CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209483Orig1s000

OTHER REVIEW(S)

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	**NDA 209483**
PMR/PMC Set (####-#)	3310-1
Product Name:	Impoyz (clobetasol propionate) cream, 0.025%
Applicant Name:	Promius Pharma, LLC
ODE/Division:	**ODE III/ Division of Dermatology and Dental Products**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Protocol DFD-06-CD-011:

A Phase 2, open label, multicenter, two-stage, sequential study to assess the potential for adrenal suppression and systemic drug absorption of DFD-06 (clobetasol propionate cream, 0.025%) applied twice daily for 15 days, in pediatric subjects (6 to less than 17 years of age) with moderate to severe plaque psoriasis (IGA = 3 or 4, BSA of 10 % or greater).

2. PMR/PMC Schedule Milestones[2, 3]

Draft Protocol Submission: 09/2016

Final Protocol Submission: 04/2017

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion,* and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

Study/Trial Completion: 04/2020
Final Report Submission: 05/2020

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

For pediatric patients, ages 6 to less than 17 years, information is needed on safety pharmacokinetic / HPA axis suppression of clobetasol propionate cream, 0.025% for the treatment of moderate to severe plaque psoriasis. Deferred pediatric studies in pediatric patients ages 6 to less than 17 years will be conducted as required by PREA.

Under PREA, the following study is recommended as a post-marketing requirement (PMR):

- A safety pharmacokinetic / hypothalamic-pituitary-adrenal (HPA) axis suppression study under maximal use conditions in children and adolescents in the age group of 6 years to 16 year and 11 months old.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☒ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval

☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination

☐ Other reason (describe in text box below)

NA

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

☐ Assess a known serious risk related to the use of the drug

☐ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.

☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.

☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.

☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

NA

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

NA

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either "Yes" or "No" and provide the appropriate responses.]

☐ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

NA

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

NA

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?**
[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☒ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☒ Other (describe) **HPA axis suppression trial**

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

- ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ **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**.

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/s/

ANGELA M BROWN
11/28/2017

STROTHER D DIXON
11/28/2017

TATIANA OUSSOVA
11/29/2017

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:	November 15, 2017
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 209483
Product Name and Strength:	Impoyz (clobetasol propionate) Cream, 0.025%
Applicant/Sponsor Name:	Promius Pharma LLC
Submission Date:	November 13, 2017
OSE RCM #:	2017-306-2
DMEPA Safety Evaluator:	Carlos M Mena-Grillasca, BS Pham
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMO

The Division of Dermatology and Dental Products (DDDP) requested that we review the revised container labels and carton labeling for clobetasol propionate cream 0.025% (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[ab]

2 CONCLUSION

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

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

[a] Mena-Grillasca C. Label and Labeling Review for Impoyz (NDA 209483). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Sep 29. RCM No.: 2017-306

[b] Mena-Grillasca C. Label and Labeling Review Memo for Impoyz (NDA 209483). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Oct 10. RCM No.: 2017-306-1

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/s/

CARLOS M MENA-GRILLASCA
11/15/2017

SARAH K VEE
11/15/2017

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:	October 18, 2017
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 209483
Product Name and Strength:	Impoyz (clobetasol propionate) Cream, 0.025%
Applicant/Sponsor Name:	Promius Pharma LLC
Submission Date:	October 16, 2017
OSE RCM #:	2017-306-2
DMEPA Safety Evaluator:	Carlos M Mena-Grillasca, BSPharm
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMO

The Division of Dermatology and Dental Products (DDDP) requested that we review the revised container labels and carton labeling for clobetasol propionate cream 0.025% (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],[b]

2 CONCLUSION

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

[a] Mena-Grillasca C. Label and Labeling Review for Impoyz (NDA 209483). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Sep 29. RCM No.: 2017-306

[b] Mena-Grillasca C. Label and Labeling Review for Impoyz (NDA 209483). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Oct 10. RCM No.: 2017-306-1

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/s/

SARAH K VEE
10/18/2017

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:	October 10, 2017
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 209483
Product Name and Strength:	Impoyz*** (clobetasol propionate) Cream, 0.025%
Applicant/Sponsor Name:	Promius Pharma LLC
Submission Date:	October 3, 2017
OSE RCM #:	2017-306-1
DMEPA Safety Evaluator:	Carlos M Mena-Grillasca, BS Pham
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMO

The Division of Dermatology and Dental Products (DDDP) requested that we review the revised container labels and carton labeling for clobetasol propionate cream 0.025% (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 container labels and carton labeling are unacceptable from a medication error perspective. The established name is not at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). In addition, the 2.5 g container label is a small label and the information is crowded and difficult to read.

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

*** Proposed proprietary name currently under review. Panorama # 2017-16776981

[a] Mena-Grillasca C. Label and Labeling Review for Impoyz (NDA 209483). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Sep 29. RCM No.: 2017-306

3 RECOMMENDATIONS FOR PROMIUS PHARMA

A. General (all container labels and carton labeling)

1. We note that your proposed proprietary name Impoyz is currently under review, has not been granted by the Agency, and is presented as a placeholder on your container labels and carton labeling.

2. Increase the prominence of the established name OR decrease the prominence of the proprietary name in order to comply with 21 CFR 201.10(g)(2) which states that the **established name be at least ½ the size of the proprietary name** taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

B. 2.5 g container label

1. Revise the net weight statement from (b) (4) to read '2.5 g'.

2. Delete the NDC number as it is not required on sample labels.

3. Revise the usual dosage statement to read '**Usual Dosage**: Apply to the affected areas twice daily. See prescribing information.'

4. Revise the storage statement from (b) (4) to read 'Store between 20˚C to 25˚C (68˚F to 77˚F)'.

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/s/

CARLOS M MENA-GRILLASCA
10/10/2017

SARAH K VEE
10/10/2017

Clinical Inspection Summary

Date	October 2, 2017
From	Bei Yu, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Angela Brown, Project Manager Hamid Tabatabai, Clinical Reviewer Snezana Trajkovic, Clinical Team Leader Division of Dermatology and Dental Products (DDDP)
NDA#	NDA 209483
Applicant	Promius Pharma, LLC
Drug	Clobetasol Propionate
NME	No
Review Priority	Standard Review
Proposed Indication	Topical Treatment of Moderate to Severe Plaque Psoriasis
Consultation Request Date	April 3, 2017
Summary Goal Date	September 13, 2017
Action Goal Date	November 13, 2017
PDUFA Date	November 30, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Blumenau, Bukhalo, and Jarell (Campbell) were inspected in support of this NDA. The final classification of the inspections of Drs. Bukhalo and Jarell (Campbell) is No Action Indicated (NAI). The preliminary classification of the inspection of Dr. Blumenau is NAI, pending receipt of the inspection report and final classification.

Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

2. BACKGROUND

The Applicant submitted this NDA to support the use of clobetasol propionate (DFD-06) cream 0.025% in the treatment of moderate to severe plaque psoriasis in patients 18 years of age and older.

Inspections were requested for two identical pivotal study protocols in support of this application:

Studies DFD-06-CD-004 and **DFD-06-CD-005**, both entitled "A Randomized, Double-Blind, Vehicle-Controlled, Multicenter, Parallel Group Study of the Efficacy and Safety of DFD-06 Cream in the Treatment of Moderate to Severe Plaque Psoriasis for 14 Days"

These two identical Phase 3 studies were multicenter, randomized, vehicle-controlled, double-blind, and parallel group studies. Subjects meeting eligibility criteria were randomly assigned to 1 of 2 treatment arms in a 2:1 ratio to receive treatment with either clobetasol propionate 0.025% cream or vehicle cream twice daily for 14 days to all affected areas on the body. The primary efficacy endpoint was proportion of subjects with treatment success [defined as Investigator's Global Assessment, IGA = 0 or 1 (clear or almost clear) and at least a 2-grade reduction from Baseline] at the Day 15 visit.

Study 004 was conducted at 27 US sites between December 2015 and May 2016. A total of 267 subjects were enrolled.

Study 005 was conducted at 27 US sites between November 2015 and May 2016. A total of 265 subjects were enrolled.

Rationale for Site Selection

Study 004: Both Dr. Blumenau's site and Dr. Bukhalo's site were selected for inspection because of high enrollment and high site efficacy effect.

Study 005: Dr. Jarell (Campbell)'s site was selected for inspection mainly because of high enrollment, high site efficacy effect, and no prior inspections for the investigator.

3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol # / # of Subjects Enrolled	Inspection Dates	Classification
Site #101 Joe Blumenau Research Across America 9 Medical Parkway Professional Plaza 4 Suite 202 Dallas, TX 75234	DFD-06-CD-004 Subjects: 20	4-10 August 2017	NAI*
Site #103 Michael Bukhalo Altman Dermatology Associates 1100 W. Central Road Suite 200 Arlington Heights, IL 60005	DFD-06-CD-004 Subjects: 24	23-30 May 2017	NAI
Site #106 Abel Jarell (James L. Campbell Jr)[#] ActivMed Practices & Research Inc. 110 Corporate Dr Suite 2 Portsmouth, NH	DFD-06-CD-005 Subjects: 24	7-14 June 2017	NAI

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

*Pending = Preliminary classification based on preliminary communication with the field; EIR has not been received from the field, or complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

[#]Dr. Campbell passed away shortly after the last subject last visit and Dr. Jarell was trained to resume as a PI to close out the study.

1. Joe Blumenau, M.D.

At this site for Protocol DFD-06-CD-004, a total of 25 subjects were screened, and 20 subjects were enrolled in and completed the study.

Informed consent forms (ICFs) for all screened subjects were reviewed. For the enrolled subjects endpoint data and electronic Case Report Forms (eCRF) were verified against data line listings. There was no evidence of underreporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Michael Bukhalo, M.D.

At this site for Protocol DFD-06-CD-004, a total of 25 subjects were screened, and 24 subjects were enrolled in and completed the study.

Records reviewed for all enrolled subjects included, but was not limited to, case report forms (CRFs), electronic CRFs, source documents, informed consent forms, investigational product accountability records, IRB and sponsor correspondence, staff training, inclusion/exclusion criteria, adverse events, efficacy endpoints, and protocol deviations. These were compared to the protocol requirements and data listings provided with the inspection assignment. The primary efficacy endpoint was verifiable. There was no evidence of underreporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Abel Jarell, M.D. (James L. Campbell Jr, M.D)

All study activity other than the official close and data-lock was performed by Dr. Campbell prior to his death, which occurred ~13 days after the last subject was seen for their last study visit. Dr. Jarell was trained by the Contract Research Organization in order to have access to the EDC system for study closeout but had no active role with study subjects or management of study data.

At this site for Protocol DFD-06-CD-005, 24 subjects were screened and enrolled in the study, one subject withdrew consent, and 23 subjects completed the study.

ICFs for all screened subjects were reviewed. Records for enrolled subjects were reviewed to verify the following: 1) that the protocol was followed, 2) subject eligibility, 3) randomization, 4) protocol adherence for assessments performed and the timing of assessments, 5) administration of the investigational product or placebo, 6) concomitant medications, 7) the identification of key personnel involved in collecting and analyzing data at the site,

8) the condition of the subject at time of entry and throughout participation in the investigation, and 9) adverse event detection and reporting. In addition, source documentation was compared with the data listings provided.

One subject was enrolled despite meeting an exclusion criterion. Subject 106015 met exclusion criteria #10 of the protocol, which includes use of a topical corticosteroid within 14 days of the baseline visit. Based on review of the source documents, it appears that this subject was off topical steroids for only 6 or 7 days prior to randomization. Although this subject did not have an adequate wash-out period for the previous treatment of topical corticosteroids, he was treated with vehicle cream in the study, so the impact of the data from this subject on the results of this study, if any, would be to slightly decrease the efficacy signal for the study drug.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

{See appended electronic signature page}

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

CONCURRENCE:

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

CC:
Central Doc. Rm. /NDA 209483
DDDP /Medical Team Leader/ Snezana Trajkovic
DDDP /Project Manager/ Angela Brown
DDDP/MO/ Hamid Tabatabai
OSI/DCCE/ Division Director/ Ni Khin
OSI/DCCE/Branch Chief/ Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Bei Yu
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague

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/s/

BEI YU
10/02/2017

PHILLIP D KRONSTEIN
10/02/2017

LABEL, LABELING, AND PACKAGING REVIEW

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

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

Date of This Review:	September 29, 2017
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 209483
Product Name and Strength:	Impoyz[***] (clobetasol propionate) Cream, 0.025%
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Promius Pharma LLC
Submission Date:	April 24, 2017 and July 31, 2017
OSE RCM #:	2017-306
DMEPA Safety Evaluator:	Carlos M Mena-Grillasca, BSPharm
DMEPA Team Leader:	Sarah K. Vee, PharmD

[***] Proposed proprietary name currently under review. Panorama # 2017-16776981

1 REASON FOR REVIEW

This review responds to a request from the Division of Dermatology and Dental Products (DDDP) to evaluate the proposed container label, carton, and Prescribing Information labeling for Impoyz*** cream, 0.025% submitted by the applicant under NDA 209483.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing to market clobetasol propionate cream, 0.025% in 60 g and 112 g tubes. In addition, they will provide professional samples in 2.5 g tubes. We consider the proposed packaging sizes adequate as it keeps in line with currently available clobetasol propionate products (e.g. Olux foam 0.05% is available in 100 g pumps, Clobex spray 0.05% is available in 125 mL, Temovate E cream 0.05% is available in 60 g tubes).

We reviewed the container labels and carton labeling and noted that the 2.5 g container label is small and crowded with information, making it difficult to read. Per 21 CFR 201.10(i) small labels are only required to include the proprietary name, established name, strength, lot number, expiration date, and name of manufacturer, packer or distributor. Therefore, we provide recommendations to improve the legibility of the 2.5 g container label.

4 CONCLUSION & RECOMMENDATIONS

We find the proposed 2.5 g, 60 g, and 112 g packaging configurations acceptable. We recommend the following label and labeling revision be implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR PROMIUS PHARMA

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

We note that your NDA has not been granted a proprietary name. Once you receive correspondence from the Agency granting a proprietary name to your NDA, revise all container labels and carton labeling to replace (b) (4) with the new name. Make sure that the established name is at least ½ the size of the proprietary name taking into account all pertinent

factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

B. Container Label (2.5 g)

1. We note that this is a small label crowded with much information, making it very difficult to read. Therefore, in alignment with 21 CFR 201.10(i) we recommend the following revisions:

a. Revise the principal display panel to only include the Proprietary name, established name, dosage form, strength, route of administration, Rx only, and net weight statements.

i. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

ii. Only include the route of administration statement "FOR TOPICAL USE ONLY".

iii. Revise the net weight statement to read "2.5 g"

iv. Reduce the size of the company logo "Promius Pharma" so that it does not compete in prominence with the proprietary name, establish name, dosage form, and strength.

b. Revise the back panel to include the following statements in the order presented:

i. "**Usual dosage**: Apply to the affected skin areas twice daily. See prescribing information."

ii. "**To Open**: Remove the cap…"

iii. "**Warning**: Keep out of reach of children"

iv. "Manufactured by DPT Laboratories for Promius Pharma, LLC
Princeton, NJ 08540"

C. Container Label (60 g)

1. Reduce the size of the company logo "Promius Pharma" so that it does not compete in prominence with the proprietary name, establish name, dosage form, and strength.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Impoyz*** that Promius Pharma LLC submitted on April 24, 2017.

Table 2. Relevant Product Information for Impoyz* **	
Initial Approval Date	N/A
Active Ingredient	Clobetasol propionate
Indication	Treatment of moderate to severe plaque psoriasis in patients 18 years of age and older.
Route of Administration	Topical
Dosage Form	Cream
Strength	0.025%
Dose and Frequency	Apply a thin layer to the affected skin areas twice daily.
How Supplied	2.5 g (samples); 60 g, 112 g tubes
Storage	Store at 20°C to 25°C (68°F to 77°F)
Container Closure	Aluminum tubes

APPENDIX B. PREVIOUS DMEPA REVIEWS

N/A

APPENDIX C. HUMAN FACTORS STUDY

N/A

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F. OTHER SOURCES

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Impoyz*** labels and labeling submitted by Promius Pharma LLC on April 24, 2017 and July 31, 2017.

- Container labels
- Carton labeling
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images (not to scale)

Proposed Container Labels (not to scale)

(b) (4)

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

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/s/

CARLOS M MENA-GRILLASCA
09/29/2017

SARAH K VEE
09/29/2017

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

PATIENT LABELING REVIEW

Date:	September 25, 2017
To:	Kendall Marcus, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** 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)** Jina Kwak, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TRADENAME (clobetasol propionate)
Dosage Form and Route:	Cream, 0.025%, for topical use
Application Type/Number:	NDA 209483
Applicant:	Promius Pharma, LLC.

1 INTRODUCTION

On January 30, 2017, Promius Pharma LLC. submitted for the Agency's review a 505 (b)(1) non-New Molecular Entity (non-NME) New Drug Application (NDA) 209483 for TRADENAME (clobetasol propionate) Cream, 0.025%. The proposed indication for TRADENAME (clobetasol propionate) Cream, 0.025% is for topical treatment of moderate to severe plaque psoriasis in patients 18 years and older.

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 February 14, 2017 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (clobetasol propionate) Cream, 0.025%.

2 MATERIAL REVIEWED

- Draft TRADENAME (clobetasol propionate) Cream, 0.025% PPI received on January 30, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 20, 2017.
- Draft TRADENAME (clobetasol propionate) Cream, 0.025% Prescribing Information (PI) received on January 30, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 20, 2017.
- Approved OLUX (clobetasol propionate) foam, 0.05% comparator labeling dated April 23, 2014.

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. In our review of the PPI the target reading level is at or below an 8th grade 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.

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/s/

SHAWNA L HUTCHINS
09/25/2017

JINA KWAK
09/25/2017

BARBARA A FULLER
09/25/2017

LASHAWN M GRIFFITHS
09/25/2017

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

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

Memorandum

Date: September 21, 2017

To: Hamid Tabatabai, Medical Officer
Division of Dermatology and Dental Products (DDDP)

Angela Brown, Regulatory Project Manager, (DDDP)

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

CC: Matt Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for clobetasol propionate cream, 0.025%

NDA: 209483

In response to DDDP consult request dated February 14, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for the original NDA submission for clobetasol propionate cream, 0.025%.

OPDP's comments on the proposed labeling which are based on the draft PI received by e-mail from DDDP on September 20, 2017, 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 proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 21, 2017, and we do not have any comments.

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

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/s/

JINA KWAK
09/21/2017

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: August 21, 2017 **Date Consulted:** February 24, 2017

From: Jane Liedtka, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

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

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Hamid Tabatabai, M.D., Medical Officer,
Division of Dermatology and Dental Products (DDDP)

Drug: Clobetasol propionate cream 0.025%

NDA: 209483

Subject: Pregnancy and Lactation Labeling

Proposed Indication:

Clobetasol Propionate cream 0.025% is a topical corticosteriod indicated for the treatment of moderate to severe plaque psoriasis in patients 18 years of age and older.

Applicant: Promius Pharma LLC.

Materials Reviewed:

- Applicant's background package for NDA 209483 submitted as SD#1 on January 30, 2017.
- Applicant's revised label, literature review and summary of pharmacovigilance database submitted as SD#4 on March 31, 2017.

- DPMH review of Pandel (hydrocortisone probutate) cream 0.1%. NDA 20453, S-007. December 9, 2016. Christos Mastroyannis, M.D., DARRTS Reference ID: 4025609.
- DPMH review of Ultravate (halobetasol propionate) lotion, 0.05%. NDA 208183. September 16, 2015. Leyla Sahin, M.D., DARRTS Reference ID: 3820029.

Consult Question:

DDDP would like to seek your input on PLLR language in the original NDA.

INTRODUCTION

On February 24, 2017, DDDP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of Clobetasol propionate cream 0.025% labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

- On August 26, 2016, (b) (4) submitted a new NDA 209483 for Clobetasol propionate cream 0.025%.
    - Clobetasol propionate cream 0.025% is a topical corticosteriod indicated for the treatment of moderate to severe plaque psoriasis in patients 18 years of age and older.
    - The moiety clobetasol propionate cream was first approved as Temovate 0.05% on April 2, 2003.
- On March 16, 2017, the Agency sent the Applicant an information request (IR) requesting that they submit a review and summary of the available published literature and a summary of the Applicant's pharmacovigilance database regarding clobetasol use in pregnant and lactating women and effect on fertility.
- On March 31, 2017, the Applicant submitted the revised labeling and the requested supporting information which was adequate.

BACKGROUND

Clobetasol and Drug Characteristics

- Clobetasol propionate cream 0.025% contains clobetasol propionate, a synthetic, fluorinated corticosteroid.
- Molecular weight ≈ 467 Daltons.
- The percent protein bound and the half-life for clobetasol are not known.
- Topical corticosteroids can be absorbed from normal intact skin. The extent of percutaneous absorption of topical corticosteroids is determined by factors like the vehicle and the integrity of the epidermal barrier. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Corticosteroids contribute to cellular signaling, immune function,

inflammation, and protein regulation.[1]

- One major concern of topical corticosteroids is suppression of the hypothalamic pituitary adrenal (HPA) axis.[2] This suppression is more commonly associated with the use of highly potent steroids, particularly when applied to a large body surface area (BSA). Topical corticosteroids are categorized according to their potency as low, medium and high potency. Clobetasol propionate cream is considered of high potency.
- The most common adverse reactions (incidence ≥ 1%) seen in clinical studies of Clobetasol propionate cream 0.025% were application site pain, pruritus, fissure and discoloration.

Reviewer's Comments
Topical corticosteroids are absorbed through the skin (skin integrity plays a significant role); therefore, they may exercise systemic effects similar to systemically administered corticosteroids. Their effects depend on their potency, surface area to which they are applied, and on the frequency of application. Clobetasol propionate cream 0.025% is considered of high potency.

Psoriasis and Pregnancy

Psoriasis affects 2% to 3% of the population, men and women equally.[3] 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). High potency topical corticosteroids only if needed in the second and third trimesters.
- Second line: ultraviolet B phototherapy
- Third line: tumor necrosis factor inhibitors (adalimumab, etanercept, infliximab), cyclosporine, and systemic steroids.[1]

REVIEW

Pregnancy

Nonclinical experience

In animal reproduction studies, increased malformations were observed after subcutaneous administration of clobetasol propionate to pregnant mice and rabbits. No comparisons of animal exposure with human exposure are provided due to minimal systemic exposure noted after

[1] Proposed labeling, Pandel (hydrocortisone probutate) cream 0.1%
[2] Campbell LS, Chevalier M, Levy RA, Rhodes A. Hypothalamic-pituitary-adrenal axis suppression related to topical glucocorticoid therapy in a child with psoriatic exfoliative erythroderma. Pediatr Dermatol. 2012 Jan- Feb; 29(1):101-4.
[3] 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. 2012; 67, (3):459-477.

topical administration of Clobetasol propionate cream 0.025%.

For further details, the reader is directed to the Nonclinical Review by Jill Merrill, PhD.

Applicant's Review of Literature

The Applicant searched the medical literature in MEDLINE, Biosis, EMBASE, International Pharmaceutical Abstracts and SciSearch® Cited Ref Sci to identify articles related to pregnancy published from April 2, 2003 to the cut-off date of December 6, 2016. One article Mahe[4] *et al* (2007) was identified which is included in Table 1 below.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms "clobetasol and pregnancy," "clobetasol and pregnant women," "clobetasol and pregnancy and birth defects," "clobetasol and pregnancy and congenital malformations," "clobetasol and pregnancy and stillbirth," "clobetasol and spontaneous abortion" and "clobetasol and pregnancy and miscarriage." No reports of adequate and well-controlled studies of clobetasol use in pregnant women were found. No publications discussing use of clobetasol specifically in pregnancy were identified (except for the Mahe[4] article noted above and in Table 1).

There was a body of literature identified regarding the safety of topical corticosteroids in pregnancy. In many cases, these publications stratified the products into mild to moderate potency and potent/very potent (superpotent) categories.

In 2012, Bae[3] *et al* reviewed the options for treatment of psoriasis in pregnant women. The authors presented the following conclusions regarding topical corticosteroids:

Corticosteroids topical: category C
Chi *et al*[5] Evidence IB

- Cochrane review that included 7 studies, including 2 cohort and 5 case-control studies, was published in 2010. One study found significant association between first-trimester use of topical corticosteroids and orofacial cleft. Another study found significant association between very potent topical corticosteroids and low birth weight.
- Conclusion: this review demonstrated no statistically significant difference between pregnant women who use and those who do not use topical corticosteroids. However, there was concern for possible association between use of very potent topical corticosteroids with low birth weight.

Chi *et al*[5] Evidence III

[4] Mahe A *et al.* The cosmetic use of skin-lightening products during pregnancy in Dakar, Senegal: a common and potentially hazardous practice: a common and potentially hazardous practice. Trans R Soc Trop Med Hyg 2007; 101: 183–187.

[5] Chi CC, Wang SH, Kirtschig G, Wojnarowska F. Systematic review of the safety of topical corticosteroids in pregnancy. J Am Acad Dermatol 2010; 62:694-705.

- Cohort study using United Kingdom General Practice Research Database found no associations of topical corticosteroid exposure with orofacial cleft, cleft palate alone, preterm delivery, and fetal death in 35,503 pregnant women prescribed topical corticosteroids from 85 d before last menstrual period to delivery or fetal death, in comparison with unexposed women (48,630). However, exposure to potent/very potent topical steroids shortly before and during pregnancy was significantly associated with fetal growth restriction, showing dose-response relationship.
- Conclusion: this study demonstrates statistically significant difference between pregnant women who use and those who do not use topical corticosteroids in terms of fetal growth restriction.

In 2017, Chi[6] *et al* published another article entitled "Updated evidence-based (S2e) European Dermatology Forum guideline on topical corticosteroids in pregnancy". The following table, reproduced from the Chi[6] publication, summarizes the majority of the available literature on the topic. The authors' conclusions were stated as follows:

- Women can be reassured that there is no significantly increased risk of birth defect, preterm delivery and fetal death while using topical corticosteroids for medical indications in pregnancy. There is also no increased risk of low birthweight when using mild/moderate topical corticosteroids in pregnancy.
- Women should be informed that there is a small risk for low birthweight when using potent/very potent topical corticosteroids in pregnancy, but this risk is less than that of systemic corticosteroids, for an additional risk for miscarriage and preterm delivery has been found in pregnant women using systemic corticosteroids.[7]
- Depending on the severity of their skin conditions, pregnant women should use topical corticosteroids of the least potency required and limit the use amounts. Pregnant women should be cautious on sites of high percutaneous absorption, for example the skin folds, armpits and vulva. Pregnant women with eczema shall apply as least amounts of topical corticosteroids as possible because the skin barrier is impaired.

[6] Chi CC *et al.* Updated evidence-based (S2e) European Dermatology Forum guideline on topical corticosteroids in pregnancy. Journal of the European Academy of Dermatology and Venereology. 2017; 31: 761-773.
[7] Gur C, Diav-Citrin O, Shechtman S et al. Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. Reprod Toxicol. 2004; 18: 93–101.

Table 1: Studies on the Safety of Topical Corticosteroids in Pregnancy*

First author; publication year; country; funding source	Study design Setting	Number of participants Ascertainment of exposure	Outcome measures	Results
Czeizel; 1997; Hungary; not reported	Case–control study Population-based, using the data set Hungarian Case-Control Surveillance of Congenital Abnormalities	20 830 cases of congenital abnormalities (CAs), 35 727 controls Prenatal logbook, questionnaire and interview	Adjusted odds ratio (OR) with 95% confidence interval (CI) of maternal ointment corticosteroid treatment in 14 CAs group	An association between cleft lip ± palate and maternal corticosteroid ointment treatment in the whole pregnancy [adjusted OR 2.21 (95% CI 1.11–4.39)] and in the first month of gestation [OR 4.19 (95% CI 1.47–11.97)] was revealed. However, the adjusted OR was not significant in the second and third months of gestation, which are the critical periods for CAs (but the OR statistic was not reported). Also, no significant association between maternal corticosteroid ointment use and other major or mild CAs was found
Mygind; 2002; Denmark; Western Danish Research Forum for Health Sciences, Danish Medical Research Council, and Foundation of Hørslev	Retrospective cohort study Based on local population in North Jutland, using Danish Medical Birth registry	363 primiparous, singleton pregnant women exposed to topical corticosteroids within 30 days before conception and/or during pregnancy, 9263 controls receiving no prescriptions Pharmaco-epidemiological prescription database	Crude and adjusted OR with 95% CI for low birthweight (LBW), malformations, preterm delivery and stillbirth	No increased risk of LBW, malformations, preterm delivery and stillbirth among the exposure group. The adjusted OR (95% CI) for LBW, malformations and preterm delivery among women receiving weak/medium-strong corticosteroids were 0.7 (0.17–2.85), 0.93 (0.23–3.80) and 1.04 (0.56–1.92), respectively, and those of strong/very strong corticosteroids were 1.23 (0.45–3.37), 0.56 (0.14–2.28) and 0.99 (0.54–1.84), respectively. The crude OR for stillbirth among women receiving prescription of topical corticosteroid during pregnancy was 2.6 (95% CI 0.83–8.05)
Edwards; 2003; Australia; not reported	Case–control study Single teaching hospital	48 cases with non-syndromic cleft lip or palate, 58 controls Retrospective interview	OR with 95% CI of topical corticosteroid use in the first trimester of pregnancy for cleft lip or palate, using univariate and multiple regression analysis	A significant increase in the prevalence of maternal first-trimester use of topical corticosteroid among cases with syndromic cleft [adjusted OR 18.6 (95% CI 1.29–270), $P = 0.032$]
Källén; 2003; Sweden; KA Wallenberg Foundation	Register analysis Population-based, Swedish Medical Birth Registry	149,932 women with first-trimester drug exposure, containing 1094 exposed to topical corticosteroid Prospective interview at the first antenatal care visit (usually week 10–12)	Expected number of cases with orofacial cleft, compared with observed number as risk ratio (RR; observed/expected) with 95% CI based on exact Poisson distribution	No significant association between topical corticosteroid use in the first trimester of pregnancy and orofacial clefts [RR 2.01 (95% CI 0.55–5.15)]
Pradat; 2003; multinational; not reported	Case–control study Multicentric database, Malformation Drug Exposure Surveillance (MADRE)	11 150 cases with congenital malformations, containing 982 cases of cleft palate or lip Reported by participating researchers	Mantel–Haenszel OR with 95% CI after stratification by registry	No correlations of first-trimester exposure to topical corticosteroids with cleft palate or lip [OR 0.52 (95% CI 0.16–1.64)], cleft palate [OR 0 (95% CI 0–3.41)] and cleft lip ± palate [OR 0.73 (95% CI 0.23–2.37)]

First author; publication year; country; funding source	Study design Setting	Number of participants Ascertainment of exposure	Outcome measures	Results
Mahé; 2007; Senegal; not reported	Cohort study Single maternity hospital	34 of 99 women with exposure to potent topical corticosteroids (28 clobetasol propionate, 60 g/month) Compared to non-users of very potent topical corticosteroids Interviewed at 6-9 months of pregnancy, local area only	Plasma cortisol, pregnancy outcome: mode of delivery, gestational age, birthweight, placental weight and status of newborn and mother. Chi-squared test and Fisher's two-tailed exact test, Kruskal–Wallis *H*-test	Increased frequency of mild vaginal bleeding ($P = 0.031$), decreased birthweight ($P = 0.046$), decreased placental weight ($P = 0.043$) and decreased placental cortisol ($P = 0.07$)
Carmichael; 2007; USA; Centers for Disease Control and Prevention	Case–control study Multistate, part of the National Birth Defects Prevention Study	1110 infants with cleft lip ± cleft palate and 4079 control infants Maternal interviews were conducted with a standardized, computer-based telephone questionnaire in English or Spanish, no earlier than 6 weeks and no later than 24 months after the infant's estimated date of delivery	OR with 95% CI of maternal use of topical corticosteroids confirmed by clinical description or surgical or autopsy report. Each case received an additional review by 1 clinical geneticist to ensure that cases from each study centre met standard eligibility criteria	No significant association between cleft lip ± cleft palate and maternal use of topical corticosteroids from 4 weeks before through 12 weeks after conception [OR 0.9 (95% CI 0.2–4.3)]
Carmichael; 2009; USA; Centers for Disease Control and Prevention	Case–control study Multistate, part of the National Birth Defects Prevention Study	1165 cases of second- or third-degree hypospadias and 3000 non-malformed controls Maternal interviews were conducted using a standardized, computer-based telephone questionnaire in English or Spanish, no earlier than 6 weeks and no later than 24 months after the infant's estimated date of delivery	OR with 95% CI of maternal use of topical corticosteroids confirmed by clinical description or operative report. Each case received an additional review by 1 clinical geneticist to ensure that cases from each study centre met standard eligibility criteria	No significant association between hypospadias and maternal use of topical corticosteroids from 4 weeks before through 18 weeks after conception [OR 0.37 (95% CI 0.12, 1.17)]
Chi; 2011; UK; British Skin Foundation, University of Oxford	Retrospective cohort study Population-based	35 503 pregnant women prescribed topical corticosteroids during the period from 85 days before last menstrual period to delivery or fetal death and 48 630 unexposed women Prescription records	Adjusted RR for orofacial cleft (and its two categories, cleft lip ± palate and isolated cleft palate), fetal growth restriction, preterm delivery and fetal death	A significant association of maternal exposure to potent/very potent topical corticosteroids with fetal growth restriction [adjusted RR 2.08 (95% CI 1.40–3.10)]. No significant association of topical corticosteroids of any potency with other pregnancy outcomes
Hviid; 2011; Denmark; Danish Medical Research Council and Lundbeck Foundation	Retrospective cohort study Nationwide	22 480 pregnant women filled prescriptions for topical corticosteroids during the first trimester and 810,156 controls receiving no prescriptions for topical corticosteroids Danish Prescription Drug Register	Adjusted OR with 95% CI of cleft lip ± palate and isolated cleft palate	A significant association of topical corticosteroid use during the first trimester with cleft lip ± palate [adjusted OR 1.45 (95% CI 1.03–2.05)]. However, exploratory analyses of the dose–response and potency–response relations did not support a causal association. The observed association may arise from multiple comparisons

First author; publication year; country; funding source	Study design Setting	Number of participants Ascertainment of exposure	Outcome measures	Results
Chi; 2013; UK; Wellbeing of Women and Chang Gung Memorial Hospital, Chiayi	Retrospective cohort study Population-based	2658 pregnant women exposed to topical corticosteroid and 7246 unexposed pregnant women	Adjusted RR with 95% CI for orofacial cleft, low birthweight, preterm delivery, fetal death and low Apgar score as well as mode of delivery	A significantly increased risk of low birthweight when the dispensed amount of potent or very potent topical corticosteroids exceeded 300 g during the entire pregnancy [adjusted RR, 7.74 (95% CI, 1.49–40.11)]. No associations of maternal topical corticosteroid exposure with orofacial cleft, preterm delivery, fetal death, low Apgar score and mode of delivery
Skuladottir; 2014; USA; Centers for Disease Control and Prevention	Case–control study Population-based	2372 cleft cases (1577 infants with cleft lip ± palate and 795 infants with cleft palate alone) and 5922 controls without major congenital malformations randomly selected from birth certificates or birth hospitals	Adjusted OR with 95% CI of maternal use of topical corticosteroids during the periconceptional period	The overall association between corticosteroids and cleft lip and palate was 1.0 (95% CI, 0.7–1.4)
Skuladottir; 2014; USA; Centers for Disease Control and Prevention	Case–control study Population-based	123 cases with cleft lip ± palate and 61 with cleft palate alone identified through the Medical Birth Registry of Norway, and 551 control mothers randomly selected from the Norwegian Mother and Child Cohort Study		No associations for any cleft type [adjusted OR, 1.0 (95% CI 0.5 2.2), cleft lip ± palate [adjusted OR 1.2 (95% CI 0.5 2.9), nor for cleft palate alone [adjusted OR 0.6 (95% CI 0.1 2.6)
Skuladottir; 2014; Norway; Western Norwegian Health Authorities	Case–control study 2 specialized surgical centres for oral cleft in Norway	573 cleft cases (377 infants with cleft lip ± palate and 196 infants with cleft palate alone) and 763 controls without major congenital malformations randomly selected from the Medical Birth Registry of Norway	Adjusted OR with 95% CI of maternal first-trimester exposure to corticosteroids	No significant associations of first-trimester use of topical corticosteroids with both cleft lip ± palate (adjusted OR 2.3 (95% CI 0.71 7.7) and cleft palate alone (adjusted OR, 3.4; CI 0.87 13)

*Source: Chi[6] *et al* pgs 765-767

A few additional articles are worth mention and are briefly summarized below:

- Katz[8] et al reported a case of severe intrauterine growth retardation that was described in the infant of a woman who used an unusually large amount (40 mg/day) of topical triamcinolone after the 12th week of gestation.
- The evidence from a Cochrane Review suggests that the major possible adverse effects on the fetus caused from topical corticosteroids were orofacial clefts when used pre-conceptionally and in the first trimester of pregnancy, and fetal growth restriction when very potent topical corticosteroids were used during pregnancy[9].
- Micromedex states that some epidemiology studies have associated oral cleft with human

[8] Katz VL, Thorp JM Jr, Bowes WA Jr. Severe symmetric intrauterine growth retardation associated with the topical use of triamcinolone. Am J Obstet Gynecol 1990;162:396-7

[9] Chi CC, Lee CW, Wojnarowska F, Kirtschig G. Safety of topical corticosteroids in pregnancy. Cochrane Database Syst Rev 2009; 3: CD007346.

pregnancy exposure to corticosteroids based on small numbers of affected children with exposures[10,11,12,13.] Odd ratios in these reports were in the 3 to 5 range. One of the studies found an association only with topical steroids and not with oral steroids.[14] A review of human teratology studies on corticosteroids concluded that there was no evidence of an increase in malformations with these agents, but that a possible association with clefts could not be excluded.[9]

(b) (4)

Reviewer's Comments

I agree with the majority of the conclusions reached by the authors of Chi[5],[6] et al (see page 4-5 of this review). Though early studies detected an association between cleft lip and/or palate with 1st trimester exposure to topical corticosteroids, these results were not confirmed in subsequent larger studies. The bulk of the evidence does not support an association between topical steroid use in pregnancy and congenital malformations of any kind. In contrast, the finding of an effect on fetal growth with the use of stronger potency steroids (especially with use of large amounts) has consistently been found. However, the systemic absorption of Clobetasol propionate cream 0.025% appears to be very low (it is in picogram range).It is unclear if there is a threshold level

[10] Edwards MJ, Agho K, Attia J, Diaz P, Hayes T, Illingworth A, et al. Case-control study of cleft lip or palate after maternal use of topical corticosteroids during pregnancy. Am J Med Genet A 2003;120:459-63

[11] Carmichael SL, Shaw GM, Ma C, Werler MM, Rasmussen SA, Lammer EJ. Maternal corticosteroid use and oro-facial clefts. Am J Obstet Gynecol 2007;197:585e1-7

[12] Pradat P, Robert-Gnansia E, Di Tanna GL, Rosano A, Lisi A, Mastroiacovo P, Contributors to the MADRE database. First trimester exposure to corticosteroids and oral clefts. Birth Defects Res A Clin Mol Teratol. 2003; 67:968-70.

[13] Kallen B. Maternal drug use and infant cleft lip/palate with special reference to corticoids. Cleft Palate Craniofac J. 2003 Nov;40(6):624-8

[14] Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. Teratology 1997;56:335-40

of fetal exposure that may be associated with risk. There does appear to be a dose-response with the use of large amounts or prolonged use more clearly associated with harm.

Pharmacovigilance Database Summary

According to the Applicant, "There were no cases of pregnancy or lactation reported in our clinical development program pharmacovigilance database".

Summary

The available data from epidemiologic studies demonstrate inconsistent results regarding use of topical corticosteroids during the first trimester of pregnancy and associated congenital malformations, specifically orofacial clefts. More recent larger studies do not support an association. Potent/very potent topical corticosteroids are associated in the majority of studies with higher risk of fetal growth restriction. How much systemic absorption is required for these effects is unknown. Since there is evidence of potential for fetal harm, DPMH recommends (b) (4)

See DPMH proposed labeling below for further details.

Lactation

Nonclinical Experience
No lactation studies with clobetasol have been conducted in animals.

Applicant's Review of Literature

The Applicant searched the medical literature in MEDLINE, Biosis, EMBASE, International Pharmaceutical Abstracts and SciSearch® Cited Ref Sci to identify articles related to clobetasol AND lactation published from April 2, 2003 to the cut-off date of December 6, 2016. No relevant publications were found.

DPMH's Review of Literature

DPMH conducted a search of Dr. Hale's *Medications and Mother's Milk*[15], the Drugs and Lactation Database (LactMed)[16], Micromedex[17], and of published literature in PubMed and EMBASE using the search terms "clobetasol AND lactation" and "clobetasol AND breastfeeding." One relevant publication (discussed below) was identified.

In *Medications and Mother's Milk*[15], Thomas Hale, a breastfeeding expert, states the following

[15] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing
[16] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[17] Truven Health Analytics information, http://www.micromedexsolutions.com/.

regarding clobetasol and lactation:

> No Data, Probably Compatible…Because this is such a high potency steroid, oral absorption by the infant could be hazardous. There are reports of excretion of corticosteroids into breast milk when administered systemically. When infants are exposed to corticosteroids through milk there is a risk of growth suppression, though the risk for such an effect is greatest with prolonged use of high dose oral or IV corticosteroids. Do not use this on a nipple or areola of a breastfeeding mother and avoid use on large surfaces.

Clobetasol is referenced in LactMed[16]. The summary of use during lactation states:

> Clobetasol has not been studied during breastfeeding. Since only extensive application of the most potent corticosteroids may cause systemic effects in the mother, it is unlikely that short-term application of topical corticosteroids would pose a risk to the breastfed infant by passage into breastmilk. However, it would be prudent to use the least potent drug on the smallest area of skin possible. It is particularly important to ensure that the infant's skin does not come into direct contact with the areas of skin that have been treated. Only the lower potency corticosteroids should be used on the nipple or areola where the infant could directly ingest the drugs from the skin; clobetasol should be avoided on the nipple[18]. Only water-miscible cream or gel products should be applied to the breast because ointments may expose the infant to high levels of mineral paraffins via licking[19]. Any topical corticosteroid should be wiped off thoroughly prior to nursing if it is being applied to the breast or nipple area.
>
> In the section of LactMed[16] entitled "Effects in Breastfed Infants", the authors describe the following two case reports:
>
> - De Stefano[20] *et al* described a nursing mother who applied isofluprednone acetate (a potent corticosteroid) topically to her nipples starting at birth. At 2 months, her breastfed infant presented with prolonged QT interval, cushingoid appearance, severe hypertension, decreased growth and electrolyte abnormalities.
> - Westermann[21] *et al* described a 40 year old nursing mother who was started on treatment three days post-partum with oral prednisolone 25 mg daily as

[18] Barrett ME *et al*. Dermatoses of the breast in lactation. Dermatol Ther. 2013; 26: 331-6.
[19] Noti A, Grob K, Biedermann M et al. Exposure of babies to C (15)-C(45) mineral paraffins from human milk and breast salves. Regul Toxicol Pharmacol. 2003; 38(3):317-25.
[20] De Stefano B *et al*. Factitious hypertension with mineralocorticoid excess in an infant. Helv Paediatr Acta. 1983; 38:185-9.
[21] Westermann L, Hugel R, Meier M *et al.* Glucocorticosteroid-resistant pemphigoid gestationis: successful treatment with adjuvant immunoadsorption. J Dermatol. 2012; 39:168-71.

> well as using topical betamethasone 0.1% twice daily (to her lesions) for pemphigus gestationis. After progression of lesions, she was gradually increased to oral prednisolone 60 mg over the next two weeks. She was then switched to clobetasol propionate 0.05% topically for continued poor response. Immunoabsorption therapy was added and she responded. By five weeks later, her oral steroid was reduced to 7.5 mg daily. She breastfed throughout her treatment and her infant was reportedly "developing normally" at 8 weeks of age and beyond.

Clobetasol is referenced in Micromedex. The Lactation Rating states:

> Infant risk cannot be ruled out…Systemic corticosteroids are detectable in small quantities in breast milk and may cause adverse effects (e.g., growth suppression). It is unknown if topical corticosteroid administration can result in systemic absorption. Because many drugs are excreted in human milk, the manufacturer recommends the use of caution when prescribing topical corticosteroids to a nursing woman[22]…Small amounts of corticosteroids enter human milk[23,24, 25]… The American Academy of Pediatrics classified the corticosteroids prednisone and prednisolone as compatible with breastfeeding[26]. It was recommended that this agent [clobetasol] not be used on the nipple area during breastfeeding[27].

Summary

The applicant did not provide any data about the presence of clobetasol in human or animal milk and there were limited publications identified. Of these publications, one described adverse events in an infant who ingested a potent topical steroid regularly due to prolonged daily applications of the product to the nursing mother's nipples. Given the low systemic absorption of clobetasol, DPMH recommends that the breastfeeding risk/benefit statement is included in section 8.2 of labeling. In addition, a "Clinical Considerations" section advising against the use of clobetasol on the nipple/areola area during breastfeeding is recommended. See DPMH proposed labeling below for further details.

[22] Ohman EM *et al*: Adrenal suppression following low-dose topical clobetasol propionate. JR Soc Med 80:422-4, 1987.
[23] Katz FH and Duncan BR: Entry of prednisone into human milk. N Engl J Med 293:1154, 1975.
[24] McKenzie SA *et al*.: Secretion of prednisone into breast milk. Arch Dis Child 50j:894-6, 1975.
[25] Ost L *et al*.: Prednisolone excretion in human milk. J Pediatr 106:1008-11, 1985.
[26] Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human breast milk. Pediatrics 108:776-789, 2001.
[27]LactMed. 2015. Clobetasol. Available at http://toxnet.nlm.nih.gov/newtoxnet/lactmed htm (search clobetasol).

Females and Males of Reproductive Potential

Nonclinical Experience

Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate cream.

In a 13-week repeat dose toxicity study in rats, topical administration of clobetasol propionate cream, 0.001, 0.005 and 0.025 % at corresponding doses of 0.004, 0.02 and 0.1 mg/kg/day resulted in corticosteroid class-related systemic effects such as reductions in body weight gain, reductions in total leukocytes and individual white cells, decrease in weight of adrenals, thymus, spleen, liver and lung. Histologically, there were decreased hematopoiesis in the bone marrow, thymic atrophy and mast cell infiltration of the mesenteric lymph nodes. All these effects were indicative of severe immune suppression consistent with long-term exposure to corticosteroids. A no observable adverse effect level (NOAEL) was determined to be clobetasol propionate cream, 0.001% (0.004 mg/kg/day) in male rats while a NOAEL could not be determined in females. The clinical relevance of the findings in animals to humans is not clear, but sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk of carcinogenesis.

Clobetasol propionate was not mutagenic in three different test systems: the Ames test, the Saccharomyces cerevisiae gene conversion assay, and the E. coli B WP2 fluctuation test.

Fertility studies conducted in the rat following subcutaneous administration of clobetasol propionate at dosage levels up to 0.050 mg/kg/day revealed that females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

For further details, see the review by Jill Merrill, Ph.D.

Applicant's Review of Literature

The Applicant searched the medical literature in MEDLINE, Biosis, EMBASE, International Pharmaceutical Abstracts and SciSearch® Cited Ref Sci to identify articles related to clobetasol and reproduction potential published from April 2, 2003 to the cut-off date of December 6, 2016. No relevant articles were identified.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding chloroprocaine and its effects on fertility and found no relevant articles.

Summary

Animal reproduction studies on administration of clobetasol did show adverse effects on fertility in female rats. Discussion with the pharmacology/toxicology team revealed that these changes were seen at subcutaneous doses high enough that the relevance to human fertility was doubtful.

Given the lack of findings in humans exposed to corticosteroids in clinical studies it was decided that this information would be in Section 13 only and that subsection 8.3 would be omitted from labeling.

CONCLUSION

The Pregnancy and Lactation, sections of Clobetasol propionate cream 0.025% labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of Clobetasol propionate cream 0.025% labeling was formatted in the PLLR format to include: "Risk Summary," and "Data" sections.
- **Lactation, Section 8.2**
  - The "Lactation" section of Clobetasol propionate cream 0.025% labeling was formatted in the PLLR format to include the "Risk Summary" and "Clinical Considerations" sections.
- **Patient Counseling Information, Section 17**
  - The "Patient Counseling Information" section of Clobetasol propionate cream 0.025% labeling was updated to correspond with sections 8.1 and 8.2 of the labeling.

RECOMMENDATIONS

DPMH participated in labeling meetings with DDDP on 8/18/17 and 8/21/17. DPMH revised sections 8.1, 8.2 and 17 of Clobetasol propionate cream 0.025% labeling for compliance with the PLLR. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Clobetasol propionate cream 0.025% Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: May cause fetal harm (8.1)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Risk Summary
There are no available data on the use of Clobetasol propionate cream 0.025% in pregnant women to inform any drug-associated risk for adverse developmental outcomes. Published data report a significantly increased risk of low birthweight with the use of greater than 300 grams of potent or very potent topical corticosteroid during a pregnancy. Advise pregnant women of the potential risk to a fetus and to use Clobetasol propionate cream 0.025% on the smallest area of skin and for the shortest duration possible (*see Data*). In animal reproduction studies, increased malformations, such as cleft palate and skeletal abnormalities, were observed after subcutaneous administration of clobetasol propionate to pregnant mice and rabbits. No comparisons of animal

exposure with human exposure may be calculated due to minimal systemic exposure in humans after topical administration of Clobetasol propionate cream 0.025% [*see Clinical Pharmacology (12.3)*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Multiple observational studies found no significant associations between maternal use of topical corticosteroids of any potency and congenital malformations, preterm delivery, or fetal mortality. However, when the dispensed amount of potent or very potent topical corticosteroid exceeded 300 g during the entire pregnancy, use was associated with an increase in low birth weight infants [adjusted RR, 7.74 (95% CI, 1.49–40.11)]. In addition, in a small cohort study, 28 sub-Saharan women using potent topical corticosteroids (27/28 used clobetasol propionate 0.05%) for skin lightening during pregnancy noted a higher incidence of low birth weight infants in the exposed group. The majority of exposed subjects treated large areas of the body (a mean quantity of 60 g/month (range, 12—170g) over long periods of time.

Animal Data
In an embryofetal development study in mice, subcutaneous administration of clobetasol propionate resulted in fetotoxicity at the highest dose tested (1 mg/kg) and malformations at the lowest dose tested (0.03 mg/kg). Malformations seen included cleft palate and skeletal abnormalities. In an embryofetal development study in rabbits, subcutaneous administration of clobetasol propionate resulted in malformations at doses of 0.003 and 0.01 mg/kg. Malformations seen included cleft palate, cranioschisis, and other skeletal abnormalities.

8.2 Lactation

Risk Summary
There is no information regarding the presence of clobetasol propionate in breast milk or its effects on the breastfed infant or on milk production. 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 clobetasol 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 Clobetasol propionate cream 0.025% and any potential adverse effects on the breastfed infant from Clobetasol propionate cream 0.025% or from the underlying maternal condition.

Clinical Considerations
To minimize potential exposure to the breastfed infant via breast milk, use Clobetasol propionate cream 0.025% on the smallest area of skin and for the shortest duration possible while

breastfeeding. Advise breastfeeding women not to apply Clobetasol propionate cream 0.025% directly to the nipple and areola to avoid direct infant exposure.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise a pregnant woman that use of Clobetasol propionate cream 0.025% may cause fetal harm and to use Clobetasol propionate cream 0.025% on the smallest area of skin and for the shortest duration possible.[*see Use in Specific Populations (8.1)]*.

Lactation

Advise a woman to use Clobetasol propionate cream 0.025% on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply Clobetasol propionate cream 0.025% directly to the nipple and areola to avoid direct infant exposure *[see Use in Specific Populations (8.2)]*.

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

/s/

JANE E LIEDTKA
08/21/2017

TAMARA N JOHNSON
08/22/2017

LYNNE P YAO
08/23/2017

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 # 209483 BLA# NA	NDA Supplement #: S- NA BLA Supplement #: S- NA	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) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: (b) (4) Established/Proper Name: clobetasol propionate Dosage Form: cream Strengths: 0.025% Route(s) of Administration: topical		
Applicant: Promius Pharma, LLC. Agent for Applicant (if applicable): NA		
Date of Application: January 30, 2017 Date of Receipt: January 30, 2017 Date clock started after Unacceptable for Filing (UN): NA		
PDUFA/BsUFA Goal Date: November 30, 2017	Action Goal Date (if different): November 16, 2017	
Filing Date: March 31, 2017	Date of Filing Meeting: March 10, 2017	
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 ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Treatment of moderate to severe plaque psoriasis		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** *http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.*	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)	

Review Classification: ***The application will be a priority review if:*** • ***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? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ 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 ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ 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)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 110799	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***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 electronic archive.***	☒	☐		

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)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** *http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm* ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	Standard
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** *http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm*	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐	X	
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 ***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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf*	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
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)]?**

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.

- 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

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 and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

- If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**?

Check the Electronic Orange Book at:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If no, include template language in the 74-day letter.

Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]

***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*

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/oopd/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)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***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.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ 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: ☒ 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				
***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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

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)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***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].*** ***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…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒	☐	☐	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (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)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required***[3]	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576 htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☐	☒	☐	No REMS
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
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? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
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) ***If yes, specify consult(s) and date(s) sent:DPMH – 2/24/17; OSI – 4/5/17***	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***NA***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** October 12, 2016	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** September 9, 2015	☒			

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 15, 2017

BACKGROUND: NDA 209483, was received on January 30, 2017. The associated IND is IND 110799 clobetasol propionate cream, 0.025%. There was a Type C meeting on July 27, 2015 and a Pre-NDA Meeting on October 12, 2016 and. (b) (4)

(b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Angela Brown	N
	Sr RPM:	Strother Dixon	Y
	CPMS/TL:	Barbara Gould	Y
Cross-Discipline Team Leader (CDTL)	Snezana Trajkvoic		Y
Divison Deputy Director	Hon-Sum Ko		Y
Division Director/Deputy	Jill Lindstrom Nancy Xu(Associate Director for Labeling)		Y Y
Office Director/Deputy	Julie Beitz		Y
Clinical	Reviewer:	Hamid Tabatabai	Y
	TL:	Snezana Trajkvoic	Y
Social Scientist Review (*for OTC products*)	Reviewer:	NA	NA
	TL:	NA	NA
OTC Labeling Review (*for OTC products*)	Reviewer:	NA	NA
	TL:	NA	NA
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	NA	NA
	TL:	NA	NA
Clinical Pharmacology	Reviewer:	Ed Bashaw	N
	TL:	Chinmay Shukla	Y

• Genomics	Reviewer:	N/A	NA
• Pharmacometrics	Reviewer:	N/A	NA
Biostatistics	Reviewer:	Rebecca Hager	Y
		Kim Carin	Y
	Director	Stephen Wilson	Y
	TL:	Mohamed Alosh	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jill Merrill	Y
	TL:	Barbara Hill	Y
Statistics (carcinogenicity)	Reviewer:	NA	NA
	TL:	NA	NA
Product Quality (CMC) Review Team:	ATL:	Yichun Sun	Y
	RBPM:	Florence Aisida	Y
• Drug Substance	Reviewer:	Lawrence Perez	Y
• Drug Product	Reviewer:	Zhengfang Ge	Y
• Process	Reviewer:	Youmin Wang	Y
• Microbiology	Reviewer:	Maria Martin Manso	N
• Facility	Reviewer:	Krishnakali Ghosh	N
• Biopharmaceutics	Reviewer:	Kalpana Paudel Vidual Kolhatkar	Y N
• Immunogenicity	Reviewer:	NA	NA
• Labeling (BLAs only)	Reviewer:	NA	NA
• Other (e.g., Branch Chiefs, EA Reviewer)	NA		NA
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Susan Redwood	N
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Silva Wanis	
	TL:	Matthew Falter	N
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Carlos Mena-Grillasca	N
	TL:	Sarah Vee	N
	RPM:	Tri Bui Nguyen	Y
		Mishale Mistry	N
OSE/DRISK (REMS)	Reviewer:	Kira Leishear	N
	TL:	Donella Fitzgerald	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Bei Yu	Y
	TL:	Philip Kronstein	N

Bioresearch Monitoring (OSI)	Reviewer:	NA	NA
	TL:	NA	NA
Division of Pediatric and Maternal Health (DPMH)	Reviewer:	Christos Mastroyannis	Y
	TL:	Tamara Johnson	N
		Lynne Yao	N
	RPM:	Denise Pica-Branco	Y
Controlled Substance Staff (CSS)	Reviewer:	NA	NA
	TL:	NA	NA
(DPV)	Reviewer:	Jessica Weintraub	N
		Vicky Chan	N
Other reviewers/disciplines N/A			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☐ YES Date if known: ☐ ☒ NO ☐ To be determined Reason:
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **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) • Is the product an NME?	 ☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☒ N/A
• 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?	☐ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	NA
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Jill Lindstrom, MD **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): June 29, 2017 **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. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	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.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	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 ADRAs completed: April 2016

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

/s/

ANGELA M BROWN
04/11/2017

STROTHER D DIXON
04/11/2017

BARBARA J GOULD
04/12/2017

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

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

Application: NDA 209483

Application Type: New NDA

Drug Name(s)/Dosage Form(s): (b) (4) (clobetasol propionate) Cream, 0.025%

Applicant: Promius Pharma, LLC.

Receipt Date: 01/30/2017

Goal Date: 11/30/2017

1. Regulatory History and Applicant's Main Proposals

NDA 209483, was received on January 30, 2017. The associated IND is IND 110799 clobetasol propionate cream, 0.025%. There was a Pre-NDA Meeting on October 12, 2016.

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 of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI 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 May 5, 2017. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

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:

YES 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:

YES 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

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 for HL format.

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. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required

Selected Requirements of Prescribing Information

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Highlights Limitation Statement

YES 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:

Product Title in Highlights

YES 10. Product title must be **bolded**.
Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval 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 title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS**

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title 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 must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title 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 five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the 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) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

YES 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

NO 21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch."

Comment: *Missing the word "contact" before manufacturer name*

Patient Counseling Information Statement in Highlights

YES 22. 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 (or will have)** 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

NO 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment: *The RPM will update the revision date at the time of approval. No revision date in the document*

Contents: Table of Contents (TOC)

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

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. 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 26. The same title 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 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. 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 (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. 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 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**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 32. 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)]*."

Comment:

N/A

33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment: *Add a period after "None"*

ADVERSE REACTIONS Section in the FPI

NO 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "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: *"Because" is replaced with* (b) (4) *otherwise the statement is verbatim*

NO 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), 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: *This statement is not verbatim and states the following,* (b) (4) *adverse 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. "*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

NO 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *Applicant stated, "See FDA-approved patient information." It did not include "(Patient Information)."*

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) 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:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

STROTHER D DIXON
02/17/2017
Signed on behalf of Angela Brown.