
1	-	1	4.2±0.9	3

[a] Tazarotene IC_{50} = 5.7 µM
Source: Final report Study V01-118A-608

ECG assessments in Phase 3 for IDP-118

In the Phase 3 Study 301, 12-lead electrocardiograms (ECGs) were collected at screening (baseline) and at Week 8/end of treatment (CTD Section 2.7.4.4.3; Study V01-118A-301). ECGs were performed after the subject had rested quietly for at least 5 minutes in a supine position. There were no meaningful differences in mean QT/QTcF duration between IDP-118 Lotion and IDP-118 Vehicle Lotion groups, and no differences between baseline and week 8 (Table 5). There were no subjects who had a QTcF > 500 msec or ≥ 60 msec increase at any post-baseline

visit (Table 14.3.1.7.1, Study V01-118A-301). There were 7 (5.5%) and 5 (8.1%) patients in the IDP-118 Lotion and IDP-118 Vehicle Lotion groups, respectively, with QTcF > 450-470 msec at post-baseline visits. Only one subject (0.8%) in the IDP-118 Lotion group had a QTcF > 470-500 msec.

Overall, the ECG data did not raise any safety concerns, and no clinically significant ECG abnormalities were reported.

Table 5. ECG Parameters Safety Population from Phase 3 (Study 301)

	IDP-118 Lotion			IDP-118 Vehicle Lotion		
	Screening	Week 8	Change from Screening	Screening	Week 8	Change from Screening
QT Interval (msec)						
N	133	120	120	67	59	59
Mean	389.4	386.0	-3.5	394.6	392.7	-0.3
SD	29.57	31.24	22.49	31.34	31.18	25.13
Median	384.0	385.5	-2.5	393.0	391.0	-2.0
Min. to Max.	319 to 481	305 to 458	-54 to 72	335 to 481	322 to 467	-53 to 57
QTcF Interval (msec)						
N	133	120	120	67	59	59
Mean	409.2	406.7	-2.5	415.4	411.0	-3.3
SD	21.93	22.03	15.17	23.10	24.07	16.81
Median	406.0	404.0	-2.5	413.0	414.0	-3.0
Min. to Max.	364 to 486	363 to 480	-43 to 46	360 to 486	363 to 466	-66 to 37

Post-marketing safety

Halobetasol propionate and tazarotene have been marketed for 25 and 18 years since first approved, respectively, and there is ample post-market safety information. Several public databases were systematically searched for potential cardiovascular system safety concerns related to these drugs, and included the FDA Postmarket Drug Safety Information for Patients and Providers (Section 5.1), the FDA AERS (Adverse Event Reporting System) (Section 5.2), the QT Drugs Database (Section 5.3) and PubMed (Section 5.4). All search results were negative regarding adverse effects on the cardiovascular system with topical use of halobetasol propionate or tazarotene.

Summary results from maximal use PK study

The following table shows the comparison of C_{max} of halobetasol propionate, tazarotene and tazarotenic acid for IDP-118 lotion compared to the corresponding listed drugs (Ultravate cream (0.05%) and Tazorac cream (0.1%)) in the maximal use PK study.

Table 10. Pharmacokinetic Parameter Comparison Maximum Use Study in Psoriasis Patients

Day	PK parameter	Halobetasol propionate		Tazarotene		Tazarotenic acid	
		IDP-118 Lotion	Ultravate Cream	IDP-118 Lotion	Tazorac Cream	IDP-118 Lotion	Tazorac Cream
14	C_{max} (pg/mL)						
	N	22	23	22	23	22	23
	Mean	87.2	58.2	31.6	10.2	471	286
	CV% mean	111	125	120	132	84.9	112
	AUC_{0-t} (pg•h/mL)						
	N	11	8	15	7	21	23
	Mean	2190	1910	387	231	8920	5330
	CV% mean	68.4	58.8	110	69.3	78.6	111
28	C_{max} (pg/mL)						
	N	-	-	22	23	22	23
	Mean	-	-	24.1	22.3	525	340
	CV% mean	-	-	113	189	99.6	103
	AUC_{0-t} (pg•h/mL)						
	N	-	-	16	6	22	23
	Mean	-	-	370	808	9960	6420
	CV% mean	-	-	118	100	101	106

Source: Study V01-118A-501; adapted from CTD Section 2.7.2.3.1.3 Tables 11, 12 and 13
(-) not compared as Ultravate Cream was administered to patients for 14 days per product label

Reviewer's comments:

- *Reviewer's calculations (see table below) show that there is sub-nanomolar systemic exposure of halobetasol propionate and tazarotene and ~1.6 nM systemic exposure of tazarotenic acid with IDP-118 lotion.*

			Cmax with IDP-118 Lotion		Cmax with corresponding listed drug*	
Compound	MW (g/mol)	Day of measurement	in pg/mL	in nM	in pg/mL	in nM
Halobetasol propionate	485	14	87.2	0.18	58.2	0.12
Tazarotenic acid	323	14	471	1.46	286	0.89
		28	525	1.63	340	1.05
Tazarotene	351	14	31.6	0.09	10.2	0.03
		28	24.1	0.07	22.3	0.06
* Ultravate cream (0.05%) for halobetasol propionate, and Tazorac cream (0.1%) for tazarotene and tazarotenic acid						

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/

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02/15/2018

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