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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<sup>®</sup>) 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 PRESCRIBING INFORMATION
  - i. Remove (b)<sub>(4)</sub> in the title of the HIGHLIGHTS section
  - ii. Space required between Limitation Statement and Product Title

## Selected Requirements of Prescribing Information

- 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.

# Selected Requirements of Prescribing Information

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## 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.

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## 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

## Selected Requirements of Prescribing Information

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

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

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

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

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

**Comment:**

#### Highlights Limitation Statement

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

**Comment:**

#### Product Title in Highlights

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

## Selected Requirements of Prescribing Information

### Comment:

#### Initial U.S. Approval in Highlights

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

### Comment:

#### Boxed Warning (BW) in Highlights

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

### Comment:

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

### Comment:

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

### Comment:

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

### Comment:

#### Recent Major Changes (RMC) in Highlights

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

### Comment:

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

### Comment:

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

### Comment:

#### Indications and Usage in Highlights

**YES**

## Selected Requirements of Prescribing Information

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

**Comment:** *The pharmacologic class for cobicistat is not accurate.*

### 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

- NO** 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:** (b) (4).

### Adverse Reactions in Highlights

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

**Comment:**

### Patient Counseling Information Statement in Highlights

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

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

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

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

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

**Comment:**

### Revision Date in Highlights

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

**Comment:**

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

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

- YES** 25. The TOC should be in a two-column format.  
***Comment:***
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
***Comment:***
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
***Comment:*** *The sponsor included WARNING heading, but it needs to be removed.*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
***Comment:***
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
***Comment:***
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
***Comment:*** *The subsection headings do not match the headings in the FPI. Lowercase lettering is used in the TOC and uppercase lettering is used in FPI. (see section 6 and 14)*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
***Comment:***

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

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

**Comment:**

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

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

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

*Comment:*

#### BOXED WARNING Section in the FPI

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

*Comment:*

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

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

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

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

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

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

*Comment:*

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

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

*Comment:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

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

## Selected Requirements of Prescribing Information

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

**Comment:**

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

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

**WARNING: [SUBJECT OF WARNING]**

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

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

- [text]
- [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

- [text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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/  
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NINA MANI  
01/27/2015

KAREN D WINESTOCK  
01/28/2015

This review was drafted on June 5, 2014.

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

**PATIENT LABELING REVIEW**

Date: January 5, 2015

To: Debra Birnkrant, MD  
Director  
**Division of Antiviral Products (DAVP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Morgan Walker, PharmD, MBA  
Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Jessica Fox, PharmD, RAC  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

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

Drug Name (established name) PREZCOBIX (darunavir and cobicistat)

Dosage Form and Route: Tablets, for oral use

Application Type/Number: NDA 205395

Applicant: Janssen Products, LP

## 1 INTRODUCTION

On March 31, 2014, Janssen Products, LP submitted for the Agency's review a New Drug Application (NDA) 205395 for PREZCOBIX (darunavir and cobicistat) tablets, with the proposed indication for the treatment of HIV-1 infection in adult patients.

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 Antiviral Products (DAVP) on April 3, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for PREZCOBIX (darunavir and cobicistat) tablets.

## 2 MATERIAL REVIEWED

- Draft PREZCOBIX (darunavir and cobicistat) tablets PPI received on March 31, 2014, and received by DMPP and OPDP on April 3, 2014.
- Draft PREZCOBIX (darunavir and cobicistat) tablets Prescribing Information (PI) received on March 31, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 18, 2014.
- Approved PREZISTA (darunavir) tablet comparator labeling dated April 7, 2014 and TYBOST (cobicistat) tablet comparator labeling dated September 24, 2014.

## 3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

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

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

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

Please let us know if you have any questions.

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

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/s/  
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MORGAN A WALKER  
01/05/2015

JESSICA M FOX  
01/05/2015

BARBARA A FULLER  
01/05/2015

LASHAWN M GRIFFITHS  
01/05/2015

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

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**Date of This Memorandum:** December 23, 2014  
**Requesting Office or Division:** Division of Antiviral Products (DAVP)  
**Application Type and Number:** NDA 205395  
**Product Name and Strength:** Prezcofix (darunavir, cobicistat) Tablets, 800 mg/150 mg  
**Submission Date:** December 22, 2014  
**Applicant/Sponsor Name:** Janssen Research and Development, L.L.C.  
**OSE RCM #:** 2014-719-2  
**DMEPA Primary Reviewer:** Mónica Calderón, PharmD, BCPS  
**DMEPA Associate Director:** Lubna Merchant, MS, PharmD

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#### 1 PURPOSE OF MEMO

Janssen has submitted the revised container label (Appendix A) for Prezcofix in response to the recommendations we made during a previous label and labeling Memo.<sup>1</sup> Thus, the Division of Antiviral Products (DAVP) requested that we review the revised label to determine if it is acceptable from a medication error perspective.

#### 2 CONCLUSIONS

The revised container label is acceptable from a medication error perspective.

---

<sup>1</sup> Calderon M. Label and Labeling Review for Prezcofix (NDA 205395). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Dec 19. 32 p. OSE RCM No.: 2014-719-1.

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/s/  
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MONICA M CALDERON  
12/24/2014

LUBNA A MERCHANT  
12/24/2014

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

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**Date of This Memorandum:** December 19, 2014  
**Requesting Office or Division:** Division of Antiviral Products (DAVP)  
**Application Type and Number:** NDA 205395  
**Product Name and Strength:** Prezcofix (darunavir, cobicistat) Tablets, 800 mg/150 mg  
**Submission Date:** November 24, 2014  
**Applicant/Sponsor Name:** Janssen Research and Development, L.L.C.  
**OSE RCM #:** 2014-719-1  
**DMEPA Primary Reviewer:** Mónica Calderón, PharmD, BCPS  
**DMEPA Team Leader:** Vicky Borders-Hemphill, PharmD

---

#### 1 PURPOSE OF MEMO

Janssen Research and Development, L.L.C has submitted the revised container label (Appendix A) for Prezcofix in response to recommendations that we made during a previous label and labeling review.<sup>1</sup> Thus, the Division of Antiviral Products (DAVP) requested that we review the revised container label to determine if it is acceptable from a medication error perspective.

Janssen has agreed with all of our recommendations with one exception, they wish to maintain the two statements “Alert: Find out about medicines...” on the side panel of the container label and “Each tablet contains...” on the principal display panel (PDP) so as to align with other Janssen HIV product labels that currently have similar text on the side panel and PDP panel, respectively. They further state the text, “Alert: Find out about medicines...” is highlighted to call the attention of the patient.

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<sup>1</sup>Calderon M. Label and Labeling Review for Prezcofix (NDA 205395). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Nov 06. 32 p. OSE RCM No.: 2014-719.

Of note, DAVP recommended Janssen remove [REDACTED] (b) (4)

(b) (4)

## 2 CONCLUSIONS

In light of the DAVP's recommendations to remove [REDACTED] (b) (4)

(b) (4)

We recommend the Applicant remove [REDACTED] (b) (4) statement from the container label.

### 2.1 RECOMMENDATIONS TO JANSSEN

#### A. Container Label

1. Remove the following statement from the PDP, [REDACTED] (b) (4) to align with DAVP's recommendation to remove the statement from the FPI.

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

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/s/  
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MONICA M CALDERON  
12/19/2014

BRENDA V BORDERS-HEMPHILL  
12/19/2014

Consultative Review  
DPP Consult #11499

Consultant Reviewer: Cara Alfaro, Pharm.D.  
Clinical Analyst  
Division of Psychiatry Products/OND/CDER

Kofi A. Kumi, Ph.D.  
Clinical Pharmacology Reviewer  
DCPI/Office of Clinical Pharmacology

Consultation Requester: Sarita Boyd  
Senior Clinical Analyst  
Division of Anti-Viral Products (DAVP)

Subject of Request: Product labeling for boosted protease inhibitors when co-administered with lurasidone (Latuda)

Date of Request: 11/21/2014

Requested Completion Date: 12/12/2014

**Background**

The Division of Anti-Viral Products (DAVP) has consulted the Division of Psychiatry Products (DPP) and the Office of Clinical Pharmacology (OCP) for labeling recommendations regarding the potential concomitant use of lurasidone and boosted protease inhibitors. DAVP has been discussing how to label the predicted drug-drug interaction between lurasidone, an atypical antipsychotic and CYP3A4 substrate, and HIV protease inhibitors that are co-administered with either ritonavir or cobicistat to increase systemic exposure of the protease inhibitor. Examples of these medications, referred to as “boosted protease inhibitors” include darunavir/ritonavir, darunavir/cobicistat, atazanavir/ritonavir and atazanavir/cobicistat. DAVP notes that although ritonavir and cobicistat are strong CYP3A inhibitors, these drugs are always combined with an HIV protease inhibitor in clinical practice and are never used alone. The net effect of boosted protease inhibitors (e.g. darunavir/cobicistat) are predicted to be borderline moderate-to-strong CYP3A inhibitors based on drug-drug interaction data with maraviroc (Selzentry). DAVP is currently reviewing the NDA for darunavir/cobicistat (Prezcobix) (IND 113198, NDA 205395)

DPP (Alfaro) and OCP (Kumi) attended a labeling meeting on 12/2/2014 to briefly discuss labeling recommendations regarding this issue. This consult serves as the final recommendation from DPP and OCP and is consistent with advice shared at the labeling meeting.

**Latuda (lurasidone)**

Latuda (lurasidone) is an atypical antipsychotic approved for the treatment of schizophrenia and the treatment of depressive episodes associated with bipolar I disorder. The recommended dose range for the treatment of schizophrenia is 40 to 160 mg/day and the recommended dose range

for the treatment of depressive episodes associated with bipolar I disorder is 20 to 120 mg/day. Latuda is available in the following tablet strengths: 20 mg, 40 mg, 60 mg, 80 mg and 120 mg.

As indicated in currently approved product labeling, co-administration of lurasidone with strong CYP3A4 inhibitors including ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil is contraindicated. Lurasidone is primarily metabolized via CYP3A4. A drug interaction study evaluating the effect of ketoconazole 400 mg/day on lurasidone pharmacokinetics demonstrated a ~7-fold increase in lurasidone C<sub>max</sub> and ~9-fold increase in lurasidone AUC when co-administered with ketoconazole. The recommended dose range for lurasidone is 20 to 160 mg/day (40 to 80 mg/day most common) and the lowest dosage form strength is 20 mg. The dose of lurasidone cannot be adequately adjusted to “off-set” the increase in C<sub>max</sub>/AUC with concomitant administration and a strong CYP3A4 inhibitor. Therefore, strong CYP3A4 inhibitors are contraindicated with lurasidone administration.

A drug interaction study evaluating the effect of diltiazem, a moderate CYP3A4 inhibitor, on the pharmacokinetics of lurasidone demonstrated a ~2-fold increase in lurasidone C<sub>max</sub> and AUC. Product labeling for Latuda advises the prescriber to reduce the dose of lurasidone by half if used with moderate CYP3A4 inhibitors such as diltiazem.

From a safety perspective, increases in lurasidone C<sub>max</sub>/AUC would result in increases in extrapyramidal symptoms including dystonia, parkinsonism and akathisia; and somnolence. In a patient receiving a strong CYP3A4 inhibitor, other atypical antipsychotics that do not have this drug interaction contraindication are available to the clinician for the management of these psychiatric disorders. Other atypical antipsychotics include olanzapine [Zyprexa] (metabolized via CYP1A2), aripiprazole [Abilify] (CYP3A4, CYP2D6; ketoconazole increased AUC of aripiprazole 63%), risperidone [Risperdal] (CYP2D6), paliperidone [Invega] (P-gp), quetiapine [Seroquel] (CYP3A4; reduce dose to 1/6 when co-administered with strong CYP3A4 inhibitors), ziprasidone [Geodon] (CYP3A4, ketoconazole increased AUC of ziprasidone by ~40%), and asenapine [Saphris] (CYP1A2). All of these atypical antipsychotics are approved for the treatment of schizophrenia. Quetiapine is the only other atypical antipsychotic approved for the treatment of depressive episodes associated with bipolar I disorder. Olanzapine in combination with fluoxetine [Symbyax] is also approved for the treatment of depressive episodes associated with bipolar I disorder.

### Questions

We are considering one of the following three approaches to labeling for our products:

1. Contraindicate lurasidone with all of these boosted protease inhibitors. This approach is conservative from a safety standpoint. Would this approach eliminate an important therapeutic option, if the drug-drug interaction can in fact be reasonably managed from a safety and efficacy standpoint?

*DPP/OCP response: Based on the data discussed above, we would advise that lurasidone be contraindicated with boosted protease inhibitors. Though you have indicated that the net effect of boosted protease inhibitors (e.g. darunavir/cobicistat) are predicted to be borderline moderate-to-strong CYP3A inhibitors based on available drug-drug interaction data, it is difficult to predict the magnitude of the drug interaction with lurasidone. Diltiazem increased*

*the AUC of lurasidone by ~2 fold while ketoconazole increased the AUC of lurasidone by ~9-fold. If the inhibition potential of boosted protease inhibitors fell in between these values, it would still be difficult to adjust the dose of lurasidone based on the usual dose range of 40 – 80 mg/day and the available dosage form strengths. There are other atypical antipsychotics available (see above) that clinicians could prescribe that would not have this drug interaction liability.*

*Therefore, of the 3 approaches you are considering for your product labeling, we would advise this approach. If drug interaction data become available that would assist in determining the extent of the interaction (e.g. boosted protease inhibitors and lurasidone), and the dose of lurasidone could be adjusted based on dosage form strengths available, a dose reduction strategy could be considered.*

(b) (4)

We appreciate the opportunity to provide advice to DAVP regarding the drug interaction potential between lurasidone (Latuda) and boosted protease inhibitors. Please feel free to contact DPP or OCP if you have any further questions.

cc: DPP/Mathis  
Kempf  
Berman  
David  
Alfaro

OCP/Zhu  
Kumi

DAVP/Boyd  
Mani

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/s/  
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CARA L ALFARO  
12/11/2014

LUCAS P KEMPF  
12/15/2014

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

---

DATE:            December 5, 2014

TO:             Debra Birnkrant, M.D.  
Director, Division of Antiviral Products (DAVP)  
Office of Antimicrobial Products  
Office of New Drugs

FROM:          Xikui Chen, Ph.D., Pharmacologist  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH:     Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations (OSI)  
and  
William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT:      Review of EIRs covering NDA 205395,  
Darunavir/Cobicistat fixed dose combination, sponsored  
by Janssen Products LP

At the request of the Division of Antiviral Products, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following bioequivalence study:

**Study Number:**    TMC114IFD1003  
**Study Title:**     "A single-dose, open-label, 3-panel, randomized, pivotal crossover study to assess the bioequivalence of darunavir when coadministered with cobicistat as either a fixed dose combination tablet (G006) or as single agents under fed and fasted conditions in healthy subjects"

Clinical Site at AZ Jan Palfijn:

The inspection of the clinical portion of the study was conducted by Sheri Oliver (ORA Investigator, ATL-DO) at AZ Jan Palfijn, Clinical Pharmacology Unit, in Merksem, Belgium, from November 3 to November 7, 2014. The audit included the reserve samples, informed consent forms, study protocols, reporting of adverse events, case report forms, subject records, personnel, standard operating procedures (SOPs), ethics committee approvals, protocol deviations, drug accountability records, and the receipt, storage and dispensing of the medications. There were no objectionable findings during the inspection and Form FDA-483 was not issued.

Analytical Site at (b) (4) :

The inspection of the bioanalytical portion of the study was conducted by (b) (4) and (b) (4) at (b) (4)

The audit included a thorough review of all records associated with the studies and method validation, correspondence, records of subject sample receipt and storage, notebooks and electronic records, SOPs, as well as examination of facilities and interviews and discussions with the firm's management and staff. There were no objectionable findings, and Form FDA-483 was not issued for the assay of darunavir in study TMC114IFD1003.

Analytical Site at (b) (4)

The cobicistat analytical data conducted at (b) (4) are not included in this review.

**Conclusion:**

Following review of the inspectional findings, I recommend that:

- The results from the clinical and darunavir bioanalytical portions of study TMC114IFD1003 are acceptable for Agency review

Xikui Chen, Ph.D.  
Bioequivalence Branch, DBGLPC, OSI

**Final Classifications:**

**NAI - AZ Jan Palfijn, Merksem, Belgium  
(FEI# 3003945358)**

**NAI - (b) (4)  
(FEI# (b) (4) )**

**DARRTS CC:**

OSI/DBGLPC/Taylor/Haidar/Bonapace/Skelly/Choi/Dasgupta/Chen  
OSI/DBGLPC/Dejernett/Nkah/Fenty-Stewart/Johnson  
CDER/OND/OAP/DAVP/Debra Birnkrant/Nina Mani/Jeffrey S Murray  
CDER/OPS/ONDQA/Angelica Dorantes  
ORA/ATL-DO/Sheri Oliver

(b) (4)

Draft: XC 11/25/2014

Edits: MFS 11/28/2014; SHH 12/01/2014; WHT 12/01/2014

OSI: File#: BE 6706

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical  
Sites/ (b) (4)

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical  
Sites/AZ Jan Palfijn, Merksem, Belgium

FACTS: (b) (4)

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/s/  
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XIKUI CHEN  
12/05/2014

SAM H HAIDAR  
12/05/2014

WILLIAM H TAYLOR  
12/05/2014

**MEMORANDUM**

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

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DATE: December 4, 2014

TO: Debra Birnkrant, M.D.  
Director, Division of Antiviral Products (DAVP)  
Office of Antimicrobial Products  
Office of New Drugs

Badrul Chowdhury, M.D., Ph.D.  
Director, Division of Pulmonary, Allergy, and  
Rheumatology Products (DPARP)  
Office of New Drugs

Wayne Dehaven, Ph.D.  
Director, Division of Bioequivalence I (DBI)  
Office of Generic Drugs

FROM: Arindam Dasgupta, Ph.D., Pharmacologist  
GLP Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations  
and  
Kara A. Scheibner, Ph.D., Pharmacologist  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations (OSI)  
and  
William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Surveillance Inspection of (b) (4)  
covering: NDA 205395 (Darunavir/Cobicistat fixed (b) (4) e

(b) (4)  
(b) (4)  
and

**Summary:**

At the request of the Division of Antiviral Products, the Division of Pulmonary, Allergy, and Rheumatology Products, and the Division of Bioequivalence I, the OSI Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of analytical portions of the following bioequivalence studies conducted by (b) (4). Additional studies were also selected as part of a surveillance approach to assess the firm's overall bioanalytical operations and capability to conduct bioequivalence studies.

Please note that a separate review is being finalized for the audit of clinical portions of study TMC114IFD1003 at AZ Jan Palfijn, Merksem, Belgium and analytical portions of study TMC114IFD1003 at (b) (4).

**Study Number:** TMC114IFD1003

**Study Title:** "A single-dose, open-label, 3-panel, randomized, pivotal crossover study to assess the bioequivalence of darunavir when coadministered with cobicistat as either a fixed dose combination tablet (G006) or as single agents under fed and fasted conditions in healthy subjects"

**Study Number:**

**Study Title:**

(b) (4)

**Study Number:**

**Study Title:**

**Conclusion:**

Following review and evaluation of the Form FDA-483 observation and the response from (b) (4), in our opinion, the analytical data generated for the study TMC114IFD1003, (b) (4) (b) (4) were not affected by the cited condition. Therefore, we recommend that the data portions of studies TMC114IFD1003, (b) (4) (b) (4) be accepted for further agency review.

Arindam Dasgupta, Ph.D.  
GLP Branch, DBGLPC, OSI  
Kara A. Scheibner, Ph.D.  
Bioequivalence Branch, DBGLPC, OSI

**Final Classification:**

**VAI -** (b) (4)  
**(FEI#** (b) (4)

DARRTS CC:  
OSI/DBGLPC/Taylor/Haidar/Bonapace/Skelly/Choi/Dasgupta/Scheibner

OSI/DBGLPC/Dejernet/Nkah/Fenty-Stewart/Johnson  
CDER/OND/OAP/DAVP/Mani/Murray/Birnkrant  
CDER/OPS/ONDQA/Dorantes  
CDER/OND/DPARP/Musse/Chowdhury  
CDER/OGD/Conner/Chang/Dehaven

[REDACTED] (b) (4)

Draft: KAS 12/1/2014

Edits: AD 12/1/2014; MFS 12/1/2014; SHH 12/3/2014; WHT 12/4/2014

OSI: File#: BE 6706, BE 6681, BE 6768

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical  
Sites/ [REDACTED] (b) (4)

FACTS: [REDACTED]

# **ATTACHMENT: 1**

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/s/  
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KARA A SCHEIBNER  
12/04/2014

ARINDAM DASGUPTA  
12/04/2014

SAM H HAIDAR  
12/04/2014

WILLIAM H TAYLOR  
12/04/2014

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**LABEL AND LABELING REVIEW**

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

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

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**Date of This Review:** November 6, 2014  
**Requesting Office or Division:** Division of Antiviral Products (DAVP)  
**Application Type and Number:** NDA 205395  
**Product Name and Strength:** Prezcobix (darunavir, cobicistat) Tablets, 800/150 mg  
**Product Type:** Multi-Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Janssen Research and Development, L.L.C.  
**Submission Date:** March 31, 2014  
**OSE RCM #:** 2014-719  
**DMEPA Primary Reviewer:** Mónica Calderón, PharmD, BCPS  
**DMEPA Associate Director:** Irene Chan, PharmD, BCPS

---

## 1 REASON FOR REVIEW

Janssen is developing Prezcobix for the treatment of HIV-1 under NDA 205395. Thus, the Division of Antiviral Products (DAVP) requested that DMEPA evaluate the Applicant's proposed container label and full prescribing information (FPI) for areas of vulnerability that could lead to medication errors.

## 2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing a single strength (800 mg/150 mg) combination tablet. The daily dose is 800 mg/150 mg (one tablet) once daily and the product will be packaged in 30-count bottles, which is supported by the dosage and administration of this product. DMEPA performed a risk assessment of the proposed FPI and determined the Dosage and Administration section is clearly stated. (b) (4)

We note that the label can be revised for improved clarity and increased prominence of important information. Additionally, all labels and labeling should be updated to reflect the conditionally acceptable proprietary name, Prezcobix.

## 4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes the FPI is acceptable from a medication error perspective and we have no recommendations. However, changes are needed for the container label to ensure safe use of the product. See section 4.1, below, for our recommendations.

### 4.1 RECOMMENDATIONS FOR JANSSEN

#### A. General Recommendation

Replace “TRADENAME” with the conditionally acceptable proprietary name, Prezcobix, where applicable throughout the labels and labeling.

#### B. Container Label

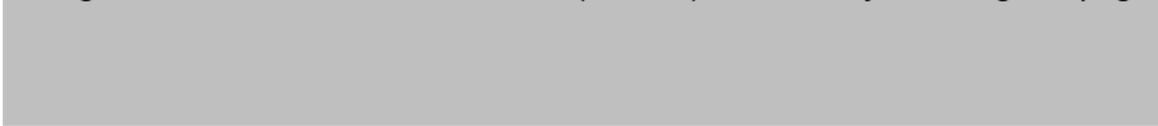
1. For consistency between all labels and labeling, add the statement [REDACTED] (b) (4) [REDACTED] to the principal display panel (PDP).
2. Remove [REDACTED] (b) (4) [REDACTED]
3. Move the “Alert: Find out about medicines...” statement to the principal display panel in order to more clearly display this important information. In order to accommodate this change, consider moving the “Each tablet contains...” statement to the side panel.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Prezcofix that Janssen submitted on August 11, 2014.

<b>Table 2. Relevant Product Information for Prezcofix</b>	
<b>Active Ingredient</b>	darunavir, cobicistat
<b>Indication</b>	For use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	Tablet
<b>Strength</b>	800 mg/150 mg
<b>Dose and Frequency</b>	One tablet once daily
<b>How Supplied</b>	Bottles of 30 tablets
<b>Storage</b>	Store at 20-25°C (between 68-77°F); with excursions permitted to 15°-30°C (59°-86°F)
<b>Container Closure</b>	white, high-density polyethylene (HDPE), 120-mL bottle  (b) (4)

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/s/  
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MONICA M CALDERON  
11/06/2014

IRENE Z CHAN  
11/06/2014

## 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 # 205395	NDA Supplement #: BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Prezcobix Established/Proper Name: darunavir/cobicistat Dosage Form: Tablet, film coated Strengths: 800 mg/150 mg		
Applicant: Janssen Products, LP Agent for Applicant (if applicable): N/A		
Date of Application: March 31, 2014 Date of Receipt: March 31, 2014 Date clock started after UN:		
PDUFA Goal Date: January 31, 2015		Action Goal Date (if different):
Filing Date: May 30, 2014		Date of Filing Meeting: May 2, 2014
Chemical Classification: 4		
Proposed indication(s)/Proposed change(s): This combination of a human immunodeficiency virus (HIV-1) protease inhibitor <span style="background-color: #cccccc; padding: 2px;">(b)(4)</span> is indicated for the treatment of HIV-1 infection in adult patients		
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><b>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</b></i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i><b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b></i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
<i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>  <i><b>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</b></i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>  <i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></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): IND 113198				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Standard
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><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></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  Comment: Following review of the application the sponsor was notified that the full user fee would be needed if they wanted the information from study 130 included in labeling and if they wanted to use this study to support their request for exclusivity. Sponsor has until June 2, 2014 to provide guidance on the path forward.</p> <p><input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>			
<p><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></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	
<p>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)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	
<p>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)]?</p> <p><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></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	
<p>Application No.</p>	<p>Drug Name</p>	<p>Exclusivity Code</p>	<p>Exclusivity Expiration</p>	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2)</i></p>				

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.

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  If yes, # years requested: 3  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>For BLAs:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)

<i>is the content of labeling (COL).</i>	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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:  <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)  <b>If no</b> , explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes</b> , BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <b>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

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

<b>(NDAs/NDA efficacy supplements only)</b>				
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>  <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification</b> <b>(NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> Date of consult sent to Controlled Substance Staff:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>PREA</u>  Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></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 &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>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?</b>  <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>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)?</b>  <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA (NDAs/NDA efficacy supplements only):</u>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Currently under OSE review. User fee goal date: June 29, 2014
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

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

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

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>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <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)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
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)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> December 19, 2012	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 2, 2014

BLA/NDA/Supp #: 205395

PROPRIETARY NAME: Prezcobix

ESTABLISHED/PROPER NAME: darunavir/cobicistat

DOSAGE FORM/STRENGTH: Tablet/800 mg/150 mg

APPLICANT: Janssen Products, LP

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** This combination of darunavir (DRV), a human immunodeficiency virus (HIV-1) protease inhibitor, and cobicistat (COBI), a CYP3A inhibitor (b)(4) is indicated for the treatment of HIV-1 infection in adult subjects.

**BACKGROUND:** Janssen has submitted an original NDA containing a fixed dose combination (FDC) tablet of 800 mg of DRV and 150 mg of COBI for treatment of HIV infection in adults. This formulation has been developed by the Sponsor in collaboration with Gilead Sciences Inc (Gilead). DRV (PREZISTA®) is an approved HIV-1 protease inhibitor, while COBI is a pharmacokinetic enhancer that is currently under FDA review.

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

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

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nina Mani	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Mary Singer		Y
Clinical	Reviewer:	Sarita Boyd	Y
	TL:	Mary Singer	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		

OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Takashi Komatsu	Y
	TL:	Julian O'Rear	N

Clinical Pharmacology	Reviewer:	Stanley Au	Y
	TL:	Shirley Seo	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Laine Myers	Y
	TL:	Hanan Ghantous	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Fuqiang Liu	Y
	TL:	Stephen Miller	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Erika Pfeiler	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Rose Xu	Y
	TL:	Krishnakali Ghosh	N
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	<u>Biopharmaceutics</u> Minerva Hughes, Reviewer (phone) <u>DMEPA</u> Monica Calderon <u>DRISK</u> Rheema Mehta <u>Patient Labeling</u> Sharon Mills, Reviewer <u>CPMS</u> Karen Winestock <u>Signatory</u> Jeffrey Murray		
Other attendees	<u>OSE</u> Danyal Chaudhry <u>Clinical</u> Kimberly Struble <u>Regulatory Project Manager</u> Mammah Borobr <u>Acting Deputy Director, Safety</u> William Tauber		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p> </li> </ul>	<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"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>If no, explain:</b></p>	
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b> Sponsor will be asked to submit narratives for deaths, SAEs, and treatment-related discontinuations for Study GS-US-216-0130 through Week 48 that have not already been submitted with Week 24 analysis.</p> <p>Statistical involvement was deemed to be unnecessary for this NDA since the above clinical trial was a single arm study with a limited number of subjects, and was only being evaluated for safety.</p>	<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
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b> BE studies are required for approval</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></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"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><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></li> </ul>	<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"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></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"> <li>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</li> </ul>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p>permit review based on medical necessity or public health significance?</p> <p><b>Comments:</b></p>	
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b>  For the pivotal BE study, Clinical Pharmacology (OCP) will review the secondary food effects analysis, while ONDQA (Biopharmaceutics) will address bioequivalence under fasting and fed conditions.</p> <p>The following comments are being sent in the 74 day letter for the TMC114IFD1003 trial</p> <ol style="list-style-type: none"> <li>1. For the high fat meal that was administered in treatment F, please clarify if the meal provided approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.</li> <li>2. For the food effect evaluation (treatments E and F), please specify whether all subjects were dosed at the same time relative to the start of the meal: 30 minutes after the start of the meal.</li> <li>3. For the darunavir/cobicistat fixed dose combination tablets, high fat meals increased darunavir AUC<sub>(0-inf)</sub> by 70% and C<sub>max</sub> by 127%. In contrast, food increased the darunavir AUC and C<sub>max</sub> by 40% for the single entity darunavir tablets (coadministered with ritonavir), according to the darunavir U.S. prescribing information. Please evaluate and submit information to the FDA regarding whether potential safety issues are associated with the higher darunavir exposure observed with the</li> </ol>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

darunavir/cobicistat fixed dose combination tablets compared to the darunavir single entity formulation (coadministered with ritonavir).	
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>BIOSTATISTICS</b>  <b>Comments:</b>	<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
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<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
<b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b>  <b>Comments:</b>	<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
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b> Biopharmaceutics will address bioequivalence under fasting and fed conditions for the pivotal BE study.  The following comments will be sent in the 74 day letter: 1. Please submit the SAS transport files for the plasma concentration (pc.xpt) and PK parameters (pp.xpt) from the pivotal bioequivalence study TMC114IFD1003 as separate files in column format, as illustrated below.  <div style="background-color: gray; width: 100%; height: 20px; margin-top: 5px;"></div>	<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

(b) (4)

<p>2. Provide the formulation composition and batch analysis data for the drug products used in clinical study GS-US-216-013; specifically, the following drug product lots:</p> <ul style="list-style-type: none"><li>i. COBI: BB1006B1, BB1006B1-A, BB1102D1</li><li>ii. DRV: BEZ0S00, BGZ0E00</li></ul>	
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"><li>• Categorical exclusion for environmental assessment (EA) requested? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</li></ul> <p><b>If no</b>, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><b>Comments:</b> The ONDQA reviewer noted that the calculated Maximum Expected Environmental Concentration (MEEC, Expected Introduction Concentration, or EIC-Aquatic based on use) was more than 1 part per billion (ppb); hence they would put in an environmental assessment consult through Biopharmaceutics.</p>	
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"><li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</li></ul> <p><b>Comments:</b> The following comments are being in the 74 day letter:</p> <ul style="list-style-type: none"><li>1. You state that microbiological purity of your drug product is ensured by the use of a validated manufacturing process, but you do not provide information detailing the validation process or the steps taken in manufacturing to ensure microbiological quality. Describe these steps and their associated validation studies.</li></ul>	<p><input type="checkbox"/> Not Applicable</p>

<p>2. It is unclear if you plan to perform microbial enumeration testing as part of your stability program. Please note that you should perform microbial enumeration testing minimally at the initial testing time point. Clarify the stability testing schedule for microbial enumeration testing.</p> <p>3. Provide a statement verifying that microbial enumeration testing methods are suitable for use with the drug product.</p>	
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b> Consult has been put in with OSI.</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><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" 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><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• 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?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<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"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Jeffrey Murray, DAVP Deputy Division Director

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V): July 29, 2014

**21<sup>st</sup> Century Review Milestones (see attached)** (listing review milestones in this document is optional):

**Filing date:** May 15, 2014

**Day 74 letter due date:** June 13, 2014

**GAM# 1:** May 29, 2014

**GAM# 2:** June 27, 2014

**Mid-cycle:** July 29, 2014

**GAM# 3/Labeling #1:** September 1, 2014

**GAM# 4/Labeling #2:** September 29, 2014

**GAM# 5/Labeling #3:** October 28, 2014

**Labeling #4:** November 21, 2014

**PeRC:** December 3, 2014

**Wrap-up:** December 22, 2014

**Comments:**

**REGULATORY CONCLUSIONS/DEFICIENCIES**

<input type="checkbox"/>	The application is unsuitable for filing.
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.  Comment: On May 28, 2014, the user fee staff notified the Division that the sponsor needed to pay the full application fee because evaluation of study 130 is considered clinical data. The sponsor was notified that the full user fee would be needed if they wanted the information from study 130 included in labeling and if they wanted to use this study to support their request for exclusivity. Sponsor has until June 2, 2014 to provide guidance on the path forward.</p> <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>
<b>ACTIONS ITEMS</b>	
<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"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• 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)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<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: <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
<input type="checkbox"/>	Other

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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NINA MANI  
05/30/2014

## PMR/PMC Development Template

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

---

NDA/BLA # 205395  
Product Name: Prezcofix (darunavir and cobicistat)

---

PMR/PMC Description: Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of darunavir and cobicistat fixed dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 3 years to less than 6 years of age and weighing at least 15 kg. The safety and antiviral activity (efficacy) of darunavir and cobicistat FDC age-appropriate formulation in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children ages 3 to less than 6 years may not be required if the dosing recommendation for the FDC age-appropriate formulation can be supported by pediatric trials already conducted with the individual drug products and if the age-appropriate FDC produces similar exposures as the individual components.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/31/2020</u>
	Study/Trial Completion:	<u>12/31/2020</u>
	Final Report Submission:	<u>12/31/2021</u>
	Other:	<u>MM/DD/YYYY</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

The product is ready for approval in adults. Pediatric development of darunavir and cobicistat fixed-dose combination is dependent on the ongoing pediatric program for cobicistat as a single agent in combination with darunavir being conducted by the cobicistat sponsor.

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 goal of the study(ies) is to evaluate the safety and efficacy of darunavir and cobicistat fixed dose combination in pediatric patients 3 years to less than 6 years of age and weighing at least 15 kg and provide a pediatric dosing recommendation.

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

***If not a PMR, skip to 4.***

– **Which regulation?**

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

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

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

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

Analysis of spontaneous postmarketing adverse events?

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

Analysis using pharmacovigilance system?

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

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

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

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

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

Age group 3 years to less than 6 years and weighing at least 15 kg:

Approval of Prezcobix (darunavir 800 mg and cobicistat 150 mg) is for adults only. The individual drug products are currently approved in adults; while only darunavir (coadministered with ritonavir) is approved in pediatric patients 3 years to less than 18 years of age. The cobicistat sponsor (Gilead) is currently conducting studies with cobicistat in combination with darunavir as individual drug products in pediatric patients, including ages 3 years to less than 6 years.

If pediatric clinical trials support safety and efficacy of cobicistat with darunavir as individual drug products in ages 3 to less than 6 years, then the Sponsor has to conduct a bioequivalence (BE) study with the age-appropriate fixed dose combination compared to the individual components. If the BE study shows comparable exposures of darunavir in the fixed dose combination compared to the individual components, then there will not be a need for a dedicated trial with the fixed dose combination, Prezcobix, in pediatric patients 3 to less than 6 years of age.

However, if the pediatric clinical trials with the individual drug products do not lead to a dosing recommendation in children 3 to less than 6 years of age or the BE study does not show comparable exposures of darunavir in the fixed dose combination compared to the individual components, then the Sponsor has to conduct a trial evaluating the fixed dose combination, Prezcobix, in children 3 years to less than 6 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)  
Antiviral activity (efficacy)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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

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

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**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.*

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(signature line for BLAs)

## PMR/PMC Development Template

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

---

NDA/BLA # 205395  
Product Name: Prezcofix (darunavir and cobicistat)

---

PMR/PMC Description: Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of darunavir and cobicistat fixed dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 6 years to less than 12 years of age and weighing at least 15 kg. The safety and antiviral activity (efficacy) of darunavir and cobicistat FDC age-appropriate formulation in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children ages 6 years to less than 12 years may not be required if the dosing recommendation for the FDC age-appropriate formulation can be supported by pediatric trials already conducted with the individual drug products and if the age-appropriate FDC produces similar exposures as the individual components.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/31/2020</u>
	Study/Trial Completion:	<u>12/31/2020</u>
	Final Report Submission:	<u>12/31/2021</u>
	Other:	<u>MM/DD/YYYY</u>

6. 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

The product is ready for approval in adults. Pediatric development of darunavir and cobicistat fixed-dose combination is dependent on the ongoing pediatric program for cobicistat as a single agent in combination with darunavir being conducted by the cobicistat sponsor.

7. 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 goal of the study(ies) is to evaluate the safety and efficacy of darunavir and cobicistat fixed dose combination in pediatric patients 6 years to less than 12 years of age and provide a pediatric dosing recommendation.

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

*If not a PMR, skip to 4.*

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

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

- Analysis using pharmacovigilance system?

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

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

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

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

9. 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.

Age group 6 years to less than 12 years

Approval of Prezcoibix (darunavir 800 mg and cobicistat 150 mg) is for adults only. The individual drug products are currently approved in adults; while only darunavir (coadministered with ritonavir) is approved in pediatric patients 3 years to less than 18 years of age. The cobicistat sponsor (Gilead) is currently conducting studies with cobicistat in combination with darunavir as individual drug products in pediatric patients, including ages 6 years to less than 12 years.

If pediatric clinical trials support safety and efficacy of cobicistat with darunavir as individual drug products in ages 6 years to less than 12 years, then the Sponsor has to conduct a bioequivalence (BE) study with the age-appropriate fixed dose combination compared to the individual components. If the BE study shows comparable exposures of darunavir in the fixed dose combination compared to the individual components, then there will not be a need for a dedicated trial with the fixed dose combination, Prezcoibix, in pediatric patients 6 years to less than 12 years of age.

However, if the pediatric clinical trials with the individual drug products do not lead to a dosing recommendation in children 6 to less than 12 years of age or the BE study does not show comparable exposures of darunavir in the fixed dose combination compared to the individual components, then the Sponsor (Janssen) needs to conduct a trial evaluating the fixed dose combination, Prezcoibix, in children 6 years to less than 12 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)  
Antiviral activity (efficacy)
- 

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
- 

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

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

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

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

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**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.*

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(signature line for BLAs)

## PMR/PMC Development Template

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

---

NDA/BLA # 205395  
Product Name: Prezcofix (darunavir and cobicistat)

---

PMR/PMC Description: Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of darunavir and cobicistat fixed-dose combination (FDC) tablets in HIV-infected pediatric subjects 12 years to less than 18 years of age. The safety and antiviral activity (efficacy) of darunavir and cobicistat FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 12 years to less than 18 years of age may not be required if the dosing recommendation for the FDC tablets can be supported by pediatric trials already conducted with the individual drug products and if the FDC produces similar exposures as the individual components.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/31/2020</u>
	Study/Trial Completion:	<u>12/31/2020</u>
	Final Report Submission:	<u>12/31/2021</u>
	Other:	<u>MM/DD/YYYY</u>

11. 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

The product is ready for approval in adults. Pediatric development of darunavir and cobicistat fixed-dose combination is dependent on the ongoing pediatric program for cobicistat as a single agent in combination with darunavir being conducted by the cobicistat sponsor.

12. 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 goal of the study(ies) is to evaluate the safety and efficacy of Prezcobix in pediatric patients 12 years to less than 18 years of age and provide a pediatric dosing recommendation.

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

***If not a PMR, skip to 4.***

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

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

- Analysis using pharmacovigilance system?

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

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

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

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

14. 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.

Age group 12 years to less than 18 years

Approval of Prezcofix (darunavir 800 mg and cobicistat 150 mg) is for adults only. The individual drug products are currently approved in adults; while only darunavir (coadministered with ritonavir) is approved in pediatric patients 3 years to less than 18 years of age. The cobicistat sponsor (Gilead) is currently conducting trials with cobicistat in combination with darunavir as individual drug products in pediatric patients, including ages 12 years to less than 18 years.

A bioequivalence study in adults supports the bioequivalence of Prezcofix to the individual drug products. If pediatric clinical trials support safety and efficacy of darunavir 800 mg and cobicistat 150 mg as individual drug products in ages 12 to less than 18 years, then Prezcofix will be available for use in this population (i.e. at same dose and frequency as approved in adults); and a dedicated adolescent trial with Prezcofix will not be needed.

However, if the pediatric clinical trials with the individual drug products do not lead to a dosing recommendation in children 12 years of age and older, the Sponsor (Janssen) will need to conduct a trial evaluating Prezcofix in children 12 years of age and older.

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)  
Antiviral activity (efficacy)
- 

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

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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

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

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**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.*

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(signature line for BLAs)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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NINA MANI  
01/14/2015