

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209355Orig1s000

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: September 24, 2018
Requesting Office or Division: Division of Dermatology and Dental Products (DDDP)
Application Type and Number: NDA 209355
Product Name and Strength: Bryhali (halobetasol propionate) lotion, 0.01%
Applicant/Sponsor Name: Dow Pharmaceutical Sciences, Inc.
FDA Received Date: August 29, 2018
OSE RCM #: 2017-2471-1
DMEPA Safety Evaluator: Madhuri R. Patel, PharmD
DMEPA Team Leader: Teresa McMillan, PharmD

1 PURPOSE OF MEMORANDUM

Division of Dermatology and Dental Products (DDDP) requested that we review the revised carton and container labels for Bryhali (halobetasol propionate) lotion (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

The revised carton and container labels for Bryhali is acceptable from a medication error perspective. We have no further recommendations at this time.

^a Patel M. Label and Labeling Review for BRYHALI (NDA 209355). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 21. RCM No.: 2017-2471.

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/s/

MADHURI R PATEL
09/24/2018

TERESA S MCMILLAN
09/24/2018

**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: August 6, 2018

To: Kendall Marcus
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)

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)

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): BRYHALI (halobetasol propionate)

Dosage Form and Route: Lotion, for topical use

Application Type/Number: NDA 209355

Applicant: Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America, LLC

1 INTRODUCTION

On December 5, 2017, Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America, LLC., submitted for the Agency's review a New Drug Application (NDA) 209355 for BRYHALI (halobetasol propionate) Lotion, for topical use in accordance with Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act. The reference listed drug (RLD) for this submission is ULTRAVATE (halobetasol propionate) Cream, NDA 019967 approved December 27, 1990. The proposed indication for BRYHALI (halobetasol propionate) Lotion, is for the topical treatment of plaque psoriasis in adults.

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 December 28, 2017 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BRYHALI (halobetasol propionate) Lotion, for topical use.

2 MATERIAL REVIEWED

- Draft BRYHALI (halobetasol propionate) Lotion, for topical use PPI received on December 5, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 26, 2018.
- Draft BRYHALI (halobetasol propionate) Lotion, for topical use Prescribing Information (PI) received on December 5, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 26, 2018.

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)

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.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SUSAN W REDWOOD
08/06/2018

LAURIE J BUONACCORSI
08/06/2018

BARBARA A FULLER
08/06/2018

LASHAWN M GRIFFITHS
08/06/2018

Clinical Inspection Summary

Date	August 2, 2018
From	Bei Yu, Ph.D., Reviewer Janice Pohlman, M.D., M.P.H., Team Leader 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	Matthew White, Regulatory Project Manager Brenda Carr, M.D., Clinical Reviewer Snezana Trajkovic, M.D., Clinical Team Leader Division of Dermatology and Dental Products (DDDP)
NDA #	209355
Applicant	Dow Pharmaceutical Sciences, Inc.
Drug	Halobetasol Propionate Lotion
NME	No
Review Priority	Standard Review
Proposed Indication	Plaque Psoriasis
Consultation Request Date	January 22, 2018
Summary Goal Date	August 6, 2018
Action Goal Date	September 28, 2018
PDUFA Date	October 5, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. McConnehey, Primka, and Stoll were inspected in support of NDA 209355. Based on the results of these inspections, the studies (V01-122A-301 and V01-122A-302) conducted at sites of Drs. Primka and Stoll 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 Drs. McConnehey, Primka and Stoll was No Action Indicated (NAI).

II. BACKGROUND

The Applicant submitted this NDA to support the use of IDP-122, halobetasol propionate lotion, 0.01%, for the treatment of adults with (b) (4) plaque psoriasis. Inspections were requested for the following two identical protocols in support of this application:

V01-122A-301 and **V01-122A-302**, both entitled “A Phase 3, Multi-Center, Double-Blind, Randomized, Vehicle Controlled Clinical Study to Assess the Safety and Efficacy of IDP-122 in the Treatment of Plaque Psoriasis”.

Study 301 was conducted at 20 clinical sites in the U.S. between November 2015 and May 2017. A total of 217 subjects were enrolled. Study 302 was conducted at 17 clinical sites in the U.S. between November 2015 and March 2017. A total of 213 subjects were enrolled.

The two identical studies were randomized, double-blind, parallel-group, multicenter studies designed to assess the safety and efficacy of IDP-122 Lotion in comparison with its vehicle for treatment of adults with moderate-to-severe plaque psoriasis. Eligible subjects were randomized in a 2:1 ratio (IDP-122: Vehicle) and applied the study drug topically to the affected areas once daily for 8 weeks. Subjects returned to the clinic for post-baseline evaluations at Weeks 2, 4, 6, and 8, and again for a post-treatment follow-up visit at Week 12.

The primary efficacy endpoint was the percent of subjects with treatment success, 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” at Week 8.

Rationale for Site Selection:

Brock McConnehey (Site #607):

- High site efficacy effect;
- The CI was inspected in Aug, 2010 with classification of VAI.

Edward Primka (Site #711):

- High site efficacy effect;
- High protocol violations;
- More subjects in the placebo treatment arm discontinued from the study;
- The CI had not been previously inspected.

David Stoll (Site #618):

- High site efficacy effect;
- The CI has been inspected in 2008 and 2011 for previous complaints made to OSI; the inspection in 2008 was NAI and inspection in 2011 for lack of CI oversight and follow-up of AEs was classified VAI for inadequate/inaccurate record violations.

III. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol # / # of Subjects Enrolled	Inspection Dates	Classification
Site #607 Brock McConnehey, D.O. 888 N. Cole Road Boise, ID 83704	V01-122A-301 Subjects: 20	30 April – 3 May, 2018	NAI
Site #711 Edward Primka, M.D. 939 E. Emerald Ave, Suite 705 Knoxville, TN 37917	V01-122A-302 Subjects: 12	26-27 March 2018	NAI
Site #618 David Stoll, M.D. 9735 Wilshire Blvd., Suite 418 Beverly Hills, CA 90212	V01-122A-301 Subjects: 20	18-22 June 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. Brock McConnehey, D.O.**

At this site for Protocol V01-122A-301, a total of 20 subjects were screened and enrolled, and 19 subjects completed the study. The informed consent forms for all 20 screened subjects were reviewed to ensure that subjects were properly consented.

The records for all 20 enrolled subjects were reviewed, including, but not limited to, Institutional Review Board (IRB) approvals and correspondence, sponsor correspondence, drug receipt and accountability, study staff training and CVs, monitoring records and subject records.

Some minor, isolated observations/findings were discussed with the clinical investigator:

- Subject (b) (6) (Vehicle) and Subject (b) (6) (IDP-122) used clobetasol in the treatment area for pruritis secondary to psoriasis prior to the final week 12 visit (post-treatment follow-up visit). The steroid was reported as a concomitant medication for psoriasis, but puritis was not reported as an AE in the AE data line listing.

OSI Reviewer Comment: Local skin reactions (including itching) were reported by the sponsor in a different AE line list in the NDA. This list was not included in the background BIMO package provided to the ORA investigator. Itching (with grade) was reported for both of these subjects in the local skin reaction AE line listing in the NDA.

- Some prior/concomitant medications were not transcribed from source records into the eCRF for some subjects:
 - Subject (b) (6) (IDP-122): A prior medication, triamcinolone ((b) (6)), was not entered into the eCRF and was not reported in data line listings. Randomization occurred on (b) (6), after a 17-day washout.
 - Subject (b) (6) (Vehicle): A prior medication, Psoriasis (from (b) (6)), was not entered into eCRF and was not reported in data line listings. The subject was randomized on (b) (6). It is not clear whether this OTC product is considered an antipsoriasis drug in the context of this clinical study but the product was discontinued more than 14 days prior to randomization.

- In addition, there are a few protocol deviations of missed doses and extra doses taken by some subjects, which were not reported in the data line listings:
 - Subject (b) (6) missed a dose on (b) (6) (date of first dose: (b) (6));
 - Subject (b) (6) missed a dose on (b) (6) (date of first dose: (b) (6));
 - Subject (b) (6) missed four doses on (b) (6) (date of first dose: (b) (6));
 - Subject (b) (6) missed a dose on (b) (6) and took the missed dose the following morning, so it ended up dosing twice on (b) (6) (date of first dose: (b) (6));

OSI Reviewer's Comment: All four subjects were in the active treatment arm. Given the infrequent occurrence of these deviations, it is unlikely to have had a major impact on efficacy over an 8-week treatment period.

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

2. Edward Primka, M.D.

At this site for Protocol V01-122A-302, 18 subjects were screened and 12 subjects were enrolled, 11 of whom completed the study. The informed consent forms for all 18 screened subjects were reviewed to ensure that subjects were properly consented.

The records for all 12 enrolled subjects were reviewed. These records included, but were not limited to, the informed consent forms, case report forms, drug accountability, and monitoring reports. The source record data and the NDA data line listings were compared, specifically

focusing on verification of the efficacy endpoints and safety endpoints. 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. David Stoll, M.D.

At this site for Protocol V01-122A-301, 21 subjects were screened and 20 subjects were enrolled and completed the study. The informed consent forms for all 21 screened subjects were reviewed to ensure that subjects were properly consented.

Records reviewed included Institutional Review Board approvals, financial disclosures, informed consent forms, medical histories, physical examinations, progress notes, laboratory reports, other eligibility criteria, subject diaries, tube weights, concomitant medications, adverse events, drug accountability, and protocol deviations. 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.

{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}

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Kassa Ayalew, M.D., M.P.H
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cc:

Central Doc. Rm. / NDA 209355
DDDP /Medical Team Leader/ Snezana Trajkovic
DDDP /Project Manager/ Matthew White
DDDP/MO/ Brenda Carr
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
08/02/2018

JANICE K POHLMAN
08/02/2018

KASSA AYALEW
08/03/2018

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

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

Memorandum

Date: August 1, 2018

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

Matthew White, Regulatory Project Manager, (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 BRYHALI™ (halobetasol propionate)
Lotion, 0.01%

NDA: 209355

In response to DDDP's consult request dated January 10, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for BRYHALI™ (halobetasol propionate) lotion, 0.01% (Bryhali).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDDP on July 26, 2018, 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 July 27, 2018, and our comments are provided below on the attached label.

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
08/01/2018

LABEL AND LABELING 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: June 21, 2018
Requesting Office or Division: Division of Dermatology and Dental Products (DDDP)
Application Type and Number: NDA 209355
Product Name and Strength: Bryhali (halobetasol propionate) lotion, 0.01%
Product Type: Single Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Dow Pharmaceutical Sciences, Inc.
FDA Received Date: December 5, 2017
OSE RCM #: 2017-2471
DMEPA Safety Evaluator: Madhuri R. Patel, PharmD
DMEPA Team Leader: Sarah K. Vee, PharmD

1 REASON FOR REVIEW

The Division of Dermatology and Dental Products (DDDP) requested that we review the proposed container labels, carton labeling, and Prescribing Information (PI) for Bryhali (halobetasol propionate) lotion, NDA 209355, submitted by Dow Pharmaceutical Sciences, Inc. on December 5, 2017 to determine if it is acceptable from a medication error perspective.

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

We reviewed proposed container labels, carton labeling, and PI to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We note the name (b) (4) ***” on the labels and labeling was found unacceptable on February 26, 2018^a, and should be replaced with the name “Bryhali”, which was found conditionally acceptable on June 14, 2018^b. We also note the container labels and carton labeling can be improved to enhance the readability and prominence of important information (e.g. established name) and facilitate identification of the product.

4 CONCLUSION & RECOMMENDATIONS

All labels and labeling should be revised to contain the conditionally acceptable proprietary name, Bryhali. We also note that the container label and carton labeling can be improved to enhance important information and facilitate identification of the product.

^a Mena-Grillasca, C. Proprietary Name Review for (b) (4) *** (NDA 209355). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 26. Panorama No. 2017-19447995

^b Patel, M. Proprietary Name Review for Bryhali (NDA 209355). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 14. Panorama No. 2018-22355829

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Replace the name, (b) (4)***”, with the conditionally acceptable proprietary name, “Bryhali”.

4.2 RECOMMENDATIONS FOR DOW PHARMACEUTICAL SCIENCES, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments for all labels and labeling

1. Replace the proprietary name with the conditionally acceptable proprietary name, “Bryhali”, and submit the updated labels and labeling for review.
2. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). Additionally, the established name is not at least half the size of the proprietary name. Thus, we request you revise the established name to be in accordance with 21 CFR 201.10(g)(2).
3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use (see below for examples):
 - a. DDMMYYYY (e.g., 31JAN2013)
 - b. MMMYYYY (e.g., JAN2013)
 - c. YYYY-MMM-DD (e.g., 2013-JAN-31)
 - d. YYYY-MM-DD (e.g., 2013-01-31)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for halobetasol propionate lotion received on December 5, 2017 from Dow Pharmaceutical Sciences, Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Bryhali and the Listed Drug		
Product Name	Bryhali	Ultravate
Initial Approval Date	n/a	December 27, 1990
Active Ingredient	halobetasol propionate	halobetasol propionate
Indication	topical treatment of plaque psoriasis	relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses
Route of Administration	topical	topical
Dosage Form	lotion	cream
Strength	0.01%	0.05%
Dose and Frequency	apply a thin layer to cover only affected areas once daily and rub in gently	apply a thin layer to the affected skin once or twice daily, as directed by your physician, and rub in gently and completely
How Supplied	white to off-white lotion supplied in a white aluminum tube as follows: <ul style="list-style-type: none"> • 45 g (NDC 0187-0002-45) • 60 g (NDC 0187-0002-60) • 100 g (NDC 0187-0002-01) 	smooth white cream having a characteristic odor and supplied in the following tube size: <ul style="list-style-type: none"> • 50 g (NDC 10631-103-50) • 2 x 50 g (NDC 10631-103-04)
Storage	20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F)	15° C and 30° C (59° F and 86° F)
Container Closure	n/a	n/a

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 21, 2018, we searched DMEPA's previous reviews using the terms, "halobetasol". Our search did not identify any relevant previous 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 – 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,^c along with postmarket medication error data, we reviewed the following Bryhali labels and labeling submitted by Dow Pharmaceutical Sciences, Inc.

- Container Label received on December 5, 2017
- Carton Labeling received on December 5, 2017
- Professional Sample Container Label received on December 5, 2017
- Professional Sample Carton Labeling received on December 5, 2017
- Prescribing Information (Image not shown) received on December 5, 2017

G.2 Label and Labeling Images

Container Label



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

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/s/

MADHURI R PATEL
06/21/2018

SARAH K VEE
06/21/2018



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: Matthew White, RPM
DDDP

Subject: QT-IRT Consult to NDA 209355

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 01/23/2018 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 126779 dated 07/26/2017 in DARRTS (<http://mercado.fda.gov/search/resources/panorama/documentum/DARRTS/090140af8044f8ec?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-122 lotion (0.01% w/w halobetasol propionate). Our conclusion is based on the following rationale:

- Previously, the Agency had indicated to the sponsor that, “comparable systemic exposure to HP observed after treatment with Ultravate cream and IDP-122 lotion under maximal usage conditions may support a request for a waiver of a thorough QT study.” In the sponsor's maximal use PK study in patients, the steady state C_{max} for halobetasol

propionate was lower for IDP-122 lotion compared to the listed drug Ultravate cream (31.2 vs. 58.2 pg/mL).

2. BACKGROUND

Product Information

IDP-122 Lotion (0.01% w/w halobetasol propionate) is indicated for treatment of plaque psoriasis in patients 18 years of age and older. Halobetasol propionate is a corticosteroid. It is approved as a monotherapy for psoriasis and is marketed as Ultravate Cream and Ointment (0.05% w/w) for >25 years in USA.

The IDP-122 Lotion clinical program included bridging clinical studies in order to rely on the Agency's previous findings of safety for the listed drug (LD) Ultravate Cream.

Sponsor's previous interaction with the Agency

At the EOP2 meeting dated 03Jun2015 and pre-NDA meeting dated 02Aug2017, the Sponsor had outlined the justification for a waiver request for conducting a Thorough QT/QTc (TQT) study with IDP-122 Lotion. The Agency had indicated that comparable systemic exposure to halobetasol propionate observed after treatment with Ultravate cream and IDP-122 lotion under maximal usage conditions may support a request for a waiver of a TQT study.

Sponsor's position related to the question

The Sponsor is requesting a waiver for conducting a Thorough QT/QTc (TQT) study with IDP-122 Lotion. Following topical dermal administration of IDP-122 Lotion in psoriasis patients, drug-related systemic exposure was low and comparable to that of the listed drug (LD) Ultravate Cream® (0.05% w/w halobetasol propionate). Based on the wealth of safety data from the extensive marketing experience with the active ingredient, and low human systemic exposure with adequate safety factors to nonclinical data resulting from IDP-122 Lotion administration, there is a lack of concern for QT interval prolongation with halobetasol propionate and IDP-122 Lotion drug product in psoriasis patients.

Halobetasol propionate has been marketed for more than 25 years since first approved in 1990, 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 4.1](#)), the FDA AERS (Adverse Event Reporting System) ([Section 4.2](#)), the QT Drugs Database ([Section 4.3](#)) and PubMed ([Section 4.4](#)). All search results were negative regarding adverse effects on the cardiovascular system with topical use of halobetasol propionate.

Summary results from maximal use PK study

The following table shows the comparison of C_{\max} of halobetasol propionate for IDP-122 Lotion and Ultravate Cream in the maximal use PK study.

Table 8. Halobetasol Propionate Pharmacokinetic Parameter Comparison in Psoriasis Patients Maximum Use Study

PK parameter (Day 14)	IDP-122 Lotion (N=22)	Ultravate Cream (N=23)
C_{max} (pg/mL)		
N	20	23
Mean	31.2	58.2
CV% mean	199	125
AUC _{0-t} (pg•h/mL)		
N	2	8
Mean	2160	1910
CV% mean	113	58.8
AUC ₀₋₂₄ (pg•h/mL)		
N	1	0
Mean	3890	-
CV% mean	NA	-

Source: Study V01-118A-501; CTD Section 2.7.2.3.1.2, Table 4

Reviewer’s comments:

- *The molecular weight of halobetasol propionate is ~485 g/mol. Thus, the C_{max} value of 31.2 pg/mL for halobetasol propionate for IDP-122 lotion corresponds to 0.06 nM (sub-nanomolar) concentration.*
- *Overall, there is low (sub-nanomolar) systemic exposure of halobetasol propionate with IDP-122 lotion, the preclinical data suggested a safety margin of at least 4-orders of magnitude over observed C_{max} in patients for hERG inhibition (IC₅₀ >10 μM), and no ECG abnormalities were observed in a 3-month dermal toxicity study in minipigs following administration of IDP-122 lotion (mean C_{max} in psoriasis patients ~3-fold lower compared to the mean C_{max} in minipigs on Day 90). Postmarketing experience did not identify significant cardiovascular adverse effects with topical use of halobetasol propionate.*

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 cderderpqt@fda.hhs.gov

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/s/

DHANANJAY D MARATHE
02/15/2018

CHRISTINE E GARNETT
02/15/2018