

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203567Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

NDA/BLA # 203567

Product Name: Jublia (efinaconazole) topical solution, 10%

PMR/PMC Description: A Multicenter, Randomized, Double-Blind Study Evaluating the Safety, Efficacy and Pharmacokinetics of Jublia Topical Solution, 10% versus Vehicle in Pediatric Subjects ages 12 to 17 years with Onychomycosis of the Toenails

PMR/PMC Schedule Milestones:	Final Protocol Submission:	09/30/2014
	Study/Trial Completion:	03/31/2018
	Final Report Submission:	09/30/2018
	Other:	MM/DD/YYYY

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

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

There is insufficient data provided by the sponsor for subjects ages 12 through 17. Therefore additional studies are required under PREA. Since the adult studies are completed and Jublia is ready for approval, then a deferral of PREA studies is appropriate.

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

This application triggers PREA. The goal of the pediatric study is to obtain pediatric safety data.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

- ☐ Analysis using pharmacovigilance system?

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

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

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

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

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

The pediatric trial will enroll subjects 12 years and older and pharmacokinetics will be assessed under maximal use conditions.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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

/s/

STROTHER D DIXON
05/28/2014

DAVID L KETTL
05/29/2014

TATIANA OUSSOVA
05/30/2014

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

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

Application: NDA 203567

Application Type: New NDA (Resubmission)

Name of Drug/Dosage Form: Jublia (efinaconazole) topical solution, 10%

Applicant: Dow Pharmaceutical Sciences

Receipt Date: December 20, 2013

Goal Date: June 20, 2014

1. Regulatory History and Applicant's Main Proposals

The sponsor originally submitted NDA 203567 (efinaconazole) topical solution, 10% on July 25, 2012. The Division of Dermatology and Dental Products issued the sponsor a complete response letter on May 13, 2013 due to Chemistry, Manufacturing and Controls (CMC) deficiencies. The sponsor resubmitted the NDA on December 20, 2013.

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

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

All SRPI format deficiencies of the PI will be conveyed to the applicant via email and in an attached red-lined label. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 16, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

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

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

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

Comment:

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

Instructions to complete this item: If the length of the HL is one-half page or less, 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 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” 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:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

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

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

Selected Requirements of Prescribing Information

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

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

Comment:

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

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

- YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

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

Selected Requirements of Prescribing Information

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

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

Comment:

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

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

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

Comment:

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

Comment:

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

Comment:

Indications and Usage in Highlights

YES

Selected Requirements of Prescribing Information

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

Comment:

Dosage Forms and Strengths in Highlights

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

Comment:

Contraindications in Highlights

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

Comment:

Adverse Reactions in Highlights

- YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

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

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

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

Comment:

Revision Date in Highlights

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

Comment: *The date will be reflected as “MM/2014” until the time of action.*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information

- N/A 34. 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

FPI Heading

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

Comment:

BOXED WARNING Section in the FPI

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

Comment:

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

Comment:

CONTRAINDICATIONS Section in the FPI

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

Comment:

ADVERSE REACTIONS Section in the FPI

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

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

Comment: Added “observed” and deleted (b) (4)

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

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

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

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

Selected Requirements of Prescribing Information

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)]

[m/year]

[section (X.X)]

[m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

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

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

1.1 [text]

1.2 [text]

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

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

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

/s/

STROTHER D DIXON
04/22/2014

BARBARA J GOULD
04/30/2014

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

PATIENT LABELING REVIEW

Date: March 31, 2014

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: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Puja Shah, PharmD
Regulatory Reviewer Office
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): JUBLIA (efinaconazole)

Dosage Form and Route: topical solution, 10%

Application Type/Number: NDA 203-567

Applicant: Dow Pharmaceutical Sciences

1 INTRODUCTION

On December 20, 2013, Dow Pharmaceutical Sciences submitted for the Agency's review a New Drug Application (NDA) 203-567 for JUBLIA (efinaconazole) topical solution in response to a Complete Response (CR) letter issued on May 13, 2013. This Class 2 resubmission includes updated labels and responses to the product quality and labeling deficiencies. The proposed indication for JUBLIA (efinaconazole) topical solution is for the topical treatment of onychomycosis of the toenails due to *Trichophyton mentagrophytes* and *Trichophyton rubrum*.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on January 24, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for JUBLIA (efinaconazole) topical solution.

2 MATERIAL REVIEWED

- Draft JUBLIA (efinaconazole) topical solution PPI received on December 20, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on January 24, 2014.
- Draft JUBLIA (efinaconazole) topical solution PPI received on December 20, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on March 17, 2014.
- Draft JUBLIA (efinaconazole) topical solution Prescribing Information (PI) received on December 20, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 17, 2014.
- Draft KERYDIN (tavaborole) comparator labeling dated February 18, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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

/s/

NATHAN P CAULK
03/31/2014

PUJA J SHAH
03/31/2014

BARBARA A FULLER
03/31/2014

LASHAWN M GRIFFITHS
03/31/2014

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

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

Memorandum

Date: March 28, 2014

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

From: Puja Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Lynn Panholzer, PharmD
Regulatory Review Officer, OPDP

Subject: NDA 203567
JUBLIATM (efinaconazole) topical solution, 10%

Background

This consult review is in response to DDDP's January 24, 2014, request for OPDP's review of the draft package insert (PI), carton/container labeling, and patient package insert (PPI) for JUBLIATM (efinaconazole) topical solution, 10%. OPDP reviewed the substantially complete version of the draft PI provided by the Division of Medical Policy Programs (DMPP) on March 28, 2014, and the carton/container labeling accessed via eRooms on March 21, 2014. Our comments on the PI are included directly on the attached copy of the labeling, and our comments on the carton/container labeling are listed below.

Carton/Container Labeling Comments

- OPDP is concerned about the lack of prominence of the established name on the carton and container labeling. The JUBLIA tradename is in bolded font, while the established name is in unbolded font, and thus less prominent. We recommend that the applicant revise the established name to reflect comparable prominence as the JUBLIA tradename.

- Furthermore, we note that the carton and container labeling includes an exact storage temperature of (b) (4) rather than the storage temperature range of 20°C – 25°C (68°F – 77 F) in section 16 of the draft PI. If appropriate, OPDP recommends the applicant revise the carton and container labeling to fully reflect the temperature range.
- We note that carton and container labeling include the following (emphasis original):
 - **“Usual dosage:** Apply to affected nail(s) once daily. See package insert for full Prescribing Information.

WARNING: For use on nails and immediately adjacent skin only.”

OPDP recommends changing (b) (4) to “toenails” to be consistent with the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the proposed PI.

Our review of the PPI and IFU was conducted jointly with DMPP and will be filed under separate cover.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov

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

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

/s/

PUJA J SHAH
03/28/2014

LABEL AND LABELING REVIEW

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

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

Date of This Review:	March 14, 2014
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 203567
Product Name and Strength:	Jublia (Efinaconazole) Topical Solution, 10%
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Dow Pharmaceutical Sciences
Submission Date:	12/20/2013
OSE RCM #:	2014-265
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Associate Director:	Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

This review responds to a request from DDDP to evaluate the proposed container labels and carton labeling for Jublia for areas of vulnerability that could lead to medication errors. Jublia is a new molecular entity (NME) currently under review.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	n/a
Previous DMEPA Reviews	B
Human Factors Study	n/a
ISMP Newsletters	n/a
Other	n/a
Labels and Labeling	C

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant is proposing to market Jublia in 4 and 8 mL bottles. The product is to be applied once daily to the surface of affected toe nails using the integrated brush; therefore, the proposed packaging configurations seem reasonable for a month supply.

We reviewed the container labels and carton labeling and noted that the route of administration statement (b) (4) does not conform to current nomenclature for topical products (i.e. "For Topical Use Only"). In addition, the container labels do not include the route of administration statement. The established name is not commensurate in prominence to the proprietary name as per CFR 201.10(g)(2).

Additionally, we note that the net quantity statement is presented in metric and English units of measure. We find this to be duplicative and it crowds the container labels. The dosage statement on the carton labeling reads "Apply to affected (b) (4)

Finally, the statements "Important: This package is not child resistant" and "Keep away

from children”

(b) (4)

4 RECOMMENDATIONS FOR THE APPLICANT

DMEPA recommends the following be implemented prior to approval of this Application.

A. Proposed Container Label and Carton Labeling (all package sizes)

1. The established name is not commensurate to the prominence of the proprietary name as per CFR 201.10(g)(2). Revise the presentation of the proprietary name to use title case (i.e. Jublia) and ensure that the established name is at least ½ the size of the proprietary name and commensurate in prominence to the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).
2. The unit of measure for the net quantity statement is presented in the English and metric systems. We find this to be duplicative and it crowds the container labels. Revise the net quantity statement to be presented only in the metric system unit of measure (i.e. mL).

B. Proposed Container Labels (all package sizes)

1. Add the route of administration statement “For Topical Use Only.”

C. Proposed Carton Labeling (all package sizes)

1. Revise the usual dosage statement to read “Apply to affected toenail(s) once daily. See package insert for full Prescribing Information.” As currently presented using the word (b) (4)
2. Revise the route of administration statement from (b) (4) to read “For Topical Use Only” in bold font and using larger font size than in the statement “Not for use in the eyes”.
3. Relocate the statement “Keep away from children” to appear below the related cautionary statement “Important: This package is not child-resistant”.

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Jublia that Dow Pharmaceutical Sciences submitted on Decemeber 20, 2013.

Table 2. Relevant Product Information for Jublia	
Active Ingredient	Efinaconazole
Indication	Treatment of onychomycosis
Route of Administration	Topical
Dosage Form	Solution
Strength	10%
Dose and Frequency	Apply to affected toenail once daily
How Supplied	4 ml and 8 mL bottles
Storage	Store at (b) (4) excursions permitted to 15–30°C (59–86°F).
Container Closure	HDPE bottles containing (b) (4) inside plug with (b) (4) brush and (b) (4) cap

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

We searched the L:Drive on March 10, 2014 using the term 'efinaconazole', to identify reviews previously performed by DMEPA.

B.2 Results

We had previously reviewed the container labels and carton labeling in OSE review 2012-1991, dated February 28, 2013 during the first review cycle of the NDA. We note that our recommendations were not communicated to the applicant in the Complete Response letter.

APPENDIX C. LABELS AND LABELING

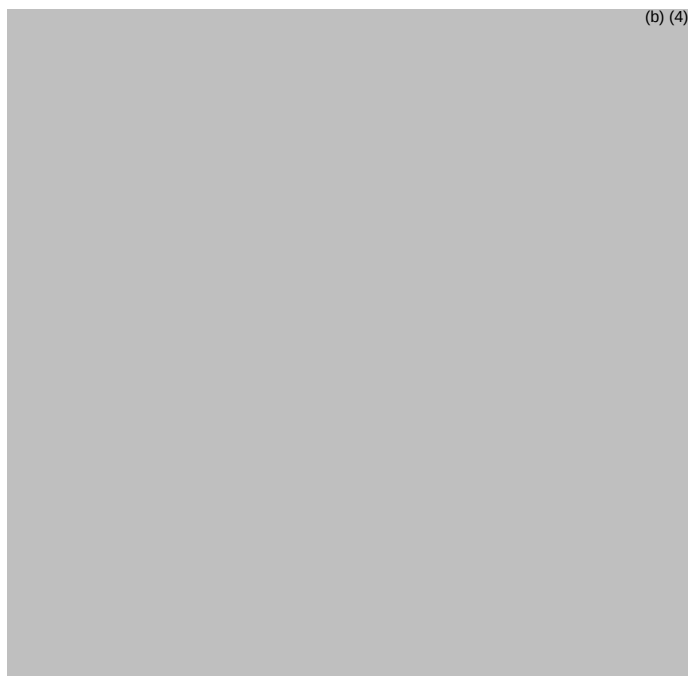
C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Jublia labels and labeling submitted by Dow Pharmaceutical Sciences on December 20, 2013.

- Container label
- Carton labeling

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

Container Labels



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

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

/s/

CARLOS M MENA-GRILLASCA
03/14/2014

LUBNA A MERCHANT
03/14/2014

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

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

Memorandum

Date: August 2, 2013

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

From: Kemi Asante, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 203567
efinaconazole Topical Solution, 10%

OPDP acknowledges receipt of DDDP's August, 10, 2012, consult request for the review of proposed product labeling for efinaconazole Topical Solution, 10%, NDA 203567. OPDP notes that this application received a complete response on May 13, 2013. Therefore, OPDP will provide comments on proposed substantially complete labeling for this application during a subsequent review cycle. OPDP requests that DDDP submits a new consult request during the subsequent review cycle.

Thank you for the opportunity to provide comments on the proposed product labeling. If you have any questions, please contact Kemi Asante at (301) 796-7425 or at kemi.asante@fda.hhs.gov.

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

/s/

OLUWASEUN A ASANTE
08/02/2013

**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**

REVIEW DEFERRAL MEMORANDUM

Date: March 5, 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: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Patient Package Insert (PPI)

Drug Name (established name): (b) (4) (efinaconazole)

Dosage Form and Route: Topical Solution 10%

Application Type/Number: NDA 203-567

Applicant: Dow Pharmaceutical Sciences

1 INTRODUCTION

On July 26, 2012, Dow Pharmaceutical Sciences submitted for the Agency's review a New Drug Application (NDA) 203-567 for (b) (4) (efinaconazole) Topical Solution 10% with the proposed indication for the topical treatment of onychomycosis. On August 10, 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) for (b) (4) (efinaconazole) Topical Solution 10%.

This memorandum documents the DMPP review deferral of the Applicant's proposed Patient Package Insert (PPI) for (b) (4) (efinaconazole) Topical Solution 10%.

2 CONCLUSIONS

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

Please notify us if you have any questions.

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

/s/

NATHAN P CAULK
03/05/2013

BARBARA A FULLER
03/05/2013

LASHAWN M GRIFFITHS
03/07/2013

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: March 1, 2013

TO: Strother Dixon, Regulatory Project Manager
Gary Chiang, 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 D. 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: 203567

APPLICANT: Dow Pharmaceutical Sciences

DRUG: (Efinaconazole) Topical Solution, 10%

NME: Yes

THERAPEUTIC
CLASSIFICATION: Standard Review

INDICATION: Treatment of onychomycosis

CONSULTATION REQUEST DATE: October 17, 2012
CLINICAL INSPECTION SUMMARY DATE: March 5, 2013
DIVISION ACTION GOAL DATE: May 24, 2013
PDUFA DATE: May 26, 2013

I. BACKGROUND:

The Applicant submitted this NDA to support the use of efinaconazole topical solution, 10% for the treatment of onychomycosis.

The pivotal study protocols, DPSI-IDP-108-P3-01 and DPSI-IDP-108-P3-02, are entitled "A Phase 3, Multicenter, Randomized, Double-Blind Study Evaluating the Safety and Efficacy of IDP-108 Topical Solution versus Vehicle in Subjects with Mild to Moderate Onychomycosis of the Toenails" and were submitted and inspected in support of the indication. The objective of these studies was to evaluate the safety and efficacy of 48 weeks of once daily topically administered IDP-108 compared with vehicle in the treatment of mild to moderate onychomycosis of the toenails. The primary efficacy endpoint for both protocols was the Clinical Cure rate at Week 52 (4-Week F/U Visit), defined as zero% clinical involvement of the target nail (nail is totally clear) in addition to Mycologic Cure, defined as negative KOH (potassium hydroxide) examination and negative fungal culture of the target nail specimen.

The sites of Drs. Wiltz and Nahm were selected for inspection because of the substantial enrollment of subjects for their respective protocols.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects	Inspection Dates	Final Classification
Hector Wiltz, M.D. FXM Research Corp. 11760 Bird Road, Suite 452 Miami, FL 33175	DPSI-IDP-108-P3-02/ Site #244/ 71 (enrolled)	22-28 Jan 2013	NAI. Pending final classification.
Walter K. Nahm, M.D., Ph.D. University Clinical Trials, Inc. 7695 Cardinal Court, Suite 210 San Diego, CA 92123	DPSI-IDP-108-P3-01/ Site #123/ 57 (enrolled)	14-16 Jan 2013	NAI. Pending final classification.
Dow Pharmaceutical Sciences, Inc. 1330 Redwood Way Petaluma, CA 94954	DPSI-IDP-108-P3-01 and DPSI-IDP-108-P3-02	14-28 Feb 2013	NAI. Pending final classification.

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. Hector Wiltz, M.D.
FXM Research Corp.
11760 Bird Road, Suite 452
Miami, FL 33175

- a. **What was inspected:** At this site, for DPSI-IDP-108-P3-02, 176 subjects were screened, 71 subjects were enrolled, and 61 subjects completed the study. Signed informed consent forms were present for all 176 screened subjects. An audit of the study records of 25 enrolled subjects was conducted. Records reviewed included, but were not necessarily limited to, case report forms, financial disclosures, IRB, sponsor, and monitor communications, source documentation including patient demographic and medical information, inclusion/exclusion criteria, primary efficacy data, drug accountability records, and adverse event 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.
- 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. Walter K. Nahm, M.D., Ph.D.
University Clinical Trials, Inc.
7695 Cardinal Court, Suite 210
San Diego, CA 92123

- a. **What was inspected:** At this site, for Protocol DPSI-IDP-108-P3-01, 95 subjects were screened, 57 subjects were enrolled, and 45 subjects completed the study. An audit of the study records of all 95 screened subjects was conducted. Signed informed consent forms were present for all screened subjects. Other records reviewed included, but were not limited to, source documents, inclusion/exclusion criteria, primary efficacy data, adverse event reports, test article disposition, IRB, sponsor, and monitor communications, and financial disclosure.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

- 3. Dow Pharmaceutical Sciences, Inc.
1330 Redwood Way
Petaluma, CA 94954

- a. **What was inspected:** At this site, for Protocols DPSI-IDP-108-P3-01 and , DPSI-IDP-108-P3-02, the following sponsor activities were inspected: history and responsibility; selection and monitoring of clinical investigators; selection of monitors; monitoring procedures and activities; safety and adverse event reporting; data collection and handling; test article accountability; conduct of Dow Pharmaceutical Sciences and the monitoring CRO, (b) (4), in their review, assessment and determination of study subjects' safety and efficacy for three clinical investigator sites; outside services and contractors used by Dow Pharmaceutical

Sciences for the study; quality assurance of Dow Pharmaceutical Sciences; financial disclosures and Form FDA 1572s for all US clinical investigators and sub-investigators used in the study; training of US clinical investigators and staff; record retention; and procedures for electronic records and electronic signatures.

Specific clinical sites reviewed included those of Drs. Walter K. Nahm, Site #123, and Hector Wiltz, Site #244. The FDA investigator also briefly reviewed the site of Dr. Adiya Gupta (Site #108) because a review of monitoring reports indicated that this site was cited by HealthCanada for not signing necessary forms nor reviewing and commenting on abnormal ECGs. Review of subsequent correspondence by the FDA investigator indicated that these issues were addressed in writing by Dr. Gupta and HealthCanada took no further action.

- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. The sponsor maintained adequate oversight of the clinical trials and adequately monitored the investigator sites (a CRO, (b) (4), was used by the sponsor for monitoring functions). No sites were closed for noncompliance. Adverse event reporting appeared adequate. Randomized subjects appear to have met all inclusion criteria and none of the exclusion criteria. Electronic data capture (EDC) appears to have operated in accordance with 21 CFR Part 11. Audit trails were in place and the EDC system provided for a backup plan, disaster recovery plan, and/or contingency plan to protect against data loss. There were no error messages or system failures during the clinical trials. Some protocol deviations were noted which included, but were not limited to, visits occurring outside of protocol-specified time windows, subjects missing some doses of the investigational product, lost subject diaries, and subjects running out of investigational medication prior to the next visit. All deviations appear to have been reported and resolved appropriately.
- c. Assessment of data integrity:** The studies appear to have been conducted adequately, and the data submitted by the sponsor appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Wiltz and Nahm's clinical investigator sites were inspected in support of this NDA. A sponsor inspection of Dow was also conducted. Neither the clinical investigators nor the sponsor was issued a Form FDA 483. These inspections are preliminarily classified as NAI (No Action Indicated). Overall, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

Note: Preliminary classifications are based on communications with the field. The EIRs have not been received from the field and are pending final review. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{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
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

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

/s/

ROY A BLAY
03/05/2013

JANICE K POHLMAN
03/05/2013

SUSAN D THOMPSON
03/05/2013

**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: February 28, 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

Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Efinaconazole Topical Solution, 10 %

Application Type/Number: NDA 203567

Applicant/sponsor: Dow Pharmaceutical Sciences, Inc.

OSE RCM #: 2012-1991

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

Contents

1	Introduction.....	1
1.1	Regulatory History	1
1.2	Product Information	1
2	Methods and Materials Reviewed.....	1
2.1	Labels and Labeling	1
3	Integrated Summary of Medication Error Risk Assessment.....	2
4	Conclusions.....	Error! Bookmark not defined.
5	Recommendations.....	2
5.1	Comments to the Applicant.....	2
	Appendices.....	4

1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Efinaconazole NDA 203567 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Efinaconazole Topical Solution, 10 % (NDA 2) is an NME currently under review.

The proposed proprietary name Jublia is currently under evaluation under OSE review 2013-240.

1.2 PRODUCT INFORMATION

The following product information is provided in the August 20, 2012 proprietary name submission.

- Active Ingredient: Efinaconazole
- Indication of Use: Treatment of onychomycosis
- Route of Administration: Topical
- Dosage Form: Solution
- Strength: 10%
- Dose and frequency: Apply once daily to clean dry nails. Wait for at least 10 minutes after showering, bathing or washing before applying.
- How Supplied/Container closure system: Trade size is a (b) (4) in a 10 mL plastic bottle with built-in flow through brush applicator. (b) (4)
- Storage: (b) (4) excursions permitted to 15°-30°C (59°-86 °F)

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Efinaconazole container labels, carton and package insert labeling submitted by the Applicant.

2.1 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 A and B)
- Insert Labeling submitted September 9, 2012

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 to market Efinaconazole in a (b) (4) package size. (b) (4)

In addition, the inclusion of a brush is consistent with other products for the same indication. However, the difference is that for Penlac the brush is attached to the cap (i.e. similar to nail polish), whereas for Efinaconazole the brush is attached to the bottle. This is also consistent with the packaging presentation for Penlac. Finally, we note that the container closure system is not child resistant; however, (1) this is consistent with Penlac container closure system and (2) the carton labeling includes the statements “Important: This package is not child resistant” and “Keep away from children”. Therefore, we find this packaging presentation adequate.

We reviewed the container labels and carton labeling and noted that the route of administration statement “For Dermatologic Use Only” does not conform to current nomenclature for topical products (i.e. “For Topical Use Only”). In addition, the container labels do not include the route of administration statement. Also, the established name appears to be ½ the size of the proprietary name; however, given the typography used for the proprietary name (all caps and bold) versus the typography used for the established name (lower case, unbolded, condensed font), we find that the prominence is not commensurate as per CFR 201.10(g)(2). Finally, we note that the net quantity statement is presented in metric and English units of measure. We find this to be duplicative and it crowds the container labels.

Finally, we performed a search of the FDA Adverse Reporting System for medication errors associated with Penlac and ciclopirox. Only one case of accidental exposure from the year 2000 was retrieved. The case describes a 74 year old woman who accidentally placed a small amount of ciclopirox nail lacquer in her left eye, mistaking it for her Tobrex eye drops. The patient experienced redness and swelling of her left eye associated with transient vision loss and blurred vision that eventually resolved. The proposed container labels for Efinaconazole do not include the route of administration statements. Therefore, DMEPA is recommending that the route of administration statements be added to the container labels for Efinaconazole to help mitigate accidental exposure to the eyes.

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 and Carton Labeling (2 mL and 6 mL bottles)

1. Update all labels and labeling to remove reference to the proprietary name, (b) (4), as this name has been denied.
2. 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). As currently presented the typography used for proprietary name (all caps and bold) versus the typography used for the established name (lower case, unbolded, condensed font) we find they are not commensurate in prominence.

3. Revise the presentation of the proprietary name from all-caps (i.e. TRADENAME) to title case (i.e. Tradename) to improve readability of the name. Words set in titlecase are easier to read than the rectangular shape that is formed by words set in all capital letters.
4. Unbold the 'Rx Only' statement. As currently presented it is more prominent than more relevant information on the labels.
5. Delete the net weight statement presented in the English unit of measure (e.g. xx fl oz). As currently presented with both the English and metric unit of measure it is duplicative and crowds the container labels.
6. Revise the presentation of the correct route of administration statements from 'For dermatologic use only' to read 'For Topical Use Only' and increase the prominence by bolding.

B. Proposed Container Labels (b) (4)

Include the route of administration statement 'For Topical Use Only' on the principal display panel.

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

Unbold the 'Physician Sample' statement. As currently presented it is more prominent than more relevant information on the labels.

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

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

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

/s/

CARLOS M MENA-GRILLASCA
02/28/2013

LUBNA A MERCHANT
02/28/2013

CAROL A HOLQUIST
02/28/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 203567	NDA Supplement #:S- NA	Efficacy Supplement Type SE- NA
Proprietary Name: (b) (4) Established/Proper Name: efinaconazole Dosage Form: Solution Strengths: 10%		
Applicant: Dow Pharmaceutical Sciences Agent for Applicant (if applicable): NA		
Date of Application: July 26, 2012 Date of Receipt: July 26, 2012 Date clock started after UN: NA		
PDUFA Goal Date: May 26, 2013	Action Goal Date (if different): May 24, 2013	
Filing Date: September 24, 2012	Date of Filing Meeting: September 19, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): onychomycosis		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 <i>and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		
☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)		

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): NA				
List referenced IND Number(s): 077732				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?	X			
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the proprietary, established/proper, and applicant names correct in tracking system?	X			
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm	X			
<i>If no, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?				X	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?				X	
<i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>			X		
http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm					

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	NA			
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			Section 2.2
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

1

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

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	
If yes, were all of them submitted on time?			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			Application had FDA 3454 only

<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	Electronic submission
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>		X		
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>	X			
Does the application trigger PREA?				
<i>If yes, notify PeRC RPM (PeRC meeting is required)²</i>				
<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?			X	
<i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?	X			(b) (4)
<i>If no, request in 74-day letter</i>				
<u>BPCA</u> (NDAs/NDA efficacy supplements only):		X		
Is this submission a complete response to a pediatric Written Request?				
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?		X		
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	X			
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?			X	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☐ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				

4

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

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			
<i>If yes, specify consult(s) and date(s) sent:</i> Clinical Microbiology – 09Aug12				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): August 17, 2009	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 17, 2012	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): November 3, 2008 – Carcinogenicity SPA-1 November 4, 2008 – Carcinogenicity SPA-2	X			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 19, 2012

NDA #: 203567

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: efinaconazole

DOSAGE FORM/STRENGTH: Solution, 10%

APPLICANT: Dow Pharmaceutical Sciences

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Onychomycosis

BACKGROUND: NDA 203567, an NME, was received on July 26, 2012. The associated IND is IND 077732 IDP 108 (efinaconazole) Solution, 10%. There was an End of Phase 2 Meeting on August 17, 2009 and a Pre-NDA Meeting on April 17, 2012. There two carcinogenicity SPAs: SPA-1 received on November 3, 2008 and SPA-2 received on November 4, 2008.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Strother D. Dixon	Y
	CPMS/TL:	Barbara Gould	Y
Cross-Discipline Team Leader (CDTL)	David Kettl, MD		Y
Clinical	Reviewer:	Gary T. Chiang, MD	Y
	TL:	David Kettl, MD	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	NA	NA
	TL:	NA	NA
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	NA	NA
	TL:	NA	NA
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Kerry Snow, MS	N

Clinical Pharmacology	Reviewer:	Chinmay Shukla, PhD	Y
	TL:	Donny Tran, PhD	Y
Biostatistics	Reviewer:	Kathleen Fritsch, PhD	Y
	TL:	Mohammad Alosch, PhD	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Linda Pellicore, PhD	Y
	TL:	Barbara Hill, PhD	Y
Statistics (carcinogenicity)	Reviewer:	Atiar Rahman, PhD	N
	TL:	Karl Lin, PhD	N
Product Quality (CMC)	Reviewer:	Bogdan Kurtyka, PhD	N
	TL:	Shulin Ding, PhD	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	NA	NA
	TL:	NA	NA
CMC Labeling Review	Reviewer:	NA	NA
	TL:	NA	NA
Facility Review/Inspection	Reviewer:	NA	NA
	TL:	NA	NA
OSE/DMEPA (proprietary name)	Reviewer:	Carlos Mena-Grillasca	N N
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:	NA	NA
	TL:	NA	NA
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	NA
	TL:	NA	NA

Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay, PhD	N
	TL:	NA	NA
Controlled Substance Staff (CSS)	Reviewer:	NA	NA
	TL:	NA	NA
Other reviewers	Nathan Caulk, Patient Labeling Reviewer		Y
Other attendees	Stanka Kukich, MD, Deputy Director, DDDP		Y
	Julie Beitz, MD, Director, ODE III		Y

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues? If yes, list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments:	☒ Not Applicable
CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason: No public health issues anticipated

○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	
• Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☒ NO
<u>Quality Microbiology (for sterile products)</u> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz, MD Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): December 14, 2012 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review:

	• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

STROTHER D DIXON
09/25/2012

BARBARA J GOULD
10/01/2012

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

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 203567

Application Type: New NDA

Name of Drug: (b) (4) (efinaconazole) Topical Solution, 10%

Applicant: Dow Pharmaceutical Sciences

Submission Date: July 25, 2012

Receipt Date: July 26, 2012

1.0 Regulatory History and Applicant's Main Proposals

NDA 203567, an NME, was received on July 26, 2012. The associated IND is IND 077732 IDP 108 (efinaconazole) Solution, 10%. There was an End of Phase 2 Meeting on August 17, 2009 and a Pre-NDA Meeting on April 17, 2012. There two carcinogenicity SPAs: SPA-1 received on November 3, 2008 and SPA-2 received on November 4, 2008.

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 October 25, 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

- 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 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:

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

Comment:

- 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: *Reference the subsection for Adverse Reactions. (6.1)*

Selected Requirements of Prescribing Information (SRPI)

- 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

- 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

- 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: *Bold the HL Limitation Statement*

Product Title

- NO 10. Product title in HL must be **bolded**.

Comment: *Bold the title in the product title*

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: *Bold the "Initial U.S. Approval" statement and the date*

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

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

Selected Requirements of Prescribing Information (SRPI)

- YES** 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:

- 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: Clarify why Dow Pharmaceutical Sciences is listed on the 356h and Valeant Pharmaceuticals North America is listed on the label.

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

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

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:

Selected Requirements of Prescribing Information (SRPI)

- 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

Selected Requirements of Prescribing Information (SRPI)

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:

- NO** 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: *The FDA-Approved Patient Labeling must not be a subsection of 17.*

- NO** 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: *Cross-references in the FPI should be in italics in section 12.1.*

- 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

- N/A** 45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- NO** 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: The statement must be verbatim. Sponsor did not include the work “observer”.

- 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: The statement should say “See FDA-approved patient labeling (Patient Information)”

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

/s/

STROTHER D DIXON
09/21/2012

BARBARA J GOULD
09/25/2012