

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208183Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA/BLA #	208183
Product Name:	<u>Ultravate (halobetasol propionate) lotion, 0.05%</u>
PMR/PMC Description:	<u>Conduct a safety, pharmacokinetics, and hypothalamic-pituitary-adrenal (HPA) axis suppression study of Ultravate (halobetasol propionate) lotion, 0.05% under maximal use conditions in adolescents 12 years to 16 years 11 months of age with plaque psoriasis receiving two weeks of treatment</u>
PMR/PMC Schedule Milestones:	Final Protocol Submission: <u>10/07/2014</u>
	Study/Trial Completion: <u>09/30/2017</u>
	Final Report Submission: <u>12/30/2017</u>
	Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☒ Other

Trials in adults are completed and ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This trial will evaluate the systemic bioavailability and risk of hypothalamic-pituitary-adrenal (HPA) axis suppression in pediatric subjects 12 years to 16 years 11 months of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Applicant has submitted protocol 000-0551-209 titled “An Open Label Evaluation of the Adrenal Suppression Potential and Pharmacokinetic Properties of Twice Daily Halobetasol Propionate Lotion, 0.05% in Subjects 12 to Less Than 18 Years of Age With Plaque Psoriasis Receiving Two Weeks of Treatment.”

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☒ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- x☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- x☒ Are the objectives clear from the description of the PMR/PMC?
- x☒ Has the applicant adequately justified the choice of schedule milestone dates?
- x☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

CRISTINA Petruccelli Attinello
11/04/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
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

Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 9-15-2015

From: Leyla Sahin, M.D.
Medical Officer,
Division of Pediatric and Maternal Health, Maternal Health Team

Through: Tamara Johnson, M.D., M.S.
Acting Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne L. Yao, M.D.
Director,
Division of Pediatric and Maternal Health

To: Division of Dermatology and Dental Products

Drug: Ultravate (halobetasol propionate) lotion, 0.05%; NDA 208183

Approved Indication for

Ultravate cream and ointment: Inflammatory and pruritic manifestations of dermatoses

Proposed Indication: Plaque psoriasis

Subject: Pregnancy and Lactation Labeling

Applicant: Ferndale Laboratories

Materials Reviewed:

- Applicant's proposed labeling
- Approved Ultravate cream and ointment labeling
- Literature review

Consult Question: Please assist with Pregnancy and Lactation Labeling

INTRODUCTION

The applicant submitted a new drug application (NDA) for Ultravate (halobetasol propionate) lotion, for a new formulation and indication on December 23, 2014. Halobetasol propionate is a super-potent topical corticosteroid that was first approved in 1990 under the tradename Ultravate in cream and ointment dosage forms, both of which are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Ultravate cream and ointment are marketed by a different manufacturer. Several generics are approved. The applicant has developed a lotion dosage form and, if approved, this would be the first such dosage form for halobetasol propionate. The proposed indication is for the topical treatment of plaque psoriasis. The Division of Dermatology and Dental Products (DDDP) consulted the Division of Pediatric and Maternal Health (DPMH) on April 22, 2015, to assist with reviewing the Pregnancy and Lactation subsections of labeling.

BACKGROUND

Disease Background

Psoriasis affects 2% to 3% of the population, men and women equally.¹ Psoriasis commonly starts during a woman's reproductive years. The disease activity during pregnancy is unpredictable and, therefore, it is possible that treatment may be needed.² Based on limited safety data, current clinical guidelines for management of psoriasis during pregnancy and lactation recommend the following:

- First line: moisturizers and topical steroids (preferably low-medium potency)
- Second line: ultraviolet B phototherapy
- Third line: tumor necrosis factor inhibitors (adalimumab, etanercept, infliximab), cyclosporine, and systemic steroids.¹

LITERATURE REVIEW

No publications on the safety of topical halobetasol in pregnancy or lactation were found in the literature. There are a few studies on the safety of topical corticosteroids in pregnancy. However, these studies did not include halobetasol or did not identify the specific topical corticosteroids that were included in the study. In addition, the study findings were conflicting regarding possible associations between topical corticosteroid use in pregnancy and oral clefts and topical corticosteroids and low birth weight.^{3,4,5} Therefore, it is not possible to draw any conclusions regarding the safety of topical halobetasol in pregnancy.

¹ Bae Y, Van Voorhees A, Hsu S, et al. Review of treatment options for psoriasis in pregnant or lactating women: From the Medical Board of the National Psoriasis Foundation. *J Am Acad Dermatol* vol 67, Number 3:459-477. 2012.

² Bangsgaard N, Rørbye C, Skov L et al. Treating Psoriasis During Pregnancy: Safety and Efficacy of Treatments. *Am J Clin Dermatol*. 2015 Jul 7. [Epub ahead of print]

³ Chi C, Phil D, Wang S, et al. Pregnancy Outcomes After Maternal Exposure to Topical Corticosteroids A UK Population-Based Cohort Study. *JAMA Dermatol* 2013;149(11):1274-1280.

⁴ Hviid A, Molgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. *CMAJ*, April 19, 2011, 183(7).

⁵ Skuladottir H, Wilcox A, McConnaughey R, et al. First trimester nonsystemic corticosteroid use and the risk of oral clefts in Norway. *Annals of Epidemiology* 24 (2014) 635-640.

DISCUSSION

Pregnancy and Lactation Labeling Rule (PLLR)

On December 4, 2014, the Food and Drug Administration (FDA) published the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,” also known as the Pregnancy and Lactation Labeling Rule (PLLR).⁶ The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential (if applicable). Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR took effect on June 30, 2015. The recommendations in this review are consistent with the PLLR format.

The Pregnancy subsection of approved Ultravate cream and ointment labeling includes reproductive toxicology data that describe teratogenic effects (cleft palate and omphalocele) and embryotoxic effects when administered systemically to rats at 13 and 33 times, and rabbits at 3 times the human topical dose. This information is included in the applicant’s proposed labeling for Ultravate lotion.

The Nursing Mothers subsection of approved Ultravate cream and ointment labeling includes a statement that systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. In addition, there is a statement that states that it is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. These statements are included in the applicant’s proposed labeling for Ultravate lotion. These statements reflect available published data⁷ and it is therefore reasonable to maintain in Ultravate lotion labeling.

There is a published case report of growth restriction and hypertension in an infant exposed to a high potency topical corticosteroid applied directly to the nipple for two months.⁸ Current expert consensus opinion recommends not applying high potency corticosteroids directly to the nipple and areola in breastfeeding women in order to avoid directly exposing the infant.^{9,10} This recommendation is reasonable and should therefore be added to the Lactation section of Ultravate lotion labeling, under Clinical Considerations.

CONCLUSION

The Pregnancy and Lactation subsections of labeling were structured to be consistent with the PLLR.

⁶ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

⁷ Murase J, Heller M, Butler D, et al. Safety of dermatologic medications in pregnancy and lactation. J AM Acad Dermatol 2014;70:401.e1-14.

⁸ De Stefano P, Bongo IG, Borgna-Pignatti C. Factitious hypertension with mineralocorticoid excess in infant. Helv Paediatr Acta 1983;38:185-9.

⁹ LactMed database <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>

¹⁰ Hale, T. Medications and Mothers’ Milk. Sixteenth Edition, 2014.

DPMH LABELING RECOMMENDATIONS

DPMH participated in a labeling meeting with DDDP on July 31, 2015. DPMH concurred with the nonclinical toxicology risk statements, including the dose multiples of the human dose, that were recommended by DDDP Toxicologist Jill Merrill, PhD, and Toxicology Team Leader Barbara Hill, PhD.

See final labeling for all of the labeling revisions negotiated with the applicant.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data on topical halobetasol propionate use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. In animal reproduction studies, halobetasol propionate administered systemically during organogenesis to pregnant rats at 13 and 33 times the human topical dose and to pregnant rabbits at 3 times the human topical dose resulted in teratogenic and embryotoxic effects [see Data]. The clinical relevance of the animal findings is not clear.

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Halobetasol propionate (b) (4) teratogenic in rats and rabbits when given systemically during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. These doses are approximately 13, 33, and 3 times, respectively, the human topical dose of halobetasol propionate, 0.05%. Halobetasol propionate was embryotoxic in rabbits but not in rats.

Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats, but not in rabbits.

8.2 Lactation

Risk Summary

There are no data on the presence of halobetasol propionate or its metabolites in human milk, the effects on the breast-fed infant, or the effects on milk production after topical application to women who are breastfeeding.

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ULTRAVATE lotion and any potential adverse effects on the breastfed infant from ULTRAVATE lotion or from the underlying maternal condition.

Clinical Considerations

Advise breastfeeding women not to apply ULTRAVATE lotion directly to the nipple and areola to avoid direct infant exposure.

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/s/

LEYLA SAHIN

09/15/2015

TAMARA N JOHNSON

09/15/2015

LYNNE P YAO

09/16/2015

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

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

Memorandum

Date: September 8, 2015

To: Cristina Attinello
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Tara Turner, Pharm.D., MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Pharm.D., BCPS, RAC, Acting Team Leader, OPDP

Subject: **NDA 208183**
ULTRAVATE® (halobetasol propionate) lotion, 0.05%, for topical use

On March 4, 2015, DDDP consulted OPDP to review the draft Package Insert (PI) and carton and container labeling for ULTRAVATE® (halobetasol propionate) lotion, 0.05%, for topical use (Ultravate) for the original NDA submission.

OPDP reviewed the proposed substantially complete version of the PI provided by DDDP via e-mail on August 20, 2015. OPDP also reviewed the proposed carton and container labeling submitted to the electronic document room by the sponsor on May 8, 2015. OPDP's comments on the PI and carton and container labeling are provided below.

Thank you for your consult. If you have any questions about OPDP's comments, please contact Tara Turner at 6-2166 or at Tara.Turner@fda.hhs.gov.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

TARA P TURNER
09/08/2015

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: August 26, 2015

TO: Cristina Attinello, M.P.H., Regulatory Project Manager
Brenda Carr, M.D., Medical Officer
Jill Lindstrom, M.D., Medical Team Leader
Division of Dermatology and Dental Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.,
Team Leader and for:

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 208183

APPLICANT: Ferndale Laboratories, Inc.

DRUG: Halobetasol propionate lotion, 0.05%

NME: No

**THERAPEUTIC
CLASSIFICATION:** Standard Review

INDICATION: Treatment of plaque psoriasis

CONSULTATION REQUEST DATE:	March 10, 2015
CLINICAL INSPECTION SUMMARY DATE:	August 28, 2015
DIVISION ACTION GOAL DATE:	October 16, 2015
PDUFA DATE:	November 8, 2015

I. BACKGROUND:

The Applicant submitted this NDA to support the use of halobetasol propionate lotion, 0.05% for the treatment of plaque psoriasis.

The identical pivotal studies "000-0551-304 and 000-0551-305 entitled, "A Multicenter, Randomized, Double-Blind, Parallel Group Comparison of Halobetasol Propionate Lotion 0.05% versus Vehicle Lotion in Subjects with Plaque Psoriasis were inspected in support of this application.

The sites of Drs. Dhawan and Tschen were chosen because of their high enrollment numbers and high treatment response rates: 90.9% for Dr. Dhawan's site (Site 07) and 80.0% for Dr. Tschen's site (Site 11).

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Sunil S. Dhawan, M.D. Center For Dermatology Clinical Research, Inc. 2557 Mowry Avenue, Suite 25 & 34 Fremont, CA 94538	000-0551-304/ 07/ 23	7-14 Apr 2015	NAI
Eduardo Tschen, M.D. Academic Dermatology Associates 1203 Coal SE Albuquerque, NM 87106	000-0551-305/ 11/ 21	23 Jun-1 Jul 2015	Pending: Preliminary NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Sunil S. Dhawan, M.D.

Center for Dermatology Clinical Research, Inc.
2557 Mowry Avenue, Suite 25 & 34
Fremont, CA 94538

- a. What was inspected:** At this site for Protocol 000-0551-304, 24 subjects were screened, 23 subjects were enrolled in the study, and 19 subjects completed the study. Signed informed consent was obtained from all screened subjects prior to study entry. The source records for all screened subjects were reviewed. Data from source records were transcribed to electronic Case Report Forms (eCRFs). Data listings were compared with source records. Records reviewed included, but were not limited to, investigator agreements, financial disclosures, training documentation, monitor and IRB correspondence, randomization procedures, primary and secondary efficacy results, protocol deviations, adverse events, and test article accountability and storage.

- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Eduardo Tschen, M.D.
Academic Dermatology Associates
1203 Coal SE
Albuquerque, NM 87106

- a. What was inspected:** At this site for Protocol 000-0551-305, 21 subjects were screened, 21 subjects were enrolled, and 21 subjects completed the study. The study records for all 21 subjects were reviewed. Records reviewed included, but were not limited to, informed consent, FDA Form 1572s, financial disclosure, inclusion/exclusion criteria, randomization, protocol-required procedures, concomitant medications, and test article accountability. Source documents were compared with Case Report Forms (CRFs) and line listings, with respect to primary and secondary efficacy endpoints, safety endpoints, adverse events, protocol deviations, and subject randomization and discontinuation.
- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Note: The observations noted above for Dr. Tschen's site are based on a review of preliminary communications. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Dhawan and Tschen were inspected in support of this NDA; neither was issued a Form FDA 483. The final classification of the inspection of Dr. Dhawan's site was No Action Indicated (NAI). The preliminary classification of the inspection of Dr. Tschen's site is NAI pending receipt and review of the Establishment Inspection Report (EIR). The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H. for:
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigation

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/s/

ROY A BLAY
08/27/2015

JANICE K POHLMAN
08/28/2015
Signing for myself and for Kassa Ayalew, Branch Chief

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:	August 26, 2015
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 208183
Product Name and Strength:	Ultravate (halobetasol propionate) Lotion, 0.05%
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Ferndale Laboratories, Inc.
Submission Date:	December 23, 2014
OSE RCM #:	2015-527
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Team Leader:	Kendra Worthy, PharmD

1 REASON FOR REVIEW

As part of the evaluation for NDA 208183, DDDP requested DMEPA evaluate the proposed container labels, carton labeling, and Full Prescribing Information for Ultravate (halobetasol propionate) lotion for areas of vulnerability that could lead to medication errors.

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
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – n/a
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for 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 Ultravate lotion in 60 mL bottles. Considering that the cream and ointment formulations are currently marketed in 50 g tubes and 2x50 g tubes, a 60 mL bottle for the lotion formulation seems adequate. Even though Ultravate has a limitation of use of not more than 50 g per week, a 60 mL bottle for a 1 month supply should not exceed the maximum weekly amount. (b) (4)

(b) (4)

In addition, we note the following areas for improvement on the container labels and carton labeling:

- The 2 g container label is crowded and difficult to read. Since this is considered a small label, we recommend (b) (4) which is already included on the carton labeling, to allow a larger font size on the route of administration, usual dosage, and storage statements.

- The route of administration statements are not prominently displayed on the principal display panel. This is important information for topical lotion products to minimize the potential for wrong route of administration, especially into the eyes.
- The limitation of use statement “50 g/wk” is abbreviated and might be misunderstood by patients. This information should be spelled out (i.e. “50 grams per week”).

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed 60 mL packaging configuration for Ultravate lotion is adequate. However, the label and labeling can be improved to increase the prominence of important information. DMEPA recommends the following be implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION OF DERMATOLOGY AND DENTAL PRODUCTS

We note a discrepancy in the unit of measure used to present the net quantity statements (i.e. (b) (4)) versus the unit of measure used to present the limitation of use statement (i.e. not more than 50 g per week). We recommend that these units of measure be consistent throughout the FPI, and container and carton labeling to facilitate patient compliance; preferably in mL or grams.

4.2 RECOMMENDATIONS FOR FERNDAL LABORATORIES INC.

A. General Comments (all container labels and carton labeling)

1. Revise the limitation of use statement from (b) (4) to read “Do not use more than 50 grams per week”.

B. Container Labels (2 g physician sample)

1. Delete the (b) (4) as this is a small label and this information is already presented on the carton labeling. As currently presented, the label is crowded and difficult to read.
2. Increase the size of the route of administration statements (i.e. For Topical Use Only, Not for Eye Use) and relocate to the white area.
3. Increase the size of the usual dosage and storage statements.
4. Delete the statement “Rev.: (b) (4)” as it is not relevant information and may be confused with the expiration date.

C. Container Labels (60 mL bottles)

1. Increase the size of the route of administration statements and relocate to the principal display panel.
2. Decrease the size of the “Rx Only” statement and relocate to the bottom portion of the principal display panel.
3. Delete the statement (b) (4) from the back panel.

4. Delete the statements “#XXXX Rev.: (b) (4)” from the principal display panel as this is not relevant information and may be confused with the lot number and expiration date. In addition, this information is also present on the back panel.
- D. Carton Labeling (2 g physician samples)
1. Revise the net quantity statement to read “Net wt. 10 x 2 g (b) (4)”.
- E. Carton Labeling (60 mL bottles)
1. Add the route of administration statements (“For Topical Use Only. Not for Eye Use”) prominently to the principal display panel.
 2. Delete the statement (b) (4) from the white box on the back panel as it is duplicative (i.e. this information is already presented on the top portion of the panel).
 3. Increase the size of the Usual Dosage statement presented on the white box on the back panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ultravate that Ferndale Laboratories submitted on June 29, 2015.

Table 2. Relevant Product Information for Ultravate Lotion, 0.05%	
Initial Approval Date	Ultravate Ointment, 0.05% was approved on Dec. 17, 1990 Ultravate Cream, 0.05% was approved on Dec. 27, 1990
Active Ingredient	Halobetasol propionate
Indication	<i>Proposed for Lotion:</i> Topical treatment of plaque psoriasis in patients eighteen (18) years of age and older. <i>Approved for Cream and Ointment:</i> Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.
Route of Administration	Topical
Dosage Form	<i>Proposed:</i> Lotion <i>Approved:</i> Cream and Ointment
Strength	0.05%
Dose and Frequency	<i>Proposed for Lotion:</i> Apply a thin layer to the affected areas twice daily. <i>Approved for Cream and Ointment:</i> Apply a thin layer to the affected areas once or twice daily.
How Supplied	<i>Proposed for Lotion:</i> 2 g physician sample (b) (4) and 60 mL bottles <i>Approved for Cream and Ointment:</i> 50 g tubes and 2 X 50 g tubes
Storage	<i>Proposed for Lotion:</i> 25°C (77°F); excursions permitted to 59°F and 86°F (15°C to 30°C) <i>Approved for Cream and Ointment:</i> Store between 15° C and 30° C (59° F and 86° F).
Container Closure	<i>Proposed for Lotion:</i> 2 g professional sample – (b) (4) with polypropylene (PP) cap 60 mL trade – white oval tapered HDPE bottles with (b) (4) top caps.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 20, 2015, we searched the L:drive and AIMS using the term Ultravate to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify previous reviews.

APPENDIX C. HUMAN FACTORS STUDY

N/A

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On August 20, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Ultravate

D.2 Results

No articles were identified.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on August 20, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.¹

Table 3: FAERS Search Strategy	
Date Range	Search date: August 20, 2015
Product	Ultravate [product name]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

E.2 Results

Our search retrieved 3 cases, but after further evaluation, we didn't identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

¹ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

E.3 List of FAERS Case Numbers

N/A

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX F.

N/A

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CARLOS M MENA-GRILLASCA
08/26/2015

KENDRA C WORTHY
08/26/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208183 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Animal Rule Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Pediatric
Proprietary Name: Established/Proper Name: halobetasol propionate Dosage Form: lotion Strengths: 0.05%		
Applicant: Ferndale Laboratories, Inc. Agent for Applicant (if applicable):		
Date of Application: 12/23/14 Date of Receipt: 12/23/14 Date clock started after UN: 1/8/15		
PDUFA Goal Date: 11/8/15		Action Goal Date (if different):
Filing Date: 3/9/2015		Date of Filing Meeting: 2/20/2015
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication: Treatment of plaque psoriasis		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	☐ 351(a) ☐ 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification: <i>The application will be a priority review if:</i> <ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):				
List referenced IND Number(s): (b) (4)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		Email sent 3-9-15 to correct goal due date.
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking</i>	☒	☐		

system.		☒	☐	☐	
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>					
Application Integrity Policy		YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		☒	☐		
If yes, explain in comment column.					They were in arrears but have since paid their fees, effective 1-8-15
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:		☐	☐		
User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?		☒	☐		
User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i> ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
User Fee Bundling Policy <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					

Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes, answer the bulleted questions below:	☐	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?	☐	☐		
<p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>				
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm	☐	☐		
If yes, please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm	☐	☒		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	☐	☐	☒	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☒	☐	☐	
If yes, # years requested: 3				

<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	See 3-9-15 email to OPQ
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?	☐	☐	☒	
<i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>				
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	☐	☐	☒	
<i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>				
<i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	☒	☐		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☐	☒	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☒	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☒	☐		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☒	☐		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	☐	☐	☒	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients</i></p>	☒	☐		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

(including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	☒	☐	☐	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	☒	☐	☐	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	☐	☒		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	☐	☒	☐	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	☐	☒	☐	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		
<i>If no, request applicant to submit SPL before the filing date.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Is the PI submitted in PLR format? ⁴	☒	☐		Will need editing; SRPI completed
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	☐	☐	☒	No PPI, MG, or IFU submitted
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☐	☐		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☐	☒	☐	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

End-of Phase 2 meeting(s)? Date(s): July 25, 2012 <i>If yes, distribute minutes before filing meeting</i>	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): October 27, 2014 <i>If yes, distribute minutes before filing meeting</i>	☒	☐		
Any Special Protocol Assessments (SPAs)? Date(s): December 5, 2012 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	☒	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2-20-15

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Cristina Attinello	Y
	CPMS/TL:	Barbara Gould	Y
Cross-Discipline Team Leader (CDTL)	Jill Lindstrom		Y
Division Director/Deputy	Kendall A. Marcus		N
Office Director/Deputy	David Kettl		Y
Clinical	Reviewer:	Brenda Carr	Y
	TL:	Jill Lindstrom	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Doanh Tran	Y
	TL:		
Biostatistics	Reviewer:	Kathleen Fritsch	Y
	TL:	Mohamed Alosch	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jill Merrill	Y
	TL:	Barbara Hill	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Hitesh Shroff	N
	TL:	Yichun Sun	Y
Biopharmaceutics	Reviewer	Vidula Kolhatkar	Y
	TL:	Kelly Kitchens	Y
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees	Jessie Weintraub Carlos Mena-Grillasca Janet Anderson Kerri-Ann Jennings Sam Bain Nalla Chidambaram		

FILING MEETING DISCUSSION:

GENERAL <ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	☒ YES ☐ NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	☐ Not Applicable ☒ No comments
CLINICAL <p>Comments: comment/IR to be sent</p>	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	☒ YES ☐ NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	☒ Not Applicable ☐ YES ☐ NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	☐ YES ☒ NO
<p>BIOSTATISTICS</p>	☐ Not Applicable

Comments: comments/IRs to be sent	☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: comment to be sent	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (protein/peptide products only) Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
New Molecular Entity (NDAs only) <ul style="list-style-type: none"> Is the product an NME? 	☐ YES ☒ NO
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> Comments:	☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
<u>Quality Microbiology</u> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? Comments:	☒ Not Applicable ☐ YES ☐ NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p>☐ Not Applicable</p> <p>☒ YES ☐ NO</p> <p>☒ YES ☐ NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p>☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE</p> <p>☐ Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p>☐ Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p>☒ N/A</p> <p>☐ YES ☐ NO</p> <p>☐ YES ☐ NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p>☐ YES ☐ NO</p>

<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	☐ YES ☐ NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	☐ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Kendall Marcus Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 6-8-15 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☐	If priority review:

	<ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRA's completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CRISTINA Petruccelli Attinello
03/09/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208183

Application Type: New NDA (new dosage form)

Name of Drug/Dosage Form: halobetasol propionate lotion, 0.05%

Applicant: Ferndale Laboratories, Inc.

Receipt Date: 1/8/2015

Goal Date: 11/8/2015

1. Regulatory History and Applicant's Main Proposals

This is a new NDA, related to IND (b) (4)

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by April 13, 2015. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present

Selected Requirements of Prescribing Information

• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **“HIGHLIGHTS OF PRESCRIBING INFORMATION”**.

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: **“These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).”** The name of drug product should appear in UPPER CASE letters.

Comment: Sponsor has "Trade Name" the drug name is below.

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement **“Initial U.S. Approval:”** followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word **“WARNING”** (even if more than one warning, the term, **“WARNING”** and not **“WARNINGS”** should be used) and other words to identify the subject of the warning (e.g., **“WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”**). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement **“See full prescribing information for complete boxed warning.”** This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A

Selected Requirements of Prescribing Information

15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “***See full prescribing information for complete boxed warning.***”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: “Trade Name” is place of product’s name

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

Selected Requirements of Prescribing Information

- NO** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- NO** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or

Selected Requirements of Prescribing Information

subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- NO** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment: Sponsor added clinical practice at the end of the sentence

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CRISTINA Petruccelli Attinello
03/09/2015