# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 205395Orig1s000

# OTHER REVIEW(S)

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

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

**Application:** NDA 205395

**Application Type:** New NDA

**Name of Drug/Dosage Form:** darunavir/cobicistat (TRADENAME under review)/Tablet

**Applicant:** Janssen Products, LP

**Receipt Date:** March 31, 2014

**Goal Date:** January 31, 2015

## 1. Regulatory History and Applicant's Main Proposals

Janssen has submitted an original NDA containing a fixed dose combination (FDC) tablet of darunavir (DRV) 800 mg, and cobicistat (COBI) 150 mg for treatment of HIV infection in adults. The sponsor has developed the formulation in collaboration with Gilead Sciences Inc. (Gilead). DRV (PREZISTA®) is an approved HIV-1 protease inhibitor, while COBI is a CYP3A inhibitor indicated to increase the systemic exposures of certain protease inhibitors (also known as a pharmacokinetic enhancer) currently under FDA review.

Janssen is requesting 3 years of market exclusivity for the FDC.

In the pediatric population, Janssen is requesting a partial waiver for HIV infected subjects from birth to less than 3 years of age, as well as subjects weighing less than 15 kg. In addition, they are requesting deferral of studies in pediatric subjects weighing greater than 15 kg.

## 2. Review of the Prescribing Information

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

## 3. Conclusions/Recommendations

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

In addition, the following labeling issues were identified:

I. HIGHLIGHTS OF PRESCIRIBNG INFORMATION
   i. Remove (b) (4) in the title of the HIGHLIGHTS section
   ii. Space required between Limitation Statement and Product Title

iii. There should be no space between Product Title and Initial US Approval
iv. Initial US approval date should follow the format outlined in
v. Product title should be changed to: TRADENAME (darunavir and cobicistat) tablet, (b) (4) for oral use
vi. The pharmacologic class for cobicistat is not accurate. See Stribild labeling.
vii. In CONTRAINDICATIONS section remove (b) (4)
viii. Please reformat the HIGHLIGHTS and FULL PRESCRIBING INFORMATION CONTENTS* so that the HIGHLIGHTS is no more than half page in length.
ix. Add a period at end of the sentence "See 17 PATIENT COUNSELING INFORMATION……."

II. FULL PRESCRIBING INFORMATION: CONTENTS*
i. The black horizontal line should appear on the TOC page, not the FPI page.
ii. Remove the word (b) (4)
iii. Remove brackets from statement at end of CONTENTS* section.

III. In FULL PRESCRIBING INFORMATION (FPI): DOSAGE AND ADMINISTRATION section:
i. Do not include information between section 2 and subsection 2.1. Incorporate that information into the subsections.
ii. Under subsection 2.4, cobicistat is misspelled.

IV. In FPI: ADVERSE REACTIONS section:
i. Information should not appear between section 6 and 6.1. A subsection heading is needed.
ii. Include the following statement preceding the adverse reactions from clinical trials: "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice".

V. In FPI: USE IN SPECIFIC POPULATIONS section:
i. The text following the title "Darunavir" should be in the same format as "Cobicistat: Studies in animals ……."

VI. In FPI: DESCRIPTION section:
i. The following correction is needed (b) (4)

VII. In FPI: Patient Counseling Information
i. Numbered sub-sections are not recommended since they may be redundant with other subsection titles in the labeling.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 8, 2014). The resubmitted PI will be used for further labeling review.

## Appendix

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

# Highlights

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

**HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI**

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

***Comment:***

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

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

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

***Comment:***

**YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
***Comment:*** *The horizontal line above TOC should appear on page one*

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

***Comment:***

**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:*** *White space between product title and intial US approval.*

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**.

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