CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204141Orig1s000

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**TOPICORT® (desoximetasone) Topical Spray, 0.25%**
Applicant	Taro Pharmaceuticals USA, Inc.
Application/Supplement Number	NDA 204141
Type of Application	Original Submission
Indication(s)	For the treatment of plaque psoriasis in patients 18 years of age or older
Established Pharmacologic Class[1]	Corticosteroid
Office/Division	ODE III/DDDP
Division Project Manager	J. Paul Phillips
Date FDA Received Application	June 12, 2012
Goal Date	April 12, 2013
Date PI Received by SEALD	March 19, 2013
SEALD Review Date	March 19, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

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

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

NO 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *All headings in HL (e.g., Indications and Usage; Dosage and Administration; Dosage Forms and Strengths) are not presented in the center of a horizontal line.*

YES 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Indications and Usage in HL references (1.1). However, there is no subsection 1.1 in the FPI. It must reference (1), not (1.1).*

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required

Selected Requirements of Prescribing Information

• **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 the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *There is a "space-and-one-half" instead of a "single space" between each line of the HL Limitation Statement. Fix spacing.*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

Selected Requirements of Prescribing Information

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.
Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.
Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".
Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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

- **"See 17 for PATIENT COUNSELING INFORMATION"**

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

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

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.
Comment: *If approve in March, revision date must read "03/2013" not "XX/2013". If approve in April, then revision date must read "04/2013".*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.
Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.
Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment: *Subsection heading 12.2 Pharmacodynamics is missing from the TOC. Also, there must not be a "colon" after subsection headings 13.1 and 16.2 in the FPI.*

N/A

31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse

Selected Requirements of Prescribing Information

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: *For section 16, there must not be a "space" before and after the "slash" mark. It must read HOW SUPPLIED/STORAGE AND HANDLING. The same comment applies to subsection 16.1. Delete the extra spaces before and after the "slash" mark.*

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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/s/

JEANNE M DELASKO
03/19/2013

LAURIE B BURKE
03/20/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	January 25, 2013
Reviewer:	Carlos M Mena-Grillasca, RPh, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, MS, PharmD Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Topicort (Desoximetasone) Topical Spray, 0.25%
Application Type/Number:	NDA 204141
Applicant/sponsor:	Taro Pharmaceuticals U.S.A., Inc.
OSE RCM #:	2012-2286

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Topicort NDA 204141 for areas of vulnerability that could lead to medication errors. The Sponsor is proposing a new topical spray formulation to the Topicort product line.

1.1 REGULATORY HISTORY

Topicort Topical Spray, 0.25% (NDA 204141) is currently under review. The proposed proprietary name Topicort is been evaluated separately under OSE review 2012-2655. In addition, the Topicort (Desoximetasone) product line includes the following products:

NDA Num.	Product	Approval Date
017856	Topicort Cream 0.25%	February 28, 1977
018586	Topicort Gel 0.05%	March 29, 1982
018763	Topicort Ointment 0.25%	October 3, 1983
018309	Topicort LP Cream 0.05%	March 28, 1980

1.2 PRODUCT INFORMATION

The following product information is provided in the Topicort (Desoximetasone) Topical Spray, 0.25% submission.

- Active Ingredient: Desoximetasone
- Indication of Use: Treatment of plaque psoriasis of the body in patients 18 years of age or older. Route of Administration: Topical
- Dosage Form: Spray
- Strength: 0.25%
- Dose and Frequency: Apply a thin film to the affected skin areas twice daily. Rub in gently.
- How Supplied: 6 mL physician sample bottles; 30 mL, 50 mL, and 100 mL
- Storage: 20º-25 ºC (68 º-77 ºF); excursions permitted 15 º-30 ºC (59 º-86 ºF).
- Container and Closure System: White High Density Polyethylene (HDPE) bottles and white (b) (4) screw caps, co-packaged with a white, manual, spray pump with screw type closure.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Topicort medication error reports. We also reviewed the Topicort container labels, carton and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date	January 15, 2013
Drug Names	Active ingredient: Desoximetasone Product Name: Topicort
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT
Time Limitation	May 22, 2012 (date of last search performed for OSE review 2012-1159, dated June 14, 2012)

The FAERS database search identified 2 cases (8585737v1 and 8673978v1). After individual review, none of the cases were included in the final analysis for the following reasons:

- Adverse event for off-label use and not related to labels and labeling (n=1)
- Wrong strength was dispensed (i.e. prescription was written for Desoximetasone cream 0.05% but product dispense was Desoximetasone cream 0.25%). The case refers to generic Desoximetasone product; hence, it is not relevant to Topicort labels and labeling (n=1)

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels and Carton Labeling submitted June 11, 2012 (Appendix B and C)
- Insert Labeling submitted September 9, 2012
- Currently approved labels/labeling for the other Topicort products (Appendix D)

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

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

The Applicant is proposing a new 0.25 % topical spray formulation. The topical spray formulation share the same dose (i.e. thin film to affected areas twice daily) with all the currently marketed Topicort formulations (i.e. cream, ointment, and gel) and have an overlapping strength (i.e. 0.25%) with the cream and ointment formulations. However, all the currently marketed Topicort products are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, whereas the spray formulation is proposed for the treatment of plaque psoriasis in adults.

The proposed package sizes (i.e. 30 mL, 50 mL and 100 mL) seems adequate as it would allow for healthcare providers to tailor the quantity prescribed to the surface area to be treated and duration of treatment.

We reviewed the container labels and carton labeling and noted that the presentation of the established name is less than ½ the size of the proprietary name. In addition, the 6 mL package size is intended as a drug sample, but lacks the 'sample' statement. We also note that the spray formulation overlaps in strength with the cream and ointment formulations. The topical spray container labels and carton labeling are not adequately differentiated from those of the cream formulation as they both use a very similar color scheme.

Finally, we reviewed the medication errors from our previous Topicort labeling review (OSE 2012-1159, dated June 14, 2012) and noted no new issues that needed addressing for the Topicort Spray dosage form.

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label and to mitigate any confusion to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this Application:

5.1 COMMENTS TO THE APPLICANT

A. Proposed Container Labels (all package sizes)

It is unclear from the container labels submitted in your Application if their placement on the bottle is in a vertical or horizontal orientation. Ensure the text on the container labels appear in a horizontal orientation, instead of a vertical orientation, in relation to the orientation the product will normally be stored, held and used by healthcare providers and patients.

B. Proposed Container Labels and Carton Labeling (all package sizes)

1. Revise the presentation of the established name to ensure that it is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).

2. As currently presented the Topicort topical spray and cream formulations share the similar (b) (4). It is important to provide adequate color differentiation to minimize selection errors, because both formulations also share the same strength. Select another color scheme for the spray formulation that is not currently utilized for another product in any of the Topicort product line.
3. Revise the presentation of the route of administration statements to appear in title case and increase the prominence of the correct route of administration statement, "For Topical Use Only", by presenting the statement on a separate line above the negative route of administration statement "Not for Oral, Ophthalmic, or Intravaginal Use". Also consider bolding the correct route of administration statement "For Topical Use Only".

C. Proposed Container Labels and Carton Labeling (b) (4)

Include a statement such as (b) (4)

If you have further questions or need clarifications, please contact Janet Anderson, project manager, at 301-796-0675.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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

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/s/

CARLOS M MENA-GRILLASCA
01/25/2013

LUBNA A MERCHANT
01/25/2013

SCOTT M DALLAS
01/25/2013

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

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: January 15, 2013

To: J. Paul Phillips
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Lynn Panholzer, PharmD
Regulatory Review Officer
Division of Professional Drug Promotion

Susannah K. Hubert, MPH
Regulatory Review Officer
Division of Consumer Drug Promotion

Subject: **NDA: 204141**
OPDP labeling comments for Desoximetasone Spray, 0.25%

Background

This consult is in response to DDDP's July 16, 2012, request for OPDP's review of the package insert (PI), patient package insert (PPI), instructions for use (IFU), and carton/container labeling for Desoximetasone Spray, 0.25%. OPDP reviewed the substantially complete version of the draft PI sent to OPDP on December 21, 2012, the draft PPI and IFU previously marked up by the Division of Medical Policy Programs and sent to OPDP on January 11, 2013, and the draft carton/container labeling submitted by the applicant on June 12, 2012. Our comments on the PI are included on the attached, marked-up copy of the labeling. We have no comments on the PPI or IFU (attached for reference).

Additionally, OPDP has the following comments on the carton/container labeling:

- Under USUAL DOSAGE, the carton and container labels state that the product is applied twice daily. However, they do not indicate that use should be discontinued when control is achieved, or that treatment beyond 4 weeks is not recommended. This is important material information regarding the dosing of the product to minimize adverse reactions. Therefore, we recommend that you consider adding this information to the carton and container labels, or that the specific twice daily dosing be deleted in favor of just the instruction to see the insert for full prescribing information.

- We note a comment from DDDP on the substantially complete draft PI indicating that there will be a 30 day "in-use" period once the pump is inserted. Would it be appropriate to add a statement to the container label such as "Use within X days of inserting spray pump," similar to the Benzamycin container labeling? Similarly, would it be appropriate to add an instruction to the

pharmacist on the carton label to, for example, “Label with an expiration date of X days after inserting spray pump,” similar to the carton labeling for Benzamycin Topical Gel?

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact:

- Lynn Panholzer (PI)
  301-796-0616 or lynn.panholzer@fda.hhs.gov
- Susannah Hubert (PPI, IFU)
  301-796-3245 or susannah.hubert@fda.hhs.gov

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

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/s/

LYNN M PANHOLZER
01/15/2013

SUSANNAH HUBERT
01/15/2013

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

PATIENT LABELING REVIEW

Date:	January 9, 2013
To:	Susan Walker, 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:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	TOPICORT (desoximetasone)
Dosage Form and Route:	Topical Spray, 0.25%
Application Type/Number:	NDA 204141
Applicant:	Taro Pharmaceuticals U.S.A., Inc.

1 INTRODUCTION

On June 12, 2012, Taro Pharmaceuticals U.S.A., Inc. submitted for the Agency's review an original New Drug Application (NDA) 204141 for TOPICORT (desoximetasone) Topical Spray. The proposed indication for TOPICORT (desoximetasone) Topical Spray is for the treatment of plaque psoriasis of the body in patients 18 years of age or older. On July 16, 2012, the Division of Dermatology and Dental Products (DDDP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TOPICORT (desoximetasone) Topical Spray.

This review is written in response to a request by DDDP for DMPP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TOPICORT (desoximetasone) Topical Spray.

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

2 MATERIAL REVIEWED

- Draft TOPICORT (desoximetasone) Topical Spray Patient Package Insert (PPI) received on June 12, 2012, and received by DMPP on December 21, 2012.
- Draft TOPICORT (desoximetasone) Topical Spray Instructions for Use (IFU) received on December 19, 2012 and received by DMPP on December 21, 2012.
- Draft TOPICORT (desoximetasone) Topical Spray Prescribing Information (PI) received on June 12, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on December 21, 2012.
- Approved CLOBEX (clobetasol propionate) Spray comparator labeling dated September 7, 2012.
- Approved Taclonex (calcipotriene and betamethasone dipropionate) Topical Suspension comparator labeling dated November 30, 2012.

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 and IFU 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. We have reformatted the PPI document using the Verdana font, size 10 and the IFU document using the Verdana font, size 11.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI and IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI or IFU.

Please let us know if you have any questions.

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

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/s/

KAREN M DOWDY
01/09/2013

BARBARA A FULLER
01/10/2013

LASHAWN M GRIFFITHS
01/11/2013

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: December 21, 2012

TO: J. Paul Phillips, Regulatory Project Manager
Melinda McCord, M.D., Medical Officer
Division of Dermatologic and Dental Products

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

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

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204141

APPLICANT: Taro Pharmaceuticals USA, Inc.

DRUG: Desoximetasone 0.25% topical spray

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of (b) (4) plaque psoriasis

CONSULTATION REQUEST DATE: July 19, 2012
CLINICAL INSPECTION SUMMARY DATE: January 14, 2013
DIVISION ACTION GOAL DATE: March 18, 2013
PDUFA DATE: April 12, 2013

I. BACKGROUND:

The Applicant submitted this NDA to support the use of desoximetasone 0.25% topical spray for the treatment of moderate to severe plaque psoriasis.

The pivotal study (Protocol DSXS 0808, entitled "A Double-blind, Vehicle-controlled, Randomized, Parallel Design, Multiple-site Clinical Study to Evaluate the Efficacy and Safety of Desoximetasone 0.25% Topical Spray in Patients with Moderate to Severe Plaque Psoriasis") was inspected in support of the indication.

The clinical sites below were selected based on examples of inconsistent results in the co-primary endpoints (clinical success and treatment success of the target lesion in subjects).

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
David H. Horowitz, M.D. Dermatology Research Associates 1900 Patterson Street, Suite 104 Nashville, TN 37203	DSXS 0808/ Site #6/ 19 subjects	10-11 Sep 2012	NAI
Christopher A. Moeller, M.D. Compliant Clinical Research of Wichita, Inc. 250 North Rock Road, Suite 340 Wichita, KS 67206	DSXS 0808/ Site #1/ 12 subjects	5-6 Sep 2012	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. David H. Horowitz, M.D.
   Dermatology Research Associates
   1900 Patterson Street, Suite 104
   Nashville, TN 37203

   a. **What was inspected:** At this site, for Protocol DSXS 0808, 21 subjects were screened, 19 were randomized, and 16 subjects completed the study. Study records for all subjects were audited. Signed informed consent forms were present for all subjects. Other records reviewed included, but were not limited to, source documents, inclusion/exclusion criteria, adverse event reports, Case Report Forms

(CRFs), drug accountability records, investigator agreements, financial interest documents, and training records.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations. The inspection assignment specifically requested reviews of the records of Subjects 29, 165, and 169 because of inconsistent results reported for the co-primary endpoints, i.e., clinical success and treatment success of the target lesion. No discrepancies were noted in the review of the source documents and corresponding line listings for these three subjects.

c. Assessment of data integrity: The study appears to have been conducted adequately, and the data submitted by this site may be used in support of the respective indication.

2. Christopher A. Moeller, M.D.
Compliant Clinical Research of Wichita, Inc.
250 North Rock Road, Suite 340
Wichita, KS 67206

a. What was inspected: At this site, for Protocol DSXS 0808, 16 subjects were screened, 12 subjects were enrolled, and 10 subjects completed the study. Study records for all subjects were audited. Signed informed consent forms were present for all subjects. Other records reviewed included, but were not limited to, source documents, Case Report Forms (CRFs), inclusion/exclusion criteria, adverse event reporting, subject disposition including early terminations, IRB and sponsor communications, financial disclosure, training documentation, study drug temperature monitoring records, and study drug dosing per the randomization schedule.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations. The inspection assignment specifically requested a review of the records of Subject 011 because of inconsistent results reported for the co-primary endpoints, i.e., clinical success and treatment success of the target lesion. The only discrepancy noted was a rounding error involving body surface area (BSA). BSA for Subject 011 was initially noted as 12.5, then lined out and replaced with 12. Instructions on the form indicated that only whole numbers were to be used, and numbers were to be rounded upwards to the nearest whole number. Therefore, the initial assessment for this subject should have been rounded upwards to 13. This rounding error occurred only once and would appear to be insignificant.

c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Horowitz and Moeller were inspected in support of this NDA. Drs. Horowitz and Moeller were not issued Form FDA 483s. The data generated by these clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

{See appended electronic signature page}

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

CONCURRENCE: *{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.
Team Leader
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/s/

ROY A BLAY
12/21/2012

JANICE K POHLMAN
12/26/2012

SUSAN D THOMPSON
12/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

CONSULTATION

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 5, 2012

FROM: Ali Mohamadi, MD, Division of Metabolism and Endocrinology Products (DMEP)

THROUGH: Dragos Roman, MD, Team Leader, DMEP
Mary Parks, MD, Division Director, DMEP

TO: Melinda McCord, MD, Medical Officer, Division of Dermatology and Dental Products (DDDP)
Gordana Diglisic, MD, Clinical Team Leader, DDDP
J. Paul Phillips, MD, Regulatory Project Manager, DDDP

SUBJECT: Hypothalamic-pituitary-adrenal (HPA) axis evaluation in pediatric patients receiving Topicort (desoximetasone) spray, 0.25%

ASSOCIATED NDA#: 204141

I. Background and basis for consult

On October 9, 2012, the Division of Metabolism and Endocrinology Products (DMEP) received a consultation request from the Division of Dermatology and Dental Products (DDDP) regarding Topicort (desoximetasone) spray (0.25%), a topical corticosteroid for which the sponsor, Taro Pharmaceuticals, has submitted a New Drug Application (NDA 204141) with the indication being "relief of (b) (4) plaque psoriasis in patients 18 years of age or older." In its NDA submission, the applicant included a request for a waiver of the requirement to complete a pediatric assessment for children with psoriasis who are (b) (4) The Pediatric and Maternal Health Staff (PMHS) has been consulted to provide a recommendation regarding the evaluation of pediatric subjects for this Class 1/Class 2 topical corticosteroid under PREA, and in turn, this consult addresses broader questions regarding the conduct of pediatric trials to assess Hypotalamic-Pituitary-Adrenal (HPA) axis function in children receiving desoximetasone spray for treatment of plaque psoriasis.

Desoximetasone, a Class II (high potency) topical corticosteroid, is approved in the United States as a cream (0.05%, 0.25%), an ointment (0.05%, 0.25%) and a gel (0.05%) for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The Indications and Usage sections of labeling for the desoximetasone products do not specify the ages in which the products are approved; however, the Pediatric Use section of the 0.25% ointment (originally approved in 1983) states that "safety and effectiveness of Topicort® ointment in pediatric patients below 10 years have not been established" (see Appendix I; Pediatric Use Section from Topicort® 0.25% ointment labeling).

Glucocorticoid (GC) treatment is well-understood to carry the potential for central suppression of the HPA axis or, in extreme cases, complete adrenal gland atrophy. Supraphysiologic glucocorticoid doses inhibit both CRH production by the hypothalamus and ACTH production by the pituitary gland. The glucocorticoid-induced adrenal suppression, when GCs are used in supraphysiologic doses, renders the adrenal glands unable to generate sufficient cortisol if GC treatment is abruptly stopped and the patient develops GC deficiency manifestations. The true prevalence of clinically significant adrenal insufficiency and adrenal crisis is considered rare since physicians usually discontinue high-dose GCs gradually to allow recovery of the HPA axis, but this prevalence is likely to be underreported in clinical practice. Labeling for desoximetasone warns of the risk of hypothalamic-pituitary-adrenal (HPA) axis suppression, especially in pediatric patients, but no data are provided regarding clinical studies in pediatric patients.

As part of its clinical program, the sponsor conducted Trial DSXS-0805, an open-label study to assess the potential for HPA axis suppression following multiple doses of desoximetasone spray (0.25%) in patients with moderate to severe plaque psoriasis. The study enrolled 24 otherwise healthy adult patients with a confirmed diagnosis of moderate to severe plaque psoriasis, stratified by involvement of total BSA, with 12 patients having involvement of 10-15% BSA and 12 having involvement of >15% BSA. Patients were to spray study drug to the affected areas twice a day (morning and evening) for 28 days; each application was to be completely rubbed in. They were to return to the clinic for assessment of psoriasis, compliance, concomitant medication use, and adverse events on Days 7, 14, and 28. To assess effect on the HPA axis, morning serum cortisols and ACTH stimulation tests were performed at baseline, then repeated on Day 28 (± 2 days) for comparison.

Interestingly, the sponsor's approach to identifying patients with HPA axis function in Trial DSXS-0805 differed from the recommendations of DDDP. The sponsor argued that patients with a basal serum cortisol concentration >5 µg/100 mL AND a response to cosyntropin stimulation of 18 µg/dL or higher 30 minutes after stimulation (representing an increase of at least 7 µg/dL above the basal concentration) would be considered to have normal HPA axis function. DDDP suggested that, since cosyntropin stimulation is considered the "gold standard" for evaluating HPA axis function, basal serum cortisol concentrations need not be monitored. Based on the sponsor's criteria, 5/24 patients (21%) had a serum cortisol concentration at Day 28 that met at least one of the criteria for adrenal suppression (2 in the group with baseline 10-15% BSA involvement and 3 in the group with baseline > 15% BSA involvement). In the 3 patients with post-treatment follow-up, suppression reversed 28 days after the end of treatment (2 patients did not return for follow-up). In comparison, when adhering to DDDP's criteria 3/24 patients (13%) had a serum cortisol concentration at Day 28 that met at least one of the criteria for adrenal suppression (1 in the group with baseline 10-15% BSA involvement and 2 in the group with baseline > 15% BSA involvement).

In its consultation request, DDDP has requested that DMEP provide recommendations for conduct of future pediatric trials to assess HPA axis function in patients receiving desoximetasone spray (0.25%). It bears noting that based on internal discussions, the Pediatric and Maternal Health Team does not seem to support the sponsor's waiver request and specifically supports assessing HPA axis function first in a cohort of older patients (i.e., ages 12-16 years), with the consideration to pursue an assessment in children between 2-12 years of age if HPA axis dysfunction is not observed in adolescents.

DDDP's consult questions to DMEP follow below:

1. *Please provide your recommendations regarding the conduct of the HPA axis evaluation in pediatric subjects for Topicort (desoximetasone) spray, 0.25%.*
2. *What is the youngest age for subjects to be enrolled in the HPA axis evaluation for Topicort (desoximetasone) spray, 0.25% (Class 1/Class 2 topical corticosteroid)?*
3. *Should we request that pediatric subjects be evaluated in sequential cohorts (e.g. 12-16 years, 6-11 years, 2-5 years etc.)?*
4. *If sequential cohorts are recommended, what criteria would allow assessment of the next youngest cohort (e.g. percent of subjects demonstrating HPA axis suppression etc.)?*
5. *Are there any special safety considerations in the youngest pediatric subjects?*
6. *What are your recommended safety assessments during the HPA Axis trial for Topicort (desoximetasone) spray, 0.25%?*

II. Materials reviewed for consult

1. DMEP Consult Request Document from DDDP (October 9, 2012)
2. Study DSXS-0805 clinical study report.
3. "Request for Waiver of Need for Pediatric Study" from the applicant (June 11, 2012)
4. Filing Memo, NDA 204141 (desoximetasone spray, 0.25%), July 20, 2012
5. Clinical trial protocols and clinical study reports for desoximetasone Phase 3 studies.
6. Currently approved labeling for desoximetasone.

III. DMEP Comments

Biochemical Evaluation of HPA Axis Function

Topical GCs are the first line of treatment for various skin disorders such as atopic dermatitis, vitiligo, and psoriasis, and they are quite effective when applied topically and nontoxic to the skin in the short term. The amount of medication required to achieve a clinical response depends upon a number of considerations, including local penetrability, age (and therefore Body Surface Area) of the patient, and whether the drug is fluorinated. The factors that determine local penetration are the structure of the compound employed, the vehicle, the basic additives, occlusion versus open use, normal skin versus diseased skin, and small areas versus large areas of application. Fluorinated steroids (eg, dexamethasone, triamcinolone acetonide, betamethasone, beclomethasone, and desoximetasone) penetrate the skin better than nonfluorinated steroids, such as hydrocortisone. Pediatric patients, in general, require a smaller amount of steroid to achieve a clinical effect, with dosing based primarily on the patient's Body Surface Area. Roughly, infants require one fifth of adults' doses, children two fifths and adolescents two thirds of adults' doses.

One of the great concerns with chronic GC administration is the likelihood of developing any of the numerous adverse effects associated with treatment. Long-term administration of GCs can be associated with development of Cushing's syndrome, adrenal insufficiency, osteoporosis, myopathy, cardiovascular disease, glaucoma, increased incidence of infection, and behavior disturbances. Indeed, GC toxicity is one of the most common causes of iatrogenic illness associated with chronic inflammatory disorders, even with topical corticosteroids (especially higher-potency ones such as desoximetasone), which can be systemically absorbed.

Iatrogenic, tertiary adrenal insufficiency by chronic administration of high doses of GCs is the most common cause of adrenal insufficiency. Physiologically, the hypothalamus secretes CRH which stimulates the release of ACTH from the anterior pituitary. ACTH leads to the release of cortisol from the zona fasciculata of the adrenal gland, which in turn exerts negative feedback on CRH and ACTH release. Administration of exogenous GCs even in small doses for only few days leads to a measurable suppression of the HPA axis by decreasing CRH synthesis and secretion and by blocking the trophic and ACTH-releasing actions of CRH on the anterior pituitary. This

leads to suppressed synthesis of POMC, ACTH and other POMC derived peptides and later, in the atrophy of the corticotrophin cells of the anterior pituitary. As a result, in the absence of ACTH, the adrenal cortex loses the stimulatory effect to produce cortisol. It has been reported that the inhibition of the HPA axis function induced by exogenous GCs may persist for 6 to 12 months after treatment is withdrawn. Because of a higher ratio of skin surface area to body mass, children are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids, of GC insufficiency after withdrawal of treatment, and of Cushing's syndrome while on treatment.

There are a number of biochemical tests used to diagnose adrenal insufficiency in patients on chronic GC therapy, although these differ with respect to sensitivity/specificity and ease of administration. In general practice, ACTH stimulation tests are the preferred methods of detecting adrenal suppression. The conventional ACTH and the low-dose ACTH stimulation tests use ACTH (synthetic ACTH such as cosyntropin injections or infusions) to measure adrenal cortisol output and are generally reliable. The 250 µg dose is the most commonly used, and the test can be performed even in the office setting. Using 1 or 10 µg of ACTH compared with 250 µg has been suggested as more sensitive in identifying adrenal hypofunction, but these preparations require dilutions and intravenous infusions rather than the simpler intramuscular and intravenous injections by which the 250 µg dose is administered. For the diagnosis of adrenal insufficiency (in both adults and children), cut-off 30-minute values for the 1-microgram test are <18 to 20 µg/dL in non-stressed patients and <25 µg/dL or an increase of <9 µg/dL from baseline in critically ill patients. The ACTH stimulation test may be unreliable in patients with recent onset of HPA axis suppression where the adrenal glands have not had sufficient time to atrophy. If patients are taking hydrocortisone or prednisolone, it is recommended to withhold the treatment for 24 hours before the test in order to avoid false positives. Other corticosteroid preparations, such as desoximethasone, do not cross-react with the cortisol assay used for the ACTH stimulation test.

An early morning random cortisol is the simplest diagnostic test and commonly used in general practice for this reason, but results are usually inconclusive, necessitating one of the more cumbersome but more reliable stimulation tests for confirmation. Because ACTH has been suppressed by the exogenous corticosteroid, serum cortisol is expected to be low. Values below 110 nmol/L (4 µg/dL) are consistent with HPA axis suppression. Values between 110 and 469 nmol/L (4 and 17 µg/dL) are inconclusive. Indeterminate values require confirmation with one of the stimulation tests to safely discontinue corticosteroid therapy. Random serum cortisol levels, or ACTH levels, are not recommended as reliable indicators of adrenal status. In lieu of completing one of the stimulation tests, many physicians prefer to proceed with a corticosteroid tapering program. When the morning serum cortisol value is >497 nmol/L (18 µg/dL), corticosteroids can be safely discontinued.

Midnight salivary cortisol has been recognized as an excellent diagnostic tool for identifying Cushing's syndrome but there has been increased interest in morning salivary cortisols as a means of screening for adrenal insufficiency. Studies have found that morning serum cortisol levels are equivalent to salivary cortisol levels at differentiating adrenal insufficiency from normal adrenal function. Salivary cortisols may be especially useful for patients with hepatic disease who have hypoalbuminaemia and cirrhosis where salivary cortisol levels correlate better with adrenal function and plasma free cortisol than do total plasma cortisols.

The insulin tolerance test (ITT) and the overnight metyrapone test, although somewhat cumbersome, evaluate the entire HPA axis and are capable of assessing partial adrenal

suppression. ITT can be used if there is concomitant need to determine whether the patient also has growth hormone deficiency, for which the ITT is also a diagnostic test. Both ITT and metyrapone tests can be used if it is pertinent to know whether the patient has secondary adrenal insufficiency due to a recent pituitary insult (e.g., pituitary surgery). In this situation, the adrenal glands can still mount a normal response to the ACTH stimulation test up to 2 to 3 weeks after the pituitary insult because of adrenal reserve. However, the ITT may uncover that the pituitary gland is not capable of responding to stress. Because the ITT relies on production of symptomatic hypoglycemia to stimulate cortisol release, it evaluates the entire HPA axis but has the associated risk of hypoglycemic seizures and must be performed under close observation. It is not recommended for frail or older patients with cardiovascular disease or seizures. The metyrapone test also evaluates the entire HPA axis but is associated with the theoretical, although unlikely, potential to precipitate acute adrenal insufficiency.

Table 1 below reviews the most frequently used diagnostic modalities to evaluate HPA axis function in patients with suspected adrenal insufficiency:

Table 1: Common tests for evaluation of adrenal insufficiency

Most useful tests	**Results**
ACTH stimulation test • 250 micrograms IV or IM • Obtain plasma cortisol levels at 0, 30, and 60 minutes	Normal if cortisol >497 nanomol/L (18 micrograms/dL) at any point of time.
Useful but less practical tests	**Results**
Insulin tolerance test (ITT) • 0.1 to 0.15 units/kg short-acting insulin IV • Obtain plasma glucose and cortisol levels at 0, 30, and 60 minutes	Normal if cortisol ≥497 nanomol/L (18 micrograms/dL) with symptomatic hypoglycaemia and glucose <2.2 mmol/L (40 mg/dL).
Metyrapone test • 30 mg/kg (maximum 3 g) given orally at midnight • Cortisol and 11-deoxycortisol levels are taken at 8 a.m. on the following day	Normal if 11-deoxycortisol >200 nanomol/L (7 micrograms/dL) regardless of cortisol level.
ACTH stimulation test – lower doses • 1 microgram IV or 10 micrograms IV • Obtain plasma cortisol levels at 0, 30, and 60 minutes	Normal if cortisol >497 nanomol/L (18 micrograms/dL) at any point of time.
Tests useful in uncertain cases	**Results**
Urine screen for synthetic glucocorticoids	If positive, shows systemic absorption of exogenous glucocorticoids.
Useful but less definitive tests	**Results**
Morning serum cortisol	• ≥497 nanomol/L (18 micrograms/dL): normal • 110 to 469 nanomol/L (4 to 17 micrograms/dL): inconclusive, best to proceed to a stimulation test • <110 nanomol/L (4 micrograms/dL): suggests adrenal insufficiency
Least useful tests	**Results**
Random serum cortisol	• ≥497 nanomol/L (18 micrograms/dL): normal • <497 nanomol/L (18 micrograms/dL): inconclusive
Serum ACTH levels	Usually normal or low, but may be high if the hypothalamic-pituitary-adrenal axis is recovering.
24-hour urinary free cortisol	Not useful.

Source: Lansang MC, Quinn SL. Best Practice: Diagnosis of Adrenal Insufficiency. BMJ Best Practice. 2012: Sep 6.

Sponsor's Waiver Request for Pediatric Studies

This DMEP reviewer has had a number of internal discussions with members of the PMHS regarding the [redacted] (b) (4) waiver of pediatric studies. In brief, PMHS believes an argument can be made for characterizing HPA axis suppression in this product, starting with adults, then adolescents before proceeding to younger children.

Precedent exists for requiring studies of potent topical steroids under PREA in patients 12 to 16 years: the PREA PMR for Taclonex® (calcipotriene/betamethasone dipropionate) ointment requires studies in patients 12-16 years, and PMHS believes this is sufficient justification to pursue HPA axis evaluation in this age range, at a minimum. Regarding patients < 12 years of age, although consensus exists that topical corticosteroids pose a greater risk of HPA axis suppression in this age group, the risk of HPA axis suppression secondary to topical corticosteroid use may not be fully characterized. Labeling for betamethasone dipropionate cream (a high potency corticosteroid) describes HPA axis suppression in 32 % of patients studied (aged 3 months to 12 years) and states that its use in pediatric patients 12 years of age and younger is not recommended. Due to this safety concern, a partial waiver of studies in patients birth to 12 years was granted for Taclonex® ointment, and a partial waiver of studies in patients in this age range is planned for Taclonex® scalp suspension. Similarly, HPA axis suppression was noted in 64% of adolescents with atopic dermatitis receiving Clobex lotion (clobetasone propionate) for 2 weeks and notably 80% of adults treated for 4 weeks. Consequently, use in pediatric patients is not recommended. On the other hand, HPA axis suppression ranged from 3-6% in pediatric atopic dermatitis patients receiving 0.1% fluocinonide cream (another super-high potency topical steroid). Therefore, the evidence for suppression among various high-potency topical corticosteroids is inconsistent.

Based on the above, PMHS believes that evaluation of desoximetasone in patients aged 12-16 years should be performed first before moving to younger pediatric patients. It believes that if studies show significant HPA axis suppression in adolescents, a partial waiver for younger patients can be granted at that time, with labeling to be updated to reflect the safety concern. From this reviewer's perspective, PMHS's recommendations appear reasonable.

IV. DMEP responses to DDDP questions

1. *Please provide your recommendations regarding the conduct of the HPA axis evaluation in pediatric subjects for Topicort (desoximetasone) spray, 0.25%.*

DMEP agrees with DDDP's criteria to define normal HPA axis function in patients receiving desoximetasone spray, namely response to cosyntropin stimulation of 18 µg/dL or higher 30 minutes after stimulation. We would recommend that testing be performed as per the "standard" protocol, namely a cosyntropin dose of 250 µg, with serum cortisol levels measured at T=0, 30, and 60 minutes, with a cutoff value of >18 µg/dL at any point of time being considered normal. Because the proposed labeling suggests 4 weeks as the cut-off point for consideration of discontinuation of therapy, and because there is no data in adults beyond 4 weeks of therapy, we recommend that stimulation testing be performed at baseline and then at 28 days following initiation of therapy. Consideration should also be given to clinical monitoring for patients who develop adrenal suppression while on therapy, or referral to an endocrinologist.

Since cosyntropin stimulation testing is considered the gold standard for diagnosis of adrenal insufficiency in both adult and pediatric patients, we do not believe there is a need to perform basal morning cortisol levels, which is a less sensitive measure that is easy to misinterpret.

2. *What is the youngest age for subjects to be enrolled in the HPA axis evaluation for Topicort (desoximetasone) spray, 0.25% (Class 1/Class 2 topical corticosteroid)?*

DMEP agrees with PMHS's recommendation for enrollment of pediatric patients: evaluation of desoximetasone in patients aged 12-16 years should be performed first before moving to younger pediatric patients. If studies show significant HPA axis suppression in adolescents, a partial

waiver for younger patients would be a reasonable consideration, with labeling to be updated to reflect the safety concern.

3. *Should we request that pediatric subjects be evaluated in sequential cohorts (e.g. 12-16 years, 6-11 years, 2-5 years etc.)?*

Please see response to Question 2 above. We do recommend that pediatric patients should be evaluated in sequential cohorts, with consideration given to starting with those ages 12-16 years, followed by 6-11 years, then 2-5 years, pending findings in the older cohort.

4. *If sequential cohorts are recommended, what criteria would allow assessment of the next youngest cohort (e.g. percent of subjects demonstrating HPA axis suppression etc.)?*

We agree with PMHS that adolescent patients should be evaluated first, and if there is no major safety signal for adrenal suppression, the sponsor may consider moving to younger patients. There is no set precedent in previous pediatric studies that defines a concerning percentage of patients demonstrating HPA axis suppression. Nonetheless, one might consider using the findings from Trial DSXS-0805 in adults to help guide whether the sponsor can move to the next cohort. Based on the sponsor's criteria, 21% of patients experienced HPA axis suppression, whereas using DDDP's criteria (with which DMEP agrees), only 15% experienced suppression. When considering these findings, along with those taken from other select studies (please see Section III of this review), a cutoff in the 20-30% range seems reasonable.

5. *Are there any special safety considerations in the youngest pediatric subjects?*

Young children who present with adrenal suppression may manifest nonspecific clinical signs and symptoms, including hypotension and/or tachycardia, weakness/lethargy, fatigue, vomiting, and dehydration. The investigational plan for Trial DSXZS-0805 included clinic visits for physical examination and adverse event reporting, which is also reasonable for a pediatric study.

6. *What are your recommended safety assessments during the HPA Axis trial for Topicort (desoximetasone) spray, 0.25%?*

Given the short-term nature of the study, the most useful safety assessments would include cosyntropin (ACTH) stimulation testing at baseline and Day 28, as well as weekly physical examinations to rule out the signs and symptoms listed in the response to Question 5 above.

Ali Mohamadi, MD
Medical Officer

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/s/

ALI MOHAMADI
12/05/2012

DRAGOS G ROMAN
12/05/2012

MARY H PARKS
12/05/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
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M E M O R A N D U M

Date: November 26, 2012

From: Elizabeth Durmowicz, MD Medical Officer
Hari Cheryl Sachs, MD, Team Leader

Through: Lynne Yao, MD, OND Acting Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Melinda McCord, MD, Clinical Reviewer
Gordana Diglisic, MD, Clinical Team Leader
Division of Dental and Dermatology Products (DDDP)

Re: PREA requirements

Applicant: Taro Pharmaceuticals

Drug: desoximetasone spray

NDA: 204141

Supporting Doc: Original NDA (June 11, 2012):
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Indication (proposed): relief of (b) (4) plaque psoriasis in adults

Dosage form/strength: topical spray (0.25%)

Consult Question: "Please provide your recommendation regarding the evaluation of pediatric subjects for this Class 1/Class 2 topical corticosteroid under PREA".

Materials Reviewed:

- PMHS Consult Request Document from DDDP (June 1, 2011)

- "Request for Waiver of Need for Pediatric Study" from the applicant (June 11, 2012
- Filing Memo, NDA 204141 (desoximetasone spray, 0.25%), July 20, 2012
- PMHS Sorilux (calcipotriene, NDA 22-563) Consults, May 20, 2010 and June 16, 2011.
- PMHS Pandel® Consult (hydrocortisone probutate, NDA 20-453) February 17, 2012
- Written Request for calcipotriene and the combination of calcipotriene and betamethasone issued to NDA 20-273, 20-611, 20-554 and 21-852 (February 20, 2007)

Brief Regulatory Background:
Desoximetasone, a topical corticosteroid, is marketed as a cream (0.05%, 0.25%), an ointment (0.05%, 0.25%) and a gel (0.05%), and is approved for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The Indications and Usage sections of labeling for the desoximetasone products do not specify the ages in which the products are approved; however, the Pediatric Use section of the 0.25% ointment (originally approved in 1983) states that "safety and effectiveness of Topicort® ointment in pediatric patients below 10 years have not been established" (see Appendix I; Pediatric Use Section from Topicort® 0.25% ointment labeling). Labeling warns of the risk of hypothalamic-pituitary-adrenal (HPA) axis suppression, especially in pediatric patients. No data are provided regarding clinical studies in pediatric patients.

Taro Pharmaceuticals submitted an NDA for desoximetasone (Topicort®) spray, 0.25%, (per the division, a Class 1/Class 2 topical steroid) for the relief of (b) (4) plaque psoriasis in patients 18 years of age or older on June 11, 2012. The applicant has requested a (b) (4) waiver of studies under PREA, (b) (4)

1. (b) (4)
2. (b) (4)
3. Other approved topical corticosteroid products exist.
4. (b) (4)

Discussion:

Under PREA, a full waiver may be granted if

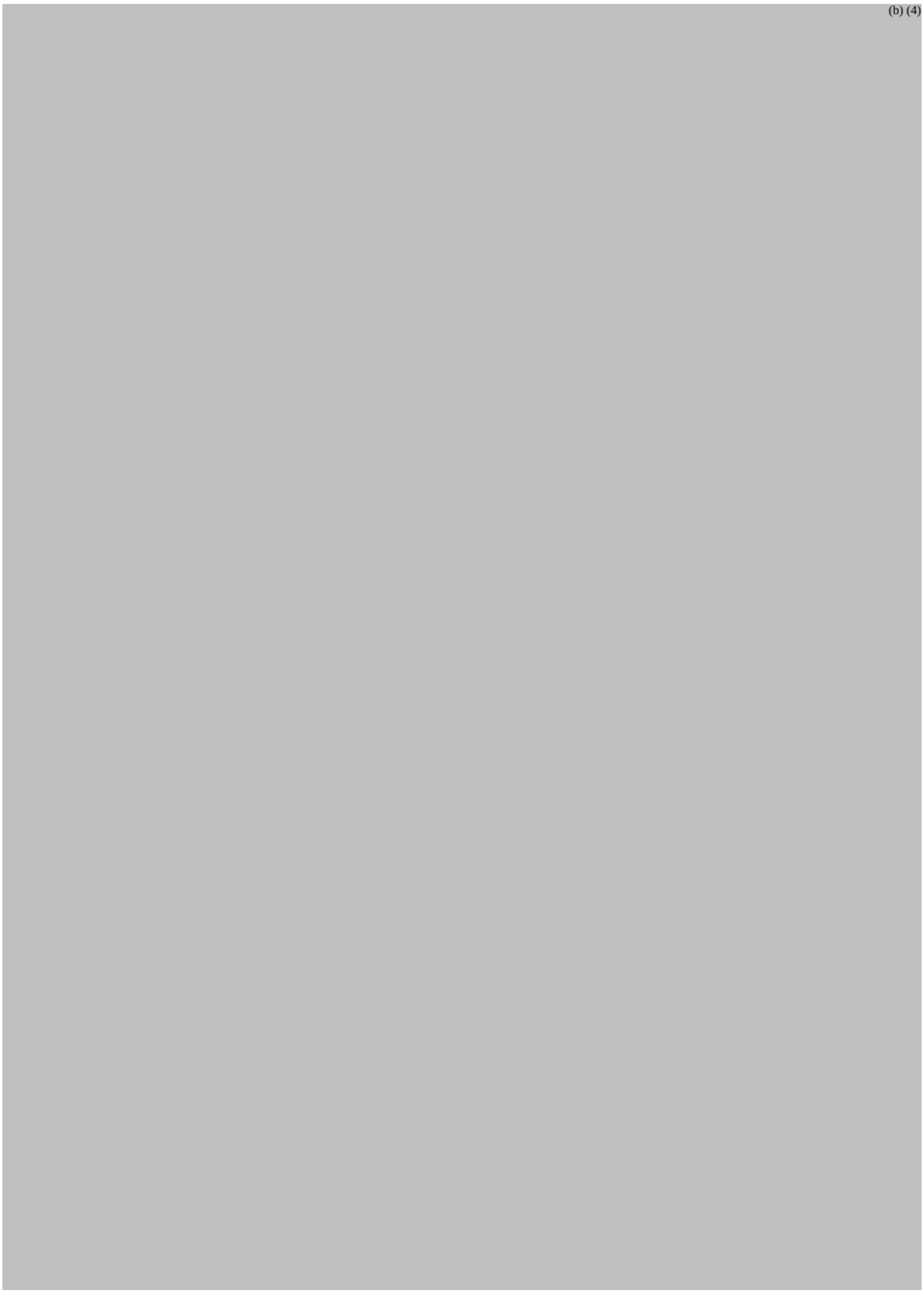
(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small);

(ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups;

or

(iii) the drug or biological product (I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and (II) is not likely to be used in a substantial number of pediatric patients.

(b) (4)



(b) (4)

Desoximetasone Spray and HPA Axis Suppression

Per the consult request from the Division and the Clinical Pharmacology Review for the Filing Memo, HPA axis suppression in adults following application of desoximetasone spray was identified; however, using FDA criteria, the finding is not statistically significant. According to the criteria used by the applicant (basal serum cortisol concentration greater than 5 μg/100 mL and response to cosyntropin stimulation of 18 μg/dL or higher 30 minutes after stimulation), 5/24 adult subjects (21%) had a serum cortisol concentration at Day 28 that met at least one of the criteria for adrenal suppression (2 in the group with baseline 10-15% BSA involvement and 3 in the group with baseline greater that 15% BSA involvement). However, per the criteria recommended by FDA (only response to cosyntropin stimulation of 18 μg/dL or higher 30 minutes after stimulation) 3/24 adult subjects (13%) had a serum cortisol concentration at Day 28 that met at least one of the criteria for adrenal suppression (1 in the group with baseline 10-15% BSA involvement and 2 in the group with baseline greater than 15% BSA involvement). In the 3 patients with post-treatment follow-up, suppression reversed 28 days after the end of treatment (2 patients did not return for follow-up). In addition, response to an information request regarding the validity of the cortisol assays is pending.

Reviewer Comment:
If the division concludes that the percent of adults experiencing HPA axis suppression is not clinically significant and/or the HPA axis suppression is reversible, studying this product in older pediatric patients appears to be reasonable. Precedent exists for requiring studies of potent topical steroids under PREA in patients 12 to 16 years: the PREA PMR for Taclonex® (calcipotriene/betamethasone dipropionate) ointment requires studies in patients 12-16 years, and, per the meeting minutes of the Pediatric Review Committee (September 19, 2012), DDDP intends to require studies of Taclonex® (calcipotriene/betamethasone dipropionate) scalp suspension in patients 12-16 years.

For patients < 12 years of age, the decision is not as straightforward. Consensus exists that topical corticosteroids pose a greater risk of HPA axis suppression in pediatric patients than adult patients due to the higher skin surface-to-body mass ratios in children, and that the risk of HPA axis suppression is related to the potency of the steroid, the body surface area treated and the duration of treatment. However, the risk of HPA axis suppression secondary to the use of high potency topical corticosteroids such as desoximetasone may not be fully characterized in pediatric patients. For example, labeling for betamethasone dipropionate cream (a high potency corticosteroid) describes HPA axis suppression in 32 % of patients studied (aged 3 months to 12 years) and states that use of betamethasone dipropionate cream in pediatric patients 12 years of age and younger is not recommended. The labeling also provides data supporting that the proportion of patients with adrenal suppression was progressively greater the younger the age group, Thus, due to the safety concern of HPA axis suppression in younger patients for betamethasone, a partial waiver of studies in patients birth to 12 years was granted for Taclonex® ointment, and a partial waiver of studies in patients birth to 12 years is planned for Taclonex® scalp suspension. Similarly, HPA axis suppression was noted in 64% of adolescents with atopic dermatitis receiving Clobex lotion (clobetasol propionate) for 2 weeks and notably 80% of adults treated for 4 weeks. Consequently, use in pediatric patients is not recommended for this high potency topical steroid.

On the other hand, not all high potency topical steroids demonstrate this degree of HPA axis suppression in pediatric patients. Although labeling for Vanos (0.1% fluocinonide cream) indicates that use in pediatric patients is not recommended, HPA axis suppression ranged from 3-6% in pediatric atopic dermatitis patients and no HPA axis suppression was observed in the youngest cohort (3 months to 2 years of age). Based on this study, Schlessinger, et al, that concluded that "the frequency of HPA axis suppression is no greater in younger children than in older children."[2] Similarly, Elocon (mometasone furoate) is approved for patients 2 years and older. HPA axis suppression was noted in 27% of 6-23 month olds treated with this high potency steroid.

There is an apparent lack of a predictable pattern of HPA axis suppression for these products, and HPA axis studies in pediatric patients receiving desoximetasone have not been performed. Therefore, PMHS recommends that the division consider characterizing HPA axis suppression in this product, starting with adults, then adolescents before proceeding to younger children. Consultation from the Division of Endocrinology may be helpful to harmonize the approach for topical steroid products.

Division's Consult Question:
"Please provide your recommendation regarding the evaluation of Pediatric subjects for this Class 1/Class 2 topical corticosteroid under PREA"

Response:
PMHS believes unless a significant number of adults experience HPA axis suppression during the adult study using a validated assay, requiring studies of desoximetasone spray in pediatric patients 12-16 years under PREA appears to be reasonable.

For patients less than 12 years of age, if HPA axis suppression is not observed in adolescents, PMHS believes that additional information about HPA axis suppression would be needed. Data describing the amount of HPA axis suppression on desoximetasone is not available. One class 2 steroid, Elocon (mometasone) ointment 0.1 %, is approved in pediatric patients 2 years and older. In addition, the risk/benefit of using a potent topical corticosteroid may be more favorable than that of alternative therapies that may be used, such as TNF blockers, methotrexate and cyclosporine. Thus, PMHS believes DDDP should also require pediatric studies in this age group. Given the epidemiology of psoriasis, studies in pediatric patients less than 2 years of age may not be feasible and a partial waiver in patients less than 2 years of age would be reasonable. Thus, PMHS believes a deferral in pediatric patients 2 years of age based on the product being ready for approval in adults would be appropriate.

PMHS recommends that evaluation of desoximetasone in adolescents should be performed before moving to younger pediatric patients. If studies show that significant HPA axis suppression is occurring in adolescents and DDDP determines that studies in younger pediatric patients should not be pursued due to safety findings, a partial waiver for the younger cohort of patients for on safety can be granted at that time. Labeling would need to be updated to reflect the safety concern.

Recommendation
A partial waiver in pediatric patients less than 2 years of age is reasonable based on the epidemiology of pediatric psoriasis. However, given the lack of pediatric HPA axis suppression data with desoximetasone, and the risk/benefit ration posed by alternative therapies, PMHS recommends the sponsor be asked to submit a pediatric plan addressing patients 2 years and older, which outlines studying HPA axis suppression; first in adolescents and then in younger children before proceeding to any confirmatory efficacy studies. In order to support their waiver request, the sponsor should also submit topical steroid use data for class 1 and 2 products to augment the epidemiological data that has been provided.

APPENDIX I: Pediatric Use Section from Topicort® 0.25% Ointment Labeling

Pediatric Use

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio. HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids.

Manifestations of adrenal suppression in pediatric patients include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to pediatric patients should be limited to the least amount compatible with an effective therapeutic regimen.

Chronic corticosteroid therapy may interfere with the growth and development of pediatric patients. Safety and effectiveness of TOPICORT Ointment in pediatric patients below the age of 10 have not been established.

APPEARS THIS WAY ON ORIGINAL

APPENDIX II: HPA Suppression for Class I and II Topical Steroids

Class	Brand	Generic	Indication	Adult HPA Axis Studies	Approved Pediatric Age Group	Specific Pediatric HPA studies	Pediatric Studies
I	Clobex lotion 0.05 %	clobetasol propionate	Corticosteroid (CSS)-responsive dermatoses	PSO x 4 weeks 8/10 (80%) Atopic Dermatitis (AD) x 2 weeks 5/9 (55%)	Not recommended	AD x 2 weeks 12-17 year olds: 9/14 (64%)	Assessment considered complete for patients 12 years and older; partial waiver for safety < 12 years of age
	Clobex shampoo (0.05%)	clobetasol propionate	Moderate to severe scalp psoriasis (PSO)		Not recommended	PSO x 4 weeks 12-17 year olds: 5/12 (42%)	
	Olux foam (0.05%)	clobetasol propionate	CSS-responsive dermatoses	AD x 2 weeks 12 years and older 6/37 (16 %)	12 years and older	AD x 2 weeks 6-11 year olds 7/15 (47%)	
	Temovate cream & ointment 0.05%	clobetasol propionate	CSS-responsive dermatoses		12 years and older		N/A
	Cordran tape (4 mcg per m^2)	flurandrenolide	CSS-responsive dermatoses		No age specified		N/A
	Diprolene ointment and cream 0.05%	betamethasone dipropionate	CSS-responsive dermatoses		13 years and older	AD x 2-3 weeks 3 mo- 12 year olds 19/60 (32%) 9-12 year olds (17%) 6-8 year olds (32%) 2-5 year olds (38%) 3 months- 1 year old (50%)	Written Request (WR) issued 7/19/1999; amended 4/19/2000 Pediatric Exclusivity (PE) not granted
	Taclonex ointment	calcipotriene hydrate and betamethasone	Psoriasis vulgaris	PSO x 4 weeks 5/32 (15.6%)	SENE (pediatric patients under 12 may be at		Deferral for pediatric studies ages 12-17 years of age; partial waiver

	Taclonex scalp	betamethasone dipropionate and calcipotriene hydrate	Moderate to severe psoriasis vulgaris of the scalp	Trial A PSO x 4 weeks 5/32 (15.6%) PSO x 8 weeks 2/11 (18.2%) Trial B PSO x 4 weeks 3/43 (7%) PSO x 8 weeks 0/36	particular risk		for safety in patients < 12 years of age
	Psorcon ointment 0.05%	diflorasone diacetate	CSS-responsive dermatoses		SENE		N/A
	Ultravate ointment and cream 0.05%	halobetasol dipropionate	CSS-responsive dermatoses		12 years and older		N/A
	Vanos cream	fluocinonide	CSS-responsive dermatoses	PSO 2/18 (11 %) AD 1/31 (3 %)	12 years and older	AD 12 - < 18 year olds 1/31 (3 %) 6 - < 12 year olds 2/30 (6.6%) 2 - < 6 years of age: 1/30 (3 %) 3 mo - < 2 years: none	PREA requirement related to atopic dermatitis
II	Cyclocort ointment 0.1%	amcinonide	CSS-responsive dermatoses		No age specified		N/A
	Diprosone ointment 0.05%	betamethasone dipropionate	CSS-responsive dermatoses		13 years and older	AD x 2-3 weeks 6 mo- 12 years (28%)	N/A
	Elocon ointment 0.1%	mometasone furoate	CSS-responsive dermatoses		2 years and older	AD x 3 weeks 6-23 months (27%)	WR issued 3/171999, amended 12/15/2000 and 9/5/2001 PE granted 11/7/2001
	Florone	diflorasone	CSS-responsive		Safety and		N/A

	ointment 0.05%	diacetate	dermatoses		effectiveness not established (SENE)		
	Halog cream and ointment 0.1%	halcinonide	CSS-responsive dermatoses		No age specified		N/A
	Lidex cream, gel, ointment and solution 0.05%	fluocinonide	CSS-responsive dermatoses		No age specified		N/A
	Topicort cream 0.25% & gel 0.05%	desoximetasone	CSS-responsive dermatoses		No age specified		N/A
	Topicort ointment 0.25%	desoximetasone	CSS-responsive dermatoses		10 years and older		None described

SENE- Safety and effectiveness have not been established

APPENDIX III: Examples of Products with PREA PMRs to Study Psoriasis in Pediatric Patients

Product	Trade Name/NDA	Approval Date	Indication	PREA PMR
calcitriol Ointment, 3 mcg/g	Vectical® NDA 22-087	01/23/2009	treatment of plaque psoriasis	Waiver: 0-2 years* Deferral: 2-16 years†
calcipotriene and betamethasone ointment	Taclonex® NDA 21-852	01/09/2006	topical treatment of psoriasis vulgaris in adults	Waiver: 0-11years+ Deferral: 12-16 years†
calcipotriene foam, 0.005%	Sorilux™ NDA 22-563	10/06/2010	treatment of plaque psoriasis in patients aged 18 years and older	Waiver: 0-2 years* Deferral: 2-16 years†
ustekinumab	Stelara™ BLA 125261	09/25/20009	Treatment of adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy	Deferral: Birth – 16 years#
alefacept	Amevive BLA 125036	01/30/2003	Treatment of adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy	Deferral: Birth – 16 years# (Sponsor to first conduct study in patients 12 – 17 years)

* Waiver granted based on too few patients too study
† Deferral granted based on product ready for approval in adults
+ Waiver granted based on data suggesting that the product would be unsafe secondary to betamethasone component resulting in potential HPA suppression.
# Deferral granted based on additional safety data needed in adults.

REFERENCES

1. Silverberg NB. Pediatric psoriasis: an update. *Ther Clin Risk Manag*. 2009;5:849-56.

2. Schlessinger J, Miller B, Gilbert RD, Plott RT. An open-label adrenal suppression study of 0.1% fluocinonide cream in pediatric patients with atopic dermatitis. *Arch Dermatol.*2006;142:1568-1572.

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/s/

HARI C SACHS
11/27/2012

LYNNE P YAO
12/03/2012

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

Application: NDA 204141

Application Type: New NDA

Name of Drug: (desoximetsone) Spray, 0.25%

Applicant: Taro Pharmaceuticals USA, Inc.

Submission Date: June 11, 2012

Receipt Date: June 12, 2012

1.0 Regulatory History and Applicant's Main Proposals

The active moiety (desoximetasone) was originally approved in 1977 as Topicort (desoximetasone) Cream, 0.25%. Since that time, there have been subsequent approvals for additional dosage forms for Gel (0.05%) and Ointment (0.05%, 0.25%).

On February 27, 2008 the sponsor submitted a new IND for desoximetasone spray. The sponsor chose not to submit and SPA or an EOP-2 meeting request. On July 20, 2011 a pre-NDA meeting was held with the sponsor. On June 11, 2012, the sponsor submitted their NDA.

In the current NDA (204141) the sponsor (Taro) has submitted information for the newest dosage form, Spray (0.25%).

2.0 Review of the Prescribing Information (PI)

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

3.0 Conclusions/Recommendations

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

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 7, 2012. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

NO 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *The Highlights and Table of Contents (TOC) in the applicant proposed MS Word labeling currently is in 12-point font, standard margins, and not in two column format. The Highlights and TOC need to be changed to the format, size and margins described above.*

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *See comment #1 above. Once formatting is corrected, the content will be reassessed.*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

NO 4. White space must be present before each major heading in HL.

Comment: *Some of the section headers are not preceeded by white space. A hard return (i.e. blank space) should be added before each of the section headers in Highlights..*

NO

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

Comment: *The reference needs to be added at the end of the Adverse Reactions section in Highlights.*

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

NO 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment: *The product title currently appears before the Highlights heading and should be deleted.*

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *The limitation statement contains the full product title rather than just the proprietary name. Only the proprietary name, in all caps, should appear in the Highlights limitation statement.*

Product Title

YES

10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Remove the empty line (extra space) between the route of administration line and the Initial US Approval line.*

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment: *Generic hypersensitivity statement. Is this discouraged under PLR?*

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

NO 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *The following words should be deleted from the adverse reactions reporting statement "between 7AM and 7PM Monday thru Friday Central Time," so that it reads verbatim as outlined above.*

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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

- **"See 17 for PATIENT COUNSELING INFORMATION"**

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

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

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *Replace "Issued" with "Revised" in front of the date at the end of highlights.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE

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

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

NO 45. If no Contraindications are known, this section must state "None".

Comment: *PLR format discourages use of theoretical contrainidications. Unless documented hypersensitivity has occurred, this section should list "None" in both Highlights and in FPI.*

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *Applicant will need to add the appropriate reference "See FDA-approved patient labeling (Patient Information)" on the line immediately following the section 17 heading in FPI.*

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

/s/

J P PHILLIPS
07/18/2012

BARBARA J GOULD
07/18/2012