CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210192Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary

Date	11/1/2017
From	Antoine El Hage, Ph.D. Susan Thompson, M.D./Team Leader Kassa Ayalew, M.D., MPH. /Branch Chief Division of Clinical Compliance Evaluation
To	Nina Mani, Ph.D. Senior Regulatory Health Project Manager Yodit Below, M.D., Medical Reviewer Kimberly Struble, PharmD., Team Leader Division of Antiviral Products (DAVP)
NDA #	NDA 210192
Applicant	ViiV Healthcare Company.
Drug	JULICA (dolutegravir, and rilpivirine (DTG/RPV) Fixed dose tablets
NME	No
Therapeutic Classification	Priority
Proposed Indication	Treatment of adult subjects with HIV-1 virus infection who are virologically suppressed (HIV-1 RNA) less than 50 copies/mL on a stable antiretroviral regimen and no history of resistance (b) (4) (b) (4)
Consultation Request Date	June 29, 2017
Summary Goal Date	November 13, 2017
Action Goal Date	November 17, 2017
PDUFA Date	December 1, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections for this NDA were conducted at two domestic clinical sites and two foreign sites. The inspection of the four clinical investigators listed below revealed no regulatory violations at three of four sites. Based on the inspections of the four clinical sites, the inspectional findings support validity and acceptability of the data as reported by the sponsor under this NDA.

The preliminary classification for Drs. Parks and Rubio is No Action Indicated (NAI). The final classification for Dr. Richmond's site is No Action Indicated. No regulatory violations were noted for the three sites listed below. Data from these sites are acceptable for use in support of the pending application. The preliminary classification for Dr. Hung is Voluntary Action Indicated (VAI). The audit revealed minor protocol deviations. The minor deviations do not appear to have a significant impact on safety or efficacy.

The final classification for the above three sites will be made later after receiving and reviewing the EIRs provided by the field investigators. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending EIRs.

II. BACKGROUND

Dolutegravir is a registered trademark of the ViiV Healthcare, a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor INTST1) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. Rilpirivine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used for the treatment of human immunodeficiency virus (HIV-1) infection in combination with other antiretroviral agents. More than 1000 HIV-1 infected subjects have been dosed with the two drugs in an ongoing Phase 2 clinical studies which demonstrated that co-administration of the two exhibited beneficial effects. The combination of the two approved products is not approved yet.

The applicant has co-formulated DTG 50 mg, RPV 25 mg into a single agent administered together as an oral tablet. The use of a fixed-dose combination may have a major impact on the global prevalence and burden of HIV, as it may represent a simple, well-tolerated, highly efficacious treatment for all HIV-1 infected subjects.

The Applicant is seeking the indication of treatment of adults with chronic HIV-1 infection. Dolutegravir plus rilpivirine a two-drug regimen, is an oral, fixed-dose combination intended to be used by switching from current integrase inhibitor (INI), NNRTI, or boosted protease inhibitor-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed with a three-or four drug regimen.

The Applicant-sponsored two studies submitted in support of the application: Study Protocols 201636/SWORD-1 and 201637/SWORD-2 for treatment of HIV-1infected adults who are virologically suppressed.

Protocol 201637 "A Phase 3, Multicenter, Randomized, Parallel Group, Non-inferiority Study Evaluating the Efficacy, Safety, and Tolerability of Switching to Dolutegravir Plus Rilipiravir from Current INI, NNRTI, or PI-Based Antiretroviral Regimen in HIV-1-Infected Adults who are Virologically Suppressed".

Subjects: 476 subjects enrolled
Sites: 108 centers in U.S. and Europe

The primary objective of this study was to demonstrate the non-inferiority antiviral activity of switching to dolutegravir (DTG) plus rilpivirine (RPV) once daily compared to continuation of current antiretroviral regimen (CAR) over 48 weeks in HIV-1 infected antiretroviral therapy (ART)-experienced subjects.

This study protocol was a 48-week phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study to assess the antiviral activity and safety of a two-drug regimen of DTG + RPV compared to CAR. Eligible subjects were randomized to continue their CAR or be switched to DTG + RPV once daily tablet. 476 HIV-1 infected subjects who were treated with cART containing 2 NTTIs plus an INI, or a PI were randomized. The goal of this study was to enroll 20% of subjects with INI-based CAR and to target populations who are underrepresented in the clinical studies including approximately 15% women and 15% subjects aged 50 years or older.

Protocol 201636: "A Phase 3, Multicenter, Randomized, Parallel Group, Non-inferiority Study Evaluating the Efficacy, Safety, and Tolerability of Switching to Dolutegravir Plus Rilpivirine from Current INI-, NNRTI, or PI-Based Antiretroviral regimen in HIV-1-Infected Adults Who are Virologically Suppressed".

Subjects: 669 screened, and 508 subjects enrolled
Sites: 66 centers 14 in U.S., Canada, Australia, and Europe
Study period: (b) (6)

The review division requested inspection of four clinical investigators because data from the studies are considered essential to the approval process. These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects with a high treatment effect that was greater than average, and 2) the need to determine if sites conducted the trials ethically and followed GCP regulations and local requirements.
Two domestic and two foreign site inspections covering the two study protocols were requested.

The CDER review division and OSI performed the site selections for site inspection. The sites were selected principally due to relatively high patient accrual in the study, lack of a prior history of inspection, and protocol violations. The clinical site inspections were intended to help verify the data integrity.

Site Selection for Study Protocols 201636 (SWORD 1) and 201637 (SWORD2)
Dr. Parks had 33 INDs in the CDER database and two previous CDER inspections in 2012 and 2013. Both inspections were classified NAI.
Dr. Hung has no listed INDs in the CDER database.
Dr. Rubio had 11 INDs in the CDER database and no prior history of inspection.
Dr. Richmond had 20 INDs in the CDER database, and two previous inspections classified as VAI in in 2002/2007

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects Enrolled	Inspection Date	Final Classification
David Parks, M.D. St. Louis, MO 63108 Site #214744	SWORD1 201636 17 subjects	8/28-9/2/2017	*NAI
Chein-Ching Hung, M.D. Kaohsiung 813, Taiwan Site #215819	SWORD1 201636 41 subjects	10/16-20/2017	*VAI
Rafael Rubio, M.D. Madrid, Spain 28041 Site #215347	SWORD2 201637 34 subjects	10/16-20/2017	*NAI
Gary Richmond, M.D. Fort Lauderdale, FL 33315 Site #214771	SWORD2 201637 9 subjects	8/7-10/2017	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

NOTE: Site inspections focused on review of informed consent documents, IRB, ethics committee correspondence, financial disclosures, training records, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, vital signs, subject source documents, including medical history records, drug accountability, and the use of concomitant medications. Source documents were compared to data listing for primary efficacy endpoints and adverse events reporting.

1. **David Parks, M.D./Site #214744 / Study Protocol 201636 (SWORD1)**
   St. Louis, MO 63108

   There were 21 subjects screened, four subjects were reported as screen failures, 17 subjects were enrolled in the study, three subjects were discontinued, and the reasons for discontinuations were documented. Subject (b) (6) was diagnosed with "medicine toxicity" and was asked to discontinue all medications except Stribild. The subject reportedly elected to discontinue after Week 12 because he did not want to discontinue other medications. Subject (b) (6) discontinued due to rash, and Subject # (b) (6) discontinued for no known reasons. Attempts were made by the site to contact subject (b) (6) the site was unable to locate the subject and there was no source documentation to show that discontinuation was due to any AEs/SAEs. None of the enrolled subjects have completed the study. All fourteen (14) subjects are continuing study treatment.

   The medical records for all subjects were reviewed for informed consent and primary efficacy endpoints. Records were organized and legible. Medical records/source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse event reporting.

   The audit revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA 483 was issued to Dr. Parks. The data generated by this site appear acceptable.

2. **Chein-Ching Hung, M.D. / Site #215819/Study Protocol 210636 (SWORD1)**
   Kaohsiung 813, Taiwan

   There were 52 subjects screened, 11 subjects were reported as screen failures, 41 subjects were randomized, and one subject was discontinued due to serious adverse events hospitalization and surgery due to appendicitis. The study is ongoing. None of the enrolled subjects completed the study. The medical records for 28 subjects were reviewed. Record*s* were organized and legible. Medical records/source documents were compared to data listings for the primary efficacy endpoint and adverse events reporting.

   The audit revealed minor protocol deviations contrary to the regulations and investigational plan. The objectionable conditions were listed on the Form FDA 483 and were issued to Dr. Hung. The deviations included one subject # (b) (4) who did not meet inclusion criteria for non-performance of HIV RNA levels to determine eligibility for enrollment, and for at least 6 subjects ((b) (4)) the non-performance of physical examinations at screening as required by the protocol.

   Overall, the data generated at Dr. Hung's site appear acceptable in support of clinical efficacy and safety and may be used in support of the pending application.

3. **Rafael Rubio, M.D. / Site #201637/Study Protocol 215347 (SWORD2)**
Madrid, Spain 28041

There were 45 subjects screened, 10 subjects were reported as screen failures, and 35 subjects were enrolled. There were two subjects who discontinued and the reasons were documented. Subject (b) (4) required prohibited medication, and Subject (b) (4) transferred to another state and continued the study. The study subjects are continuing the study. None of the enrolled subjects completed the study. The ORA investigator reported three subjects experienced adverse events not included in the data listing due to late input (after the cut-off date). Subject # (b) (4) experienced dental infection, Subject# (b) (4) experienced mild pharyngitis, and Subject# (b) (4) experienced mild foot pain. The medical records for 35 subjects were reviewed.

The medical records/source documents were compared to case report form and data listings for primary efficacy endpoint and adverse event reporting. No deficiencies were noted. The inspection revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA-483 Inspectional Observations was issued to Dr. Rubio. The medical records were organized and legible.

The data generated by this site appear acceptable. The inspection did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

4. **Gary Richmond, M.D./ Site #214771/Study Protocol 210637 (SWORD2)**
Fort Lauderdale, FL 33315

There were 11 subjects screened, two subjects were reported as screen failures, and nine subjects were enrolled. The ORA investigator reported that that the study is ongoing. None of the subjects discontinued after study enrollment. The medical records for all subjects were reviewed.

The medical records/source documents were compared to case report form and data listings for primary efficacy endpoint and adverse event reporting. No deficiencies were noted. The inspection revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA-483 Inspectional Observations was issued. The field investigator reported that the medical records were organized and legible. The data generated by this site appear acceptable.

{See appended electronic signature page}

Antoine El Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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Kassa Ayalew, M.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Enforcement
Office of Scientific Investigations

cc:
Central Doc. Rm. NDA 210192
DAVP /Division Director/Debra Birnkrant
DAVP /Medical Team Leader/Kimberly Struble
DAVP /Project Manager/Nina Mani
DAVP/Medical Officer/Yodit Below
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/ Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Susan Thompson
OSI/DCCE/GCPAB/Reviewer/Antoine El Hage
OSI/ GCP Program Analysts/Yolanda Patague/ Joseph Peacock

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/s/

ANTOINE N EL HAGE
11/03/2017

SUSAN D THOMPSON
11/03/2017

KASSA AYALEW
11/03/2017

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

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

Memorandum

Date: October 31, 2017

To: Nina Mani, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP
Wendy Lubarsky, Regulatory Review Officer
Karen Winestock, Supervisory Consumer Safety Officer

Subject: OPDP Labeling Comments for JULUCA (dolutegravir and rilpivirine) Tablets Product Labeling (PI) and Patient Package Information (PPI).

NDA: 210192 – JULUCA (dolutegravir and rilpivirine) Tablets For Oral Use

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In response to DAVP's consult request dated June 2, 2017, OPDP has reviewed the proposed product labeling (PI) and patient package Insert (PPI) labeling for the original NDA submission for Juluca (dolutegravir and rilpivirine) Tablets.

PI: OPDP has reviewed the proposed draft product labeling received by electronic mail from DAVP on October 23, 2017, and have provided comments in the attached PI. Specifically, OPDP comments were added on pages 5, 7, and 19.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI was completed on October 30, 2017 under separate cover.

Thank you for your consult. If you have any questions, please contact Koung Lee at (240) 402-8686 or koung.lee@fda.hhs.gov.

Attachments: Product labeling

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/s/

KOUNG U LEE
10/31/2017

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:	October 30, 2017
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:	Ruth Lidoshore, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Koung Lee, RPh, MSHS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	JULUCA (dolutegravir and rilpivirine)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 210192
Applicant:	ViiV Healthcare Company c/o GlaxoSmithKline LLC

1 INTRODUCTION

On June 1, 2017, ViiV Healthcare Company c/o GlaxoSmithKline LLC submitted for the Agency's review an original New Drug Application (NDA) 210192 for JULUCA (dolutegravir and rilpivirine) tablets. This submission proposes an indication for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (b) (4) (b) (4)

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 June 2, 2017, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for JULUCA (dolutegravir and rilpivirine) tablets.

2 MATERIAL REVIEWED

- Draft JULUCA (dolutegravir and rilpivirine) PPI received on June 1, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 23, 2017.
- Draft JULUCA (dolutegravir and rilpivirine) Prescribing Information (PI) received on June 1, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 23, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

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.

In our collaborative review of the PPI we:

- 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)

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.

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/s/

RUTH I LIDOSHORE
10/30/2017

KOUNG U LEE
10/30/2017

BARBARA A FULLER
10/30/2017

LASHAWN M GRIFFITHS
10/30/2017

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)

Date of This Memorandum:	October 16, 2017
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 210192
Product Name and Strength:	Juluca (dolutegravir/rilpivirine) 50 mg/25 mg, Tablet
Applicant/Sponsor Name:	ViiV Healthcare Company
Submission Date:	October 13, 2017
OSE RCM #:	2017-1064-1
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Antiviral Products requested that we review the revised container label and Prescribing Information for Juluca (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and Prescribing Information for Juluca are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Roosta, N. Label and Labeling Review for Juluca (NDA 210192). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 15. RCM No.: 2017-1064.

APPENDIX A. LABEL AND LABELING SUBMITTED ON INSERT DATE

Container labels

(b) (4)

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/s/

OTTO L TOWNSEND
10/16/2017

M E M O R A N D U M

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

DATE: September 22, 2017

TO: Richard Pazdur, MD
Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products (OHOP)

Edward M. Cox, MD, MPH
Director
Division of Antiviral Products (DAVP)
Office of Antimicrobial Products (OAP)

FROM: Amanda Lewin, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of Quintiles Phase One Services, Overland Park, KS.

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study (b) (4) conducted at Quintiles Phase One Services, Overland Park, KS.

No significant deficiencies were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

(b) (4)

(b) (4) I recommend that the data from study 201676 (NDA 210192) be accepted for further Agency review.

Inspected Studies:

(b) (4)

Following study was not audited during the inspection:

NDA 210192

Study Number: 201676
Study Title: "An Open-label, Randomized, Two-way Crossover, Single dose, Pivotal Bioequivalence Study of a Fixed-dose Combination of Dolutegravir and Rilpivirine in Healthy Volunteers"
Dates of conduct: (b) (4)

Clinical site: Quintiles Phase One Services
6700 W 115th Street
Overland Park, KS

(b) (4)

Conclusion:

(b) (4)

(b) (4) I recommend that the data from study 201676 (NDA 210192) should also be accepted for further Agency review.

Studies of similar design conducted between the last inspection (b) (4) and the end of the current Surveillance Interval should be accepted for review by the Agency without an inspection.

Amanda, Ph.D.
Pharmacologist

Final Classification:

NAI– Quintiles Phase One Services
Overland Park, KS
FEI#: (b) (4)

cc:
OTS/OSIS/Kassim/Kadavil/Haidar/Turner-Rinehardt/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Lewin
OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au

Draft: AL 09/21/2017
Edit: GB 9/22/2017; AD 09/22/2017

ECMS: Cabinets/CDER_OC/OSI/OSIS—Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/Clinical Sites/Quintiles Phase One Services, Overland Park, KS/NDA (b) (4)

OSIS File #: BE (b) (4)

FACTS: (b) (4)

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/s/

AMANDA E LEWIN
09/22/2017

GOPA BISWAS
09/22/2017

ARINDAM DASGUPTA
09/22/2017

LABEL AND LABELING REVIEW

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

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

Date of This Review:	September 15, 2017
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 210192
Product Name and Strength:	Juluca (dolutegravir/rilpivirine) 50 mg/25 mg tablet
Product Type:	Multi-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	ViiV Healthcare Company
Submission Date:	June 1, 2017
OSE RCM #:	2017-1064
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

This review documents our evaluation of the proposed Prescribing Information (PI), patient package insert, and the container label from a medication error prospective. ViiV Healthcare Company submitted NDA 210192, which would introduce Juluca (dolutegravir/rilpivirine) to the market.

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
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, the Patient Package Insert and the container label to identify deficiencies that may lead to medication errors and to identify other areas that could be improved. We identified areas in the PI and container label that can be improved to increase readability and prominence of important information.

Prescribing Information:

In section 16, some of the temperatures listed do not include a corresponding degree measurement. Numbers included in a temperature range in the PI should be followed by an appropriate unit of measure. We recommend to add ºC after the number ‘15’and ºF after the number ‘59’ within this section.

Container Labeling:

We note the container label includes the dosage form “Tablets” underneath the strength presentation “50 mg/25 mg”, instead of directly under the active ingredients (established names) “dolutegravir and rilpivirine”. To improve readability of this prominent information on the PDP, please consider relocating the dosage form “Tablets” to directly underneath the established names “dolutegravir and rilpivirine”. This would place the strength presentation “50 mg/25 mg” directly under the dosage form. See Section 4.2.2 for an illustration of this format.

We note that the container label appears cluttered. Specifically, the barcode and accompanying National Drug Code on the left side of the label competes in prominence with the proprietary name, established name, strength and other important information making them difficult to read. We recommend that the Applicant decrease the prominence of the barcode and accompanying National Drug Code to create more white space between the PDP and the barcode.

The container label does not contain a designated space for an expiration date and lot number. This may be a cause for possible administration errors, in which an expired drug could be dispensed to a patient. We recommend to designate a location on the container label that affords sufficient space for both the expiration date and lot number, ensuring there are no other numbers located in close proximity to the expiration that could be mistaken for the expiration date. Expiration date should follow either the MMMYYYY (e.g., JAN2018) format or the MMMDDYYYY (e.g., JAN012013) format.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed PI and container label that can be improved to increase clarity and prominence of important information to promote the safe use of this product.

We find the proposed Patient Package Insert for Juluca acceptable from a medication error perspective.

If you have questions or need clarifications, please contact Danyal Chaudhry, OSE Project Manager, at 301-796-3813.

4.1 RECOMMENDATIONS FOR THE DIVISION

In section 16, we recommend to add ºC after the number “15”and ºF after the number “59” to ensure all corresponding units of measure are included. This is also consistent with the container label.

> For example, change the statement, “Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].” To read, “Store at 25°C

(77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]."

4.2 RECOMMENDATIONS FOR VIIV HEALTHCARE COMPANY

1. Consider relocating the dosage form "Tablets" to directly underneath the established names "dolutegravir and rilpivirine"[a]. This would place the strength presentation "50 mg/25 mg" directly under the dosage form.

   For example:
   Juluca
   (dolutegravir and rilpivirine)
   Tablets
   50 mg/25 mg

2. Decrease the size of the barcode and accompanying National Drug Code to create more room between the PDP and the left side panel, so that it does not compete in prominence with the proprietary name, established name, strength and other important information on the PDP.

3. Designate a location on the container label that affords sufficient space for both the expiration date and lot number, ensuring there are no other numbers located in close proximity to the expiration that could be mistaken for the expiration date. Expiration date should follow either the MMMYYYY (e.g., JAN2018) format or the MMMDDYYYY (e.g., JAN012013) format.

[a] United States Pharmacopoeia (USP) General Chapter <1121> Nomenclature

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Juluca that ViiV Healthcare Company submitted on June 1, 2017.

Table 2. Relevant Product Information for Juluca	
Initial Approval Date	N/A
Active Ingredient	Dolutegravir/rilpivirine
Indication	For the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults who are virologically-suppressed (HIV-1 RNA <50 c/mL) on a stable antiretroviral regimen and no history of (b) (4) (b) (4)
Route of Administration	Oral
Dosage Form	Tablet
Strength	Dolutegravir 50 mg/ rilpivirine 25 mg
Dose and Frequency	One tablet by mouth once daily
How Supplied	Bottles of 30 tablets each
Storage	25°C (77°F); excursions permitted 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature]; store in original bottle; protect from (b) (4) and moisture
Container Closure	Will be supplied in high-density polyethylene bottles containing a desiccant with child-resistant closures that includes an (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 3, 2017, we searched the L:drive and AIMS using the terms, 'Juluca' to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Juluca labeling documents submitted by ViiV Healthcare Company on June 1, 2017.

- Prescribing Information
- Patient Package Insert
- Container label

G.2 Label and Labeling Images

Container Label:

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

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

/s/

NASIM N ROOSTA
09/15/2017

OTTO L TOWNSEND
09/17/2017

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 # 210192	NDA Supplement #: BLA Supplement #:	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: JULUCA Established/Proper Name: dolutegravir and rilpivirine Dosage Form: Tablets; Fixed –Dose Combination Strengths: 50mg / 25 mg Route of Administration: Oral		
Applicant: ViiV Healthcare Company Agent for Applicant (if applicable):		
Date of Application: June 1, 2017 Date of Receipt: June 1, 2017 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA Goal Date: December 1, 2017	Action Goal Date (if different): November 17, 2017	
Filing Date: July 31, 2017	Date of Filing Meeting: July 6, 2017	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☒ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication: JULUCA is for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) (b) (4) (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☒ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***N/A*** ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 075382, IND 114820, IND 101429, IND 109678, IND 067699	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***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 electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☒		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		

• 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)].**	☐	☐		
• 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)]?** ***If you answered yes to any of the above bulleted 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 for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*	☐	☐		

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***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.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
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: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included.* ***Forms** include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		PeRC Meeting scheduled for November 1, 2017
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☒	☐	Based on DAVP advice, a full waiver is being sought by the applicant
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."*** **Comment:** The proprietary name was submitted on June 7, 2017 and is coded as above.	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		See June 13, 2017 submission.
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in***	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576 htm

PLLR format before the filing date.				
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** *Division of Bone Reproductive and Urinary Products – June 7, 2017* *OSI (Clinical Inspections) – June 29, 2017* *OSI (Biopharm Inspections) – June 29, 2017*	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	☒		
Pre-NDA meeting? **Date:** Pre-NDA Meeting – April 19, 2016	☒	☐		

Any Special Protocol Assessments (SPAs)? **Date(s):**	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 6, 2017

BACKGROUND: ViiV has submitted an original NDA containing a fixed dose combination (FDC) tablet of 50 mg of dolutegravir (DTG) and 25 mg of rilpivirine (RPV) for treatment of HIV infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) (b) (4) (b) (4). This formulation has been developed by the Sponsor in collaboration with GSK and Janssen Research and Development LLC. TIVICAY® (DTG) and TRIUMEQ® (abacavir/DTG/lamivudine), and EDURANT® (rilpivirine) and ODEFSY® (emtricitabine, rilpivirine, & tenofovir alafenamide) are the currently approved products containing either DTG or rilpivirine.

ViiV is using a Pediatric Rare Disease Voucher to obtain Priority review for this application. (b) (4).

ViiV is requesting a full pediatric waiver since the DAVP concluded and communicated to the Sponsor that the DTG/RPV FDC product for use as a complete regimen would not represent a meaningful benefit over existing therapies in pediatric subjects.

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)	Kimberly Struble		Y
Division Director	Debra Birnkrant		Y
Office Director/Deputy	Jeffrey Murray		Y
Clinical	Reviewer:	Yodit Belew	Y
	TL:	Kimberly Struble	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Lisa Naeger	Y

	TL:	Jules O'Rear	Y
Clinical Pharmacology	Reviewer:	Su-Young Choi	Y
	TL:	Shirley Seo	N
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Mushfiqur Rashid	Y
	TL:	Greg Soon	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	John Dubinion	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Steve Miller/ Andrei Ponta shadowing	Y/Y
	RBPM:	Luz Rivera	Y
• Drug Substance	Reviewer:	Gene Holbert/TL: Ben Stevens	N/N
• Drug Product	Reviewer:	Yushi Feng/TL: Bala Shanmugam	N/N
• Process	Reviewer:	Ying Wang/ TL: Steven Frisbee	N/N
• Microbiology	Reviewer:	Ying Wang/ TL: Steven Frisbee	N/N
• Facility	Reviewer:	Aditi Thakur/TL: Christina Capacci-Daniel	Y/N
• Biopharmaceutics	Reviewer:	Parnali Chatterjee/ Secondary: Elsbeth Chikhale/ Tertiary: Angelica Dorantes	Y/N/N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Ruth Lidoshore	Y
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Wendy Lubarsky	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Nasim Roosta	N
	TL:	Otto Townsend	N
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/disciplines			
• OSI (Clinical Sites)	Reviewer:	Tony El-Hage	N
	TL:		
Other attendees	Danyal Chaudhary- OSE RPM		Y
	Elizabeth Everhart – OSE-DRISK		
	Christine Kim- DAVP RPM		
	Poonam Mishra – DD Safety DAVP		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**: No comments for Sponsor	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: Clinical site inspections consult was sent on June 29, 2017.	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: ***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***
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**: No comments for Sponsor	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**: Comments for Sponsor	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed? Biopharmaceutical consult for site inspections was sent on June 29, 2017.	☒ YES ☐ NO
BIOSTATISTICS **Comments**: No comments for Sponsor	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: No comments for Sponsor	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: No comments for Sponsor	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**: At this time, no facilities will be inspected. .	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Debra Birnkrant **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): September 14, 2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	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.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

NINA MANI
07/10/2017

KAREN D WINESTOCK
07/10/2017

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

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

Application: NDA 210192

Application Type: New NDA

Drug Name(s)/Dosage Form(s): JULUCA (dolutegravir and rilpivirine) tablets, for oral use

Applicant: ViiV Healthcare

Receipt Date: June 1, 2017

Goal Date: December 1, 2017

1. Regulatory History and Applicant's Main Proposals

ViiV has submitted an original NDA for JULUCA, which contains 2 active ingredients in a fixed-dose combination (FDC): dolutegravir (DTG, GSK1349572), an integrase inhibitor (INI), and rilpivirine (RPV, TMC278, GSK1329758), a non-nucleotide reverse transcriptase inhibitor (NNRTI). Both active ingredients have been previously approved as separate agents or in combination with other HIV drugs. The DTG/RPV FDC product has been developed by ViiV Healthcare in partnership with GSK and Janssen Research and Development LLC (Janssen).

The proposed indication for JULUCA is for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) (b) (4)

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 of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

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 unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

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

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required

Selected Requirements of Prescribing Information

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval 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 title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS**

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title 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 must be placed immediately beneath the BW title, and should be centered 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 title 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 five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the 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) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. 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 (or will have)** 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 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

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

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. 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 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. 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 (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. 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)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment: *CIs are listed.*

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of 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 practice."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), 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:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) 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: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

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

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

/s/

NINA MANI
07/05/2017

KAREN D WINESTOCK
07/06/2017