

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205223Orig1s000

OTHER REVIEW(S)

To: NDA 205223
From: Lin Qi, Ph.D., Product Quality Reviewer, Branch V/Division II/ONDQA
Through: Dorota Matecka, Ph.D., CMC Lead, Branch V/Division II/ONDQA
Date: March 21, 2014
Re: NDA 205223 Final Labeling

The latest versions of the labeling and the labels for the applicator and the overwrap as revised and submitted in the submission dated March 7, 2014 are acceptable from the CMC perspective.

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/s/

LIN QI
03/21/2014

DOROTA M MATECKA
03/21/2014

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

| | |
|--------------------------------|--|
| Product Title ¹ | METRONIDAZOLE vaginal gel 1.3% |
| Applicant | Valeant Pharmaceuticals North America LLC |
| Application/Supplement Number | NDA 205223 |
| Type of Application | Original |
| Indication(s) | Treatment of bacterial vaginosis in non-pregnant women |
| Office/Division | OAP/DAIP |
| Division Project Manager | Jane Dean |
| Date FDA Received Application | May 24, 2013 |
| Goal Date | March 24, 2014 |
| Date PI Received by SEALD | February 6, 2014 |
| SEALD Review Date | February 7, 2014 |
| SEALD Labeling Reviewer | Abimbola Adebowale |
| Acting SEALD Division Director | Sandra Kweder |

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

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

Selected Requirements of Prescribing Information

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:

- NO** 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: *The Indications and Usage, Dosage and Administration, Contraindications, Adverse Reactions and Use in Specific Populations headings in HL are not presented in the center of the horizontal line. Center them.*

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

Comment: *There is white space between the HL heading and HL Limitation Statement in HL. Delete because there must be no white space between the HL heading and HL Limitation Statement in HL.*

Selected Requirements of Prescribing Information

- 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**.

Comment:

Selected Requirements of Prescribing Information

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

Selected Requirements of Prescribing Information

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

Comment:

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

- NO** 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 bolded revision date at the end of HL should read as “Revised: 2/2014” instead of “Revised: XX/XXXX.”*

Contents: Table of Contents (TOC)

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

Selected Requirements of Prescribing Information

- 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:
- NO** 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: *The subsection heading “4.2 Use of disulfiram” in the TOC is not in title case. Change to title case (i.e. Use of Disulfiram).*
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: *The TOC subsection heading “4.2 Use of disulfiram” does not match the FPI subsection heading “Use of Disulfiram.” Match them.*
- 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:

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 |

Selected Requirements of Prescribing Information

| |
|---|
| 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:

NO

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: Under subsection “5.2 Carcinogenicity in Animals” in the FPI, the cross-reference should read as [see *Nonclinical Toxicology (13.1)*] instead of “[see *Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)*]” i.e. section heading not subsection heading.

Under section “10 OVERDOSAGE” in the FPI, the cross-reference should read as [see *Warnings and Precautions (5) and Adverse Reactions (6.2)*] instead “[see *Warnings and Precautions (5) and Adverse Events (6.2)*].”

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

Selected Requirements of Prescribing Information

- 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

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

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 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:

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

Comment:

Selected Requirements of Prescribing Information

- 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.

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/s/

ABIMBOLA O ADEBOWALE
02/07/2014

ERIC R BRODSKY
02/07/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

PMR Development Template

NDA 205223
Product Name: Metronidazole vaginal gel 1.3%

PMR Description: 2123-01: A clinical trial to evaluate the safety of metronidazole gel 1.3% single dose in the treatment of bacterial vaginosis in females 12-<18 years of age

| | | |
|------------------------------|----------------------------|----------------|
| PMR/PMC Schedule Milestones: | Final Protocol Submission: | <u>08/2014</u> |
| | Study/Trial Completion: | <u>12/2015</u> |
| | Final Report Submission: | <u>06/2015</u> |

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

Metronidazole vaginal gel 1.3% will be approved for the treatment of bacterial vaginosis in women (b) (4). This PMR is required under the Pediatric Research Equity act to evaluate safety in adolescent females..

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.”

The trials supporting approval were conducted in adults. Studies in female children were waived for those under the age of 12, and deferred for those between the ages of 12 and 18. The goal of the PMR is to evaluate safety in this patient population. Safety data is lacking in this population as previous drugs approved for the treatment of BV had extrapolated efficacy and safety from adults.

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) Not applicable**

- 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: Not applicable**

- 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 clinical trial is proposed to be multi-center, placebo-controlled and will be performed in females 12 to <18 years of age.

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 clear, feasible, and appropriate?

X Does the study/clinical trial meet criteria for PMRs?

X Are the objectives clear from the description of the PMR?

X Has the applicant adequately justified the choice of schedule milestone dates?

X Has the applicant had sufficient time to review the PMR, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

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

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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/s/

JANE A DEAN
01/17/2014

HALA H SHAMSUDDIN
01/21/2014

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

Label, Labeling and Packaging Review

Date: January 15, 2014

Reviewer: Rachna Kapoor, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Metronidazole Vaginal Gel, 1.3%

Application Type/Number: NDA 205223

Applicant/sponsor: Valeant Pharmaceuticals North America, LLC

OSE RCM #: 2013-1719

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

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1 INTRODUCTION

This review evaluates the proposed container label, carton labeling, and prescribing information for Metronidazole Vaginal Gel, NDA 205223, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Valeant Pharmaceuticals North America, LLC submitted an original New Drug Application for Metronidazole Vaginal Gel, 1.3% for the topical treatment of bacterial vaginosis in non-pregnant women on May 24, 2013. This product will be marketed without a proprietary name.

1.2 PRODUCT INFORMATION

The following product information is provided in the May 24, 2013 submission.

- Active Ingredient: metronidazole
- Indication of Use: treatment of bacterial vaginosis in non-pregnant women
- Route of Administration: intravaginally
- Dosage Form: gel
- Strength: 1.3% (5 g of gel containing 65 mg of metronidazole)
- Dose and Frequency: one applicator administered once intravaginally at bedtime
- How Supplied: in cartons containing one single-dose, prefilled disposable applicator delivering 5 g of vaginal (b)(4) containing approximately 65 mg of metronidazole
- Storage: store at controlled room temperature 15° – 30°C (59° – 86°F). Protect from freezing

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) for metronidazole vaginal gel medication error reports (See Appendix A for a description of the FAERS database). We also reviewed the metronidazole vaginal gel labels and labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

| Table 1: FAERS Search Strategy | |
|---------------------------------------|------------------------------------|
| Date | January 6, 2014 |
| Drug Names | Metrogel Vaginal, Metrogel-Vaginal |
| MedDRA Search Strategy | Medication Errors (HLGT) |

The FAERS search performed according to the strategy in Table 1 retrieved three cases. Each case was reviewed for relevancy and duplication. After individual review, all of the cases were excluded from the final analysis for the following reasons:

- Confusion due to the proprietary name of the product (#5714193 Vrsn 1 and #6620166 Vrsn 1)
- Duplicate therapy (#3871053 Vrsn 1) (See Appendix D for case narratives)

2.2 LABELS AND LABELING

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

- Container Label submitted August 14, 2013 (Appendix B)
- Carton Labeling submitted August 14, 2013 (Appendix C)
- Patient Information submitted May 24, 2013 (no image)

3 CONCLUSIONS

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

Additionally, DMEPA concludes that the Instructions for Use can be improved for legibility and clarity of information.

4 RECOMMENDATIONS

4.1 COMMENTS TO THE APPLICANT

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

- A. Container Label
 - i. Add the statement “Single-dose” to the principal display panel. We recommend this addition to help prevent the product from being used multiple times.
 - ii. Increase the font size for the route of administration statement “For Intravaginal Use Only” so that it is more prominent than the “Not for Ophthalmic, Dermal, or Oral Use” statement. We recommend this revision to help prevent wrong route administration errors since there are other topical metronidazole products currently available.

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

- iii. Relocate the intended route of administration “For Intravaginal Use Only” from the side panel to the principal display panel to increase prominence of that statement.

B. Carton Labeling

- i. See both A.i and A.ii and revise carton labeling accordingly.

C. Instructions for Use

- i. In (b) (4) place each Figure directly under each step for easier comprehension of the instructions for use. For example, relocate Figure (b) (4) directly below the statement “Remove the pre-filled applicator and plunger from the foil packaging”. Relocate Figure (b) (4) directly below the statement (b) (4)
(b) (4) Relocate Figure 3 directly below the statement “Remove the pink cap (b) (4). And relocate Figure 4 directly under the statement (b) (4)
(b) (4)
- ii. We recommend providing color in the Figures for increased legibility and clarity of the Instructions for Use.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

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

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

Appendix B: Container Label



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immediately following this page

Appendix D: Case narratives

| Case # | Vrsn | FDA Recd Date | Narrative | MFR Ctrl # |
|---------|------|---------------|---|------------|
| 3871053 | 1 | 11/21/2002 | <p>ABORTION SPONTAENOUS (miscarriage). Report from pharmacist. This 24 year old woman pregnant with triplets and at the end of her first trimester of pregnancy. She developed a urinary tract infection and was given a prescription for Macrobid (nitrofurantoin). The prescribed drug was part of a preprinted list of five medications on a prescription; the physician checked the physician checked the medication(s) on the list that he wanted to have dispensed. The physician apparently checked only Macrobid but the pharmacist apparently dispensed all five medications on the list. The patient was given Diflucan (fluconazole), Zithromax (azithromycin), Ortho Tricyclen (ethinyl estradiol/norgestimate), and MetroGel-Vaginal (metronidazole intravaginal gel) 0.75% in addition to the Macrobid.</p> <p>On 03MAR02 the woman started treatment with all five medications as follows: Macrobid 100 mg twice daily for seven days, Diflucan 150 mg one dose, Zithromax apparently taken as four 250 mg tablets at one time, and one application (37.5 mg) of MetroGel-Vagina inserted vaginally for seven days. Or (b) (6) the woman had a miscarriage of her triplets. She had a medical history of two previous uncomplicated pregnancies. No other medications were reported.</p> | 0020444 |
| 5714193 | 1 | 1/12/1993 | <p>REPORTER CALLED TO EXPRESS HIS CONCERN OVER THE POSSIBLE CONFUSION BETWEEN PRESCRIPTIONS WRITTEN FOR METRO GEL (TOPICAL) AND METRO GEL (VAGINAL). IT SEEMS THAT OB/GYN DOCTORS ARE WRITING FOR JUST "METRO GEL"- USE AS DIRECTED AND NOT INDICATING THE PRODUCT DISPENSED SHOULD BE THE VAGINAL PRODUCT. PHARMACIST MAY DISPENSE THE TOPICAL PRODUCT SINCE THE FULL NAME WAS NOT INCLUDED. POSSIBLE PHYSICIANS NEED TO BE INFORMED AND EDUCATED ABOUT THE DIFFERENCES BETWEEN THESE TWO PRODUCTS AND THE IMPORTANCE OF CLEARLY STATING IF THE TOPICAL OR VAGINAL PRODUCT IS TO BE DISPENSE.</p> <p>MEDICATION ERROR</p> | |
| 6620166 | 1 | 4/14/2008 | <p>Patient bought in script for "MetroGel Vag" 45 gm Applic HS. The pharmacist on duty thought the MD's abbreviation for applicatorful was the word "apply". The pharmacist also was confused by the qty. Since only 70 gms are available of Metrogel generic. Pharmacist thought MD did not want the product that contained the applicators, but just wanted metronidazole 0.75% # 45gm " apply at bedtime". She mistakenly filled it for the cream instead of the gel. Patient got home and was confused on how to apply the product. She called the MD's office and that is how the mistake was discovered. MD called us and we changed the medication to the generic MetroGel and gave patient a credit.</p> <p>No harm, just delay in therapy.</p> <p>Delay in correct therapy, progression of yeast infection. Pharmacist on duty thought the MD's abbreviation for applicatorful was the word "apply".</p> <p>medication error</p> | |

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/s/

RACHNA KAPOOR
01/15/2014

YELENA L MASLOV
01/15/2014

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

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

Memorandum

Date: December 24, 2013

To: Jane Dean, RN, MSN
Project Manager, Division of Anti-Infective Products

From: Christine Corser, Pharm.D., RAC
Regulatory Review Officer, Office of Prescription Drug Promotion

Subject: NDA #205223
Metronidazole Vaginal Gel 1.3%

As requested in your consult dated July 22, 2013, OPDP has reviewed the draft PI for Metronidazole Vaginal Gel 1.3%.

OPDP's comments on the PI are based on the substantially complete version of the labeling titled, "NDA205223_Label_Draft_11-4-13_v12-17-13.docx" received by DAIP via email on December 18, 2013.

OPDP's comments on the PI are provided in the attached, clean version of the labeling.

If you have any questions about OPDP's comments, please contact Christine Corser at 6-2653 or Christine.corser@fda.hhs.gov.

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/s/

CHRISTINE G CORSER
12/24/2013

**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: December 20, 2013

To: John Farley, MD, MPH
Director
Division of Anti-Infective Products (DAIP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Christine Corser, Pharm.D., RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name): Metronidazole Vaginal Gel 1.3%

Dosage Form and Route: Gel, for intravaginal use

Application Type/Number: NDA 205-223

Applicant: Valeant Pharmaceuticals North America LLC

1 INTRODUCTION

On May 23, 2013, Valeant Pharmaceuticals North America LLC submitted for the Agency's review a New Drug Application (NDA-205223) for Metronidazole Vaginal Gel 1.3% for the topical treatment of bacterial vaginosis in non-pregnant women.

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 Anti-Infective Products (DAIP) on July 22, 2013, and July 22, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Metronidazole Vaginal Gel 1.3%.

2 MATERIAL REVIEWED

- Draft Metronidazole Vaginal Gel 1.3% PPI and IFU received on August 14, 2013, and received by DMPP on December 18, 2013.
- Draft Metronidazole Vaginal Gel 1.3% PPI and IFU received on August 14, 2013 and received by OPDP on December 18, 2013.
- Draft Metronidazole Vaginal Gel 1.3% Prescribing Information (PI) received on August 14, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on December 18, 2013.
- Draft Metronidazole Vaginal Gel 1.3% Prescribing Information (PI) received on August 14, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on December 18, 2013.

3 REVIEW METHODS

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 reformatted the PPI and IFU documents using the Verdana font, size 11.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are 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 and IFU are 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 and IFU.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
12/20/2013

CHRISTINE G CORSER
12/20/2013

MELISSA I HULETT
12/20/2013

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 # 205223 | NDA Supplement #: S- | Efficacy Supplement Type SE- |
| Proprietary Name: Metronidazole Vaginal Gel 1.3% Established/Proper Name: Metronidazole Dosage Form: Vaginal Gel (topical) Strengths: 1.3% | | |
| Applicant: Valeant Pharmaceuticals North America LLP Agent for Applicant (if applicable): | | |
| Date of Application: May 24, 2013 Date of Receipt: May 24, 2013 Date clock started after UN: | | |
| PDUFA Goal Date: March 24, 2014 | | Action Goal Date (if different): |
| Filing Date: July 23, 2013 | | Date of Filing Meeting: July 2, 2013 |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) : Type 5 | | |
| Proposed indication(s)/Proposed change(s): Treatment of bacterial vaginosis in non-pregnant women | | |
| Type of Original NDA: AND (if applicable) Type of NDA Supplement: | <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) | |
| <i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 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> | <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted | |
| Resubmission after withdrawal? <input type="checkbox"/> | | Resubmission after refuse to file? <input type="checkbox"/> |
| Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i> | <input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product) | |

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

| <u>User Fee Status</u> <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: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> 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: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears | | | | | | | | | | | | | | | | | | | |
| 505(b)(2) (NDAs/NDA Efficacy Supplements only) | | YES | NO | NA | Comment | | | | | | | | | | | | | | | | |
| 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)]? <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> | | | X | | | | | | | | | | | | | | | | | | |
| Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm | | | | | | | | | | | | | | | | | | | | | |
| If yes, please list below: <table border="1" style="width:100%; border-collapse: collapse;"> <thead> <tr> <th style="width:25%;">Application No.</th> <th style="width:30%;">Drug Name</th> <th style="width:20%;">Exclusivity Code</th> <th style="width:25%;">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table> | | | | | | Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | |
| 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 may block the approval but not the submission of a 505(b)(2) application.</i> | | | | | | | | | | | | | | | | | | | | | |
| Exclusivity | | YES | NO | NA | Comment | | | | | | | | | | | | | | | | |
| Does another product (same active moiety) have orphan | | | | | | | | | | | | | | | | | | | | | |

| | | | | |
|--|---|--|--|--|
| <p>exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i></p> | | | | |
| <p>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)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p> | | | | |
| <p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3 years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> | X | | | |
| <p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p> | | | | |
| <p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p> | | | | |

| Format and Content | | | | |
|---|--|-----------|-----------|----------------|
| <p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> | <input checked="" type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) | | | |
| | <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD) | | | |
| <p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p> | | | | |
| Overall Format/Content | YES | NO | NA | Comment |
| <p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p> | X | | | |
| <p>Index: Does the submission contain an accurate comprehensive index?</p> | | | | |

¹
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

| | | | | |
|--|------------|-----------|-----------|----------------|
| <p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p> | X | | | |
| <p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p> | | | | |
| | | | | |
| | | | | |
| | | | | |
| Forms and Certifications | | | | |
| <p><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></p> | | | | |
| Application Form | YES | NO | NA | Comment |
| <p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i></p> | X | | | |
| <p>Are all establishments and their registration numbers listed on the form/attached to the form?</p> | | | | |
| Patent Information (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| <p>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</p> | X | | | |
| Financial Disclosure | YES | NO | NA | Comment |
| <p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> | X | | | |

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

| | | | | |
|--|---|-----------|-----------|----------------|
| PREA | | | | |
| 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> | X | | | |
| 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? <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)? <i>If no, request in 74-day letter</i> | X | | | |
| BPCA (NDAs/NDA efficacy supplements only): 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> | | X | | |
| Proprietary Name | YES | NO | NA | Comment |
| Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i> | | X | | |
| REMS | YES | NO | NA | Comment |
| Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i> | | | X | |
| Prescription Labeling | <input type="checkbox"/> Not applicable | | | |
| Check all types of labeling submitted. | <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) | | | |

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

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

| | | | | |
|---|--|-----------|-----------|----------------|
| | <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i> | X | | | |
| Is the PI submitted in PLR format? ⁴ If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i> | X | | | |
| | | | X | |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP? | | | | |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available) | | | | |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)? | | | | |
| OTC Labeling | <input checked="" type="checkbox"/> Not Applicable | | | |
| Check all types of labeling submitted. | <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> 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> | | | | |

4

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

| | | | | |
|---|------------|-----------|-----------|---|
| If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i> | | | | |
| 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) <i>If yes, specify consult(s) and date(s) sent:</i> | | | | |
| Meeting Minutes/SPAs | YES | NO | NA | Comment |
| End-of Phase 2 meeting(s)? Date(s): | | X | | |
| <i>If yes, distribute minutes before filing meeting</i> | | | | |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): | | X | | PreNDA meeting cancelled after sponsor received preliminary comments to their meeting questions |
| <i>If yes, distribute minutes before filing meeting</i> | | | | |
| Any Special Protocol Assessments (SPAs)? Date(s): 2/7/13 | X | | | |
| <i>If yes, distribute letter and/or relevant minutes before filing meeting</i> | | | | |

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 2, 2013

NDA #: 205223

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: Metronidazole

DOSAGE FORM/STRENGTH: Vaginal Gel/1.3%

APPLICANT: Valeant Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of bacterial vaginosis in non-pregnant women

BACKGROUND: The NDA is a new strength of topical metronidazole to be used for treatment of bacterial vaginosis in non-pregnant women.

REVIEW TEAM:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|---|-----------|------------------|-------------------------------------|
| Regulatory Project Management | RPM: | Dean/Minor | Y/Y |
| | CPMS/TL: | LeSane | Y |
| Cross-Discipline Team Leader (CDTL) | Tom Smith | | Y |
| Clinical | Reviewer: | Hala Shamsuddin | Y |
| | TL: | | |
| Social Scientist Review (<i>for OTC products</i>) | Reviewer: | | |
| | TL: | | |
| OTC Labeling Review (<i>for OTC products</i>) | Reviewer: | | |
| | TL: | | |
| Clinical Microbiology (<i>for antimicrobial products</i>) | Reviewer: | Lynette Berkeley | N |

| | | | |
|---|-----------|--------------------|---|
| | TL: | Kerry Snow | N |
| Clinical Pharmacology | Reviewer: | Seong Jang | Y |
| | TL: | Phil Colangelo | Y |
| Biostatistics | Reviewer: | Cheryl Dixon | Y |
| | TL: | Karen Higgins | N |
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Owen McMaster | Y |
| | TL: | Wendy Schmidt | N |
| Statistics (carcinogenicity) | Reviewer: | | |
| | TL: | | |
| Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>) | Reviewer: | | |
| | TL: | | |
| Product Quality (CMC) | Reviewer: | Lin Qi | Y |
| | TL: | Dorota Matecka | Y |
| Quality Microbiology (<i>for sterile products</i>) | Reviewer: | | |
| | TL: | | |
| CMC Labeling Review | Reviewer: | Lin Qi | Y |
| | TL: | | |
| Facility Review/Inspection | Reviewer: | Ranjani Prabhakara | N |
| | TL: | | |
| OSE RPM | Reviewer: | Mihaela Jason | Y |
| OC/OSI | Reviewer: | Kassa Ayalew | Y |
| ONDQA RPM | Reviewer: | Navi Bhandari | Y |

| | | | |
|--|--|--|----------|
| Bioresearch Monitoring (OSI) | Reviewer: | | |
| | TL: | | |
| Controlled Substance Staff (CSS) | Reviewer: | | |
| | TL: | | |
| Other reviewers: Pediatric and Maternal Health Team | | | |
| Other attendees | Katherine Laessig, MD Deputy Director, DAIP | | Y |
| | John Farley, MD, MPH Acting Director, DAIP | | Y |

FILING MEETING DISCUSSION:

| | |
|--|--|
| <p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p> | <input checked="" type="checkbox"/> Not Applicable |
| <p>CLINICAL</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain: DAIP and OSI Site Selection meeting on July 1, 2013 and determined no sites were needed to be inspected (see Clinical Filing Checklist)</p> | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |

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

| | |
|--|--|
| Comments: | <input type="checkbox"/> Review issues for 74-day letter |
| NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments: | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| PRODUCT QUALITY (CMC) Comments: See CMC Filing Checklist | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter |
| <u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? • If EA submitted, consulted to EA officer (OPS)? Comments: | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments: Product Quality Microbiology determined a review was not necessary at this time. (See CMC Filing Checklist) | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |

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

| | |
|--|--|
| <ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| REGULATORY PROJECT MANAGEMENT | |
| <p>Signatory Authority: John Farley, MD, MPH, Acting Director, Division of Anti-Infective Products</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p> | |
| REGULATORY CONCLUSIONS/DEFICIENCIES | |
| <input type="checkbox"/> | The application is unsuitable for filing. Explain why: |
| <input checked="" type="checkbox"/> | The application, on its face, appears to be suitable for filing. <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p> |

| ACTIONS ITEMS | |
|-------------------------------------|---|
| <input checked="" type="checkbox"/> | 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). |
| <input type="checkbox"/> | If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). |
| <input type="checkbox"/> | 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. |
| <input type="checkbox"/> | BLA/BLA supplements: If filed, send 60-day filing letter |
| <input type="checkbox"/> | If priority review: <ul style="list-style-type: none"> • 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) |
| <input checked="" type="checkbox"/> | Send review issues/no review issues by day 74 |
| <input checked="" type="checkbox"/> | Conduct a PLR format labeling review and include labeling issues in the 74-day letter |
| <input type="checkbox"/> | Update the PDUFA V DARRTS page (for NME NDAs in the Program) |
| <input type="checkbox"/> | 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] |
| <input type="checkbox"/> | 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/

JANE A DEAN
07/26/2013

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: NDA 205223
Application Type: New NDA
Name of Drug: Metronidazole Vaginal Gel 1.3%
Applicant: Valeant Pharmaceuticals
Submission Date: May 24, 2013
Receipt Date: May 24, 2013

1.0 Regulatory History and Applicant's Main Proposals

The NDA is a new strength of topical metronidazole to be used for treatment of bacterial vaginosis in non-pregnant women.

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 letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by August 16, 2013. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information (SRPI)

4.0 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).
- 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:**
- YES** 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:**

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

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

Comment:

Product Title

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

Comment:

Initial U.S. Approval

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

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

- N/A 12. All text must be **bolded**.
Comment:
- N/A 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
Comment:
- N/A 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.
Comment:
- N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)
Comment:
- N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).
Comment:

Recent Major Changes (RMC)

- YES 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:
- YES 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:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

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

Comment:

Patient Counseling Information Statement

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

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

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

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

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

Comment:

Revision Date

- 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:

YES

Selected Requirements of Prescribing Information (SRPI)

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:

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

Comment:

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

Comment:

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

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

Comment:

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

Comment:

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

Comment:

Contraindications

- 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:

(b) (4)

- 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

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

JANE A DEAN
07/26/2013

Division of Anti-Infective Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 205223

Name of Drug: Metronidazole Vaginal Gel 1.3%

Applicant: Valeant Pharmaceuticals

Labeling Reviewed

Submission Date: May 24, 2013

Receipt Date: May 24, 2013

Background and Summary Description: The NDA is a new strength of topical metronidazole to be used for treatment of bacterial vaginosis in non-pregnant women.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review.

Recommendations

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by August 16, 2013. The resubmitted PI will be used for further labeling review.

Adverse Reactions

NO 1. 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.”

| | |
|----------------------------|---------------|
| Jane A. Dean, RN, MSN | July 22, 2013 |
| Regulatory Project Manager | Date |

| | |
|---|---------------|
| Maureen Dillon Parker/Frances V. LeSane | July 25, 2013 |
| Chief, Project Management Staff | Date |

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/s/

JANE A DEAN
07/26/2013