CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212887Orig1s000
212888Orig1s000

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date:	December 3, 2020
To:	Andrew Gentles, PharmD Regulatory Project Manager **Division of Antivirals (DAV)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Patient Package Inserts (PPIs)
Drug Name (established name):	• EDURANT (rilpivirine) Tablets, for oral use • CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) Co-packaged, for intramuscular use • VOCABRIA (cabotegravir) Tablets, for oral use
Application Type/Number:	NDA 202022 S-014 NDA 212888 NDA 212887
Applicant:	Viiv Healthcare Co

1 INTRODUCTION

On July 28, 2020, Viiv Healthcare Co, re-submitted for the Agency's review a Prior Approval Supplement-Efficacy (PAS-014) to the New Drug Application (NDA 202022) for EDURANT (rilpivirine) tablets, for oral use. The purpose of the re-submission is to provide a complete response to the deficiencies outlined in the Complete Response Letter dated December 20, 2019. EDURANT (rilpivirine) tablets, for oral use, was approved on May 20, 2011, and is indicated in combination with other antiretroviral (ARV) agents, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve patients 12 years of age and older and weighing at least 35 kg with plasma HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy.

In addition, the Applicant re-submitted a New Drug Application (NDA-212887) for VOCABRIA (cabotegravir) tablets, for oral use, for the proposed indication of use in combination with EDURANT (rilpivirine) for short-term use in adults with HIV-1 infection who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) and who have no known or suspected resistance to either cabotegravir or rilpivirine for:

- Oral lead-in (OLI) to assess the tolerability of cabotegravir prior to administration of long-acting CABENUVA (cabotegravir; rilpivirine) injectable suspensions.
- Oral therapy for patients who will miss planned injection dosing with CABENUVA injectable suspensions.

The purpose of the re-submission is to provide a complete response to the deficiencies outlined in the Complete Response Letter dated December 20, 2019.

In addition, the Applicant re-submitted for the Agency's review a New Drug Application (NDA-212888) for CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) co-packaged, for intramuscular use, for the proposed indication of use as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable regimen with no history of treatment failure on any INSTI-or NNRTI-containing regimen and with no known or suspected resistance to either cabotegravir or rilpivirine. The purpose of the re-submission is to provide a complete response to the deficiencies outlined in the Complete Response Letter dated December 20, 2019.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed PPIs for EDURANT (rilpivirine) Tablets, for oral use, CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) Co-packaged, for intramuscular use, and VOCABRIA (cabotegravir) Tablets, for oral use.

2 MATERIAL REVIEWED

- Draft EDURANT (rilpivirine), CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), and

VOCABRIA (cabotegravir) PPIs received on July 28, 2020, and received by DMPP on November 30, 2020.

- Draft EDURANT (rilpivirine), CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), and VOCABRIA (cabotegravir) PIs received on July 28, 2020, and received by DMPP on November 30, 2020.

3 CONCLUSIONS

We find the Applicant's proposed PPIs are acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the PPIs.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
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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 Review:	December 1, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 212887
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	ViiV Healthcare Company (ViiV)
FDA Received Date:	November 30, 2020
OSE RCM #:	2019-908-2
DMEPA Safety Evaluator:	Melina Fanari, RPh
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label received on November 30, 2020 for Vocabria. The Division of Antivirals (DAV) requested that we review the revised container label for Vocabria (Appendix A) to determine if it is 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 is acceptable from a medication error perspective. We have no additional recommendations at this time.

[a] Vaughan, V. Label and Labeling Review for Vocabria (NDA 212887). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Nov 19. RCM No.: 2019-908-1.

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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)

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Date of This Review:	November 19, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 212887 and NDA 202022/S-14
Product Name, Dosage Form, and Strength:	Vocabria (cabotegravir) Tablet, 30 mg Edurant (rilpivirine) Tablet, 25 mg
Product Type:	Single Ingredient Products
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	ViiV Healthcare Company (ViiV) Janssen Products, LP (Janssen)
FDA Received Date:	July 28, 2020
OSE RCM #:	2019-908-1
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the Class II resubmission approval process for Vocabria (cabotegravir) tablets [NDA 212887] and Edurant (rilpivirine) tablets [NDA 202022/S-14], the Division of Antivirals (DAV) requested that we review the proposed labels and labeling for areas that may lead to medication errors.

2 REGULATORY HISTORY

We previously reviewed the labels and labeling for Vocabria submitted to NDA 212887, received on April 29, 2019. We identified areas of vulnerability that could lead to medication errors with the Patient Package Insert and container labels.[a]

On December 19, 2019, NDA 212887 and NDA 202022/S-14 was issued Complete Response (CR) letters[b,c] due to product quality issues identified for NDA 212888 Cabenuva (cabotegravir; rilpivirine) extended-release injectable suspensions. The approval of NDA 212887 and NDA 202022/S-14 are contingent upon the approval of Cabenuva (NDA 212888).

On July 28, 2020, ViiV submitted a response to address the deficiencies outlined in FDA's December 19, 20219 CR letter.

3 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 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 or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[a] Vaughan, V. Label and Labeling Review for Vocabria (NDA 212887). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 15. RCM No.: 2019-908.
[b] Farley, J. Complete Response for Vocabria. Silver Spring (MD): FDA, CDER, OND, DAV (US); 2019 DEC 19. NDA 212887.
[c] Murray, J. Complete Response for Edurant. Silver Spring (MD): FDA, CDER, OND, DAV (US); 2019 DEC 19. NDA 202022/S-14.

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include identified medication error issues with the submitted Edurant Patient Package Insert and Vocabria container label, DMEPA's rationale for concern, and the proposed recommendations to minimize the risk for medication error.

Table 2: Identified Issue and Recommendation for Division of Antivirals

Edurant Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Patient Package Insert (Edurant)			
1.	We note that the patient package insert (PPI) does not provide clarity that Vocabria is cabotegravir. Additionally, we note inconsistent presentation with the Prescribing Information, which presents Vocabria as "Vocabria (cabotegravir)."	Patients may receive prescriptions labeled as either Vocabria or cabotegravir, which could lead to confusion without clarification.	We recommend revising the PPI to include "VOCABRIA (cabotegravir)" in the *What is Edurant?* section of the PPI and throughout where applicable.

Table 3: Identified Issue and Recommendation for ViiV Healthcare Company (entire table to be conveyed to Applicant)

Vocabria Container Labels, Carton Labeling, and Packaging			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label (Vocabria)			
1.	The principal display panel of the container does not include a warning about concurrent administration for contraindicated medicines.	The Vocabria Prescribing Information lists several medicines in which concurrent Vocabria use is contraindicated.	We recommend including an alert on the principal display panel to inform end users to find out about the medicines that should not be taken with Vocabria, for example: ALERT: Find out about medicines that should NOT be taken with VOCABRIA.

5 CONCLUSION

Our evaluation of the proposed Edurant Patient Package Insert and Vocabria container label identified areas of vulnerability that could lead to medication error. Above, we have provided a recommendation in Table 2 for the Division for the Edurant Patient Package Insert and Table 3 for the Applicant for the Vocabria container label. We ask that the Division convey Table 3 in its entirety to the Applicant so that recommendations are implemented prior to approval of NDA 212887 and NDA 202022/S-14.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Vocabria received on July 28, 2020 from ViiV Healthcare Company.

Table 4. Relevant Product Information for Vocabria	
Initial Approval Date	N/A
Active Ingredient	cabotegravir
Indication	VOCABRIA is indicated in combination with EDURANT (rilpivirine) for short-term treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as: • oral lead-in to assess the tolerability of cabotegravir prior to administration of cabotegravir extended-release injectable suspension, a component of CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions. • oral therapy for patients who will miss planned injection dosing with CABENUVA.
Route of Administration	Oral
Dosage Form	Tablet
Strength	30 mg
Dose and Frequency	Oral Lead-in Dosing to Assess Tolerability of Cabotegravir Oral lead-in should be used for approximately 1 month (at least 28 days) to assess the tolerability of cabotegravir prior to the initiation of CABENUVA. The recommended oral daily dose is one 30-mg tablet of VOCABRIA in combination with one 25-mg tablet of EDURANT (rilpivirine). The last oral dose should be taken on the same day injections with CABENUVA are started. Take VOCABRIA once daily with EDURANT at approximately the same time each day with a meal Oral Dosing to Replace Planned Missed Injections of CABENUVA (Up to 2 Consecutive Monthly Injections) If a patient plans to miss a scheduled injection of CABENUVA (cabotegravir; rilpivirine) extended release injectable

	suspensions by more than 7 days, take daily oral therapy to replace up to 2 consecutive monthly injection visits. The recommended oral daily dose is one 30-mg tablet of VOCABRIA (cabotegravir) and one 25-mg tablet of EDURANT (rilpivirine). Take VOCABRIA with EDURANT at approximately the same time each day with a meal. The first dose of oral therapy should be taken approximately 1 month after the last injection dose of CABENUVA and continued until the day injection dosing is restarted.
How Supplied	Each VOCABRIA tablet contains 30 mg of cabotegravir and is a white, oval, film-coated, biconvex tablet debossed with "SV CTV" on one side. Bottle of 30 tablets (NDC 49702-248-13)
Storage	Store below 30°C (86°F)
Container Closure	Bottles with child-resistant closure

Table 5 presents relevant product information for Edurant received on July 28, 2020 from ViiV Healthcare Company.

Table 5. Relevant Product Information for Edurant	
Initial Approval Date	May 20, 2011
Active Ingredient	rilpivirine
Indication	EDURANT is indicated in combination with VOCABRIA (cabotegravir) for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as *[see Dosage and Administration (2.2)]*: • oral lead-in to assess the tolerability of rilpivirine prior to administration of rilpivirine extended-release injectable suspension, a component of CABENUVA (cabotegravir, rilpivirine) extended-release injectable suspensions. • oral therapy for patients who will miss planned injection dosing with CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions.
Route of Administration	Oral
Dosage Form	Tablet
Strength	25 mg
Dose and Frequency	Recommended Dosage in Combination with Cabotegravir

	<u>Oral Lead-In Dosing to Assess Tolerability of Rilpivirine</u> Oral lead-in should be used for approximately 1 month (at least 28 days) to assess the tolerability of rilpivirine prior to the initiation of CABENUVA. The recommended oral daily dose is one 25 mg tablet of EDURANT (rilpivirine) in combination with one 30 mg tablet of VOCABRIA (cabotegravir). EDURANT should be taken with VOCABRIA (cabotegravir) orally once daily at approximately the same time each day with a meal. Because EDURANT is indicated in combination with VOCABRIA (cabotegravir), the prescribing information for VOCABRIA (cabotegravir) tablets should also be consulted. The last oral dose should be taken on the same day injections with CABENUVA are started. <u>Oral Dosing to Replace Planned Missed Injections of CABENUVA (Up to 2 Consecutive Monthly Injections)</u> If a patient plans to miss a scheduled CABENUVA injection visit by more than 7 days, take daily oral therapy to replace up to 2 consecutive monthly injection visits. The recommended oral daily dose is one 25 mg tablet of EDURANT and one 30 mg tablet of VOCABRIA (cabotegravir), taken orally once daily at approximately the same time each day with a meal. The first dose of oral therapy should be taken approximately 1 month after the last injection dose of CABENUVA and continued until the day injection dosing is restarted.
How Supplied	EDURANT (rilpivirine) tablets are supplied as white to off-white, film-coated, round, biconvex, 6.4 mm tablets. Each tablet contains 27.5 mg of rilpivirine hydrochloride, which is equivalent to 25 mg of rilpivirine. Each tablet is debossed with “TMC” on one side and “25” on the other side. EDURANT tablets are packaged in bottles in the following configuration: 25 mg tablets-bottles of 30 (NDC 59676-278-01).
Storage	Store EDURANT tablets in the original bottle in order to protect from light. Store EDURANT tablets at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 9, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Vocabria and NDA 212887. Our search identified one previous review[d], and we considered our previous recommendations to see if they are applicable for this current review.

[d] Vaughan, V. Label and Labeling Review for Vocabria (NDA 212887). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 15. RCM No.: 2019-908.

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,[e] along with postmarket medication error data, we reviewed the following Vocabria labels and labeling submitted by ViiV Healthcare Company.

- Vocabria container label received on July 28, 2020
- Edurant currently approved container label available from http://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/03880372-2c68-45c6-a53a-f420c49541d6/spl-doc?hl=edurant
- Prescribing Information and Patient Package Information(Image not shown) received on July 28, 2020 for:
    - Vocabria , available from \\CDSESUB1\evsprod\nda212887\0041\m1\us\114-labeling\1141-draft\draft-annotated.pdf
    - Edurant, available from \\CDSESUB1\evsprod\nda202022\0191\m1\us\draft-annot-labeling-text.pdf

G.2 Label and Labeling Images

- Vocabria container label

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

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/s/

VALERIE S VAUGHAN
11/19/2020 12:53:52 PM

SEVAN H KOLEJIAN
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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)

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Date of This Review:	November 09, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 212888
Product Name, Dosage Form, and Strength:	Cabenuva (cabotegravir; rilpivirine) Extended-Release Injectable Suspensions, cabotegravir 600 mg/3 mL and rilpivirine 900 mg/3 mL cabotegravir 400 mg/2 mL and rilpivirine 600 mg/2 mL
Product Type:	Multiple Ingredients Co-Packaged Combination Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	ViiV Healthcare Company (ViiV)
FDA Received Date:	July 28, 2020
OSE RCM #:	2019-910-2
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the Class II resubmission approval process for Cabenuva (cabotegravir; rilpivirine) injectable suspensions, the Division of Antivirals (DAV) requested that we review the proposed labels and labeling for areas that may lead to medication errors.

2 REGULATORY HISTORY

We previously reviewed the labels, labeling, and human factors (HF) validation study results for Cabenuva submitted to NDA 212888, received on April 29, 2019. We identified areas of vulnerability that could lead to medication errors with the Instructions for Use, container labels, and carton labeling but determined that submission of additional HF validation study results was not warranted.[a,b]

On December 18, 2019, ViiV submitted revised container labels, carton labeling, and Instructions for Use. Our review of the revised labels and labeling did not identify areas of vulnerability that may lead to medication errors.[c]

On December 19, 2019, NDA 212888 was issued a Complete Response (CR) letter due to product quality and facility inspection issues.[d]

On July 28, 2020, ViiV submitted a response to address the deficiencies outlined in FDA's December 19, 2019 CR letter.

3 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 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

[a] Purcell J, et. al. Human Factors Study Report, Labels, and Labeling Review for Cabenuva (NDA 212888). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 29. RCM No.: 2019-910 and 2019-912.

[b] Gentles, A. Information Request for "FDA Communication: NDA 212888 - Labeling comments for USPI, Carton, and IFU" Message to Beth Austin. Silver Spring (MD): FDA, CDER, OND, DAV (US); 2019 DEC 12.

[c] Vaughan, V. Label and Labeling Review Memorandum for Cabenuva (NDA 212888). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 03. RCM No.: 2019-910-1.

[d] Farley, J. Complete Response for Cabenuva. Silver Spring (MD): FDA, CDER, OND, DAV (US); 2019 DEC 19. NDA 212888.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Other	F – N/A
Labels and Labeling	G

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

4 FINDINGS AND CONCLUSION

We note that the applicant proposes to revise the intended pronunciation of the proprietary name, Cabenuva, from kah ben' ue vah to kab' en' ue vah in the Patient Package Insert and Instructions for Use. The difference in pronunciation does not change our previous decision regarding the acceptability of the proprietary name.

Our evaluation of the proposed Prescribing Information, Patient Package Insert, Instructions for Use, container labels, and carton labeling did not identify areas of vulnerability that may lead to medication error. We have no additional comments at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cabenuva received on July 28, 2020 from ViiV Healthcare Company.

Table 2. Relevant Product Information for Cabenuva	
Initial Approval Date	N/A
Active Ingredient	cabotegravir; rilpivirine
Indication	CABENUVA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine
Route of Administration	Gluteal intramuscular
Dosage Form	Extended-Release Injectable Suspensions
Strength	cabotegravir 600 mg/3 mL and rilpivirine 900 mg/3 mL cabotegravir 400 mg/2 mL and rilpivirine 600 mg/2 mL
Dose and Frequency	Initiation Injections (CABENUVA 600-mg/900-mg Kit) Initiate injections on the last day of oral lead-in. CABENUVA contains cabotegravir and rilpivirine extended-release injectable suspensions. The recommended initial injection doses of CABENUVA in adults are a single 600-mg (3-mL) gluteal intramuscular injection of cabotegravir and a single 900-mg (3-mL) gluteal intramuscular injection of rilpivirine. Administer cabotegravir and rilpivirine at separate gluteal injection sites (on opposite sides or 2 cm apart) during the same visit. Continuation injections should be initiated a month after the initiation injections. Continuation Injections (CABENUVA 400-mg/600-mg Kit) After the initiation injections, the recommended monthly continuation injection doses of CABENUVA in adults are a single 400-mg (2-mL) gluteal intramuscular injection of cabotegravir and a single 600-mg (2-mL) gluteal intramuscular injection of rilpivirine at each visit. Administer cabotegravir and rilpivirine at separate gluteal injection sites (on opposite sides or 2 cm apart) during the same visit. Patients may be given CABENUVA up to 7 days before or after the date the patient is scheduled to receive monthly injections.

Table 1. Recommended Oral Lead-In and Intramuscular Injection Dosing Schedule in Adults

Drug	Oral Lead-In (at Least 28 Days) Month 1	Intramuscular (Gluteal) Initiation Injections (One-Time Dosing) At Month 2 (On the Last Day of Oral Lead-In Dosing)	Intramuscular (Gluteal) Continuation Injections (Once-Monthly Dosing) Month 3 Onwards
Cabotegravir	30 mg once daily with a meal	600 mg (3 mL)	400 mg (2 mL)
Rilpivirine	25 mg once daily with a meal	900 mg (3 mL)	600 mg (2 mL)

Planned Missed Injections (Oral Dosing to Replace Up to 2 Consecutive Monthly Injections)

If a patient plans to miss a scheduled injection visit by more than 7 days, take daily oral therapy to replace up to 2 consecutive monthly injection visits. The recommended oral daily dose is one 30-mg tablet of VOCABRIA (cabotegravir) and one 25-mg tablet of EDURANT (rilpivirine). The first dose of oral therapy should be taken approximately 1 month after the last injection dose of CABENUVA and continued until the day injection dosing is restarted. Refer to Table 2 for injection dosing recommendations.

Unplanned Missed Injections

If monthly injections are missed or delayed by more than 7 days and oral therapy has not been taken in the interim, clinically reassess the patient to determine if resumption of injection dosing remains appropriate. If injection dosing will be continued, see Table 2 for dosing recommendations.

Table 2. Injection Dosing Recommendations after Missed Injections[a]

Time Since Last Injection	Recommendation
Less than or equal to 2 months	Resume with 400-mg (2-mL) cabotegravir and 600-mg (2-mL) rilpivirine intramuscular monthly injections as soon as possible.
Greater than 2 months	Re-initiate the patient with 600-mg (3-mL) cabotegravir and 900-mg (3-mL) rilpivirine intramuscular injections then continue to follow the 400-mg (2-mL) cabotegravir and 600-mg (2-mL) rilpivirine intramuscular monthly injection dosing schedule.

[a] Refer to oral dosing recommendations if a patient plans to miss a scheduled injection visit.

How Supplied

CABENUVA is supplied in 2 dosing kits. Each kit contains one vial of cabotegravir extended-release injectable suspension and one vial of rilpivirine extended-release injectable suspension, co-packaged as follows:

CABENUVA 400-mg/600-mg Kit (NDC 49702-253-15) containing:

- One single-dose vial of cabotegravir extended-release injectable suspension containing 400 mg/2 mL (200 mg/mL) of cabotegravir.

	• One single-dose vial of rilpivirine extended-release injectable suspension containing 600 mg/2 mL (300 mg/mL) of rilpivirine. CABENUVA 600-mg/900-mg Kit (NDC 49702-240-15) containing: • One single-dose vial of cabotegravir extended-release injectable suspension containing 600 mg/3 mL (200 mg/mL) of cabotegravir. • One single-dose vial of rilpivirine extended-release injectable suspension containing 900 mg/3 mL (300 mg/mL) of rilpivirine. Each dosing kit also contains 2 syringes, 2 syringe labels, 2 vial adapters, and 2 needles for intramuscular injection (23-gauge, 1½ inch). The vial stoppers are not made with natural rubber latex.
Storage	Store CABENUVA in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton until ready to use. Do not freeze. Do not mix with any other product or diluent.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 2, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Cabenuva and NDA 212888. Our search identified two previous reviews[e,f], and we confirmed that our previous recommendations were implemented.

[e] Purcell, J. Label Labeling and Human Factors Study Report Review for Cabenuva (NDA 212888). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 29. RCM No.: 2019-910 and 2019-912.

[f] Vaughan, V. Label and Labeling Review Memorandum for Cabenuva (NDA 212888). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 03. RCM No.: 2019-910-1.

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,[g] along with postmarket medication error data, we reviewed the following Cabenuva labels and labeling submitted by ViiV Healthcare Company.

- Container label received on July 28, 2020
- Carton labeling received on July 28, 2020
- Information Pack received on July 28, 2020
- Instructions for Use received on July 28, 2020
- Prescribing Information and Patient Package Insert (Image not shown) received on July 28, 2020, available from \\CDSESUB1\evsprod\nda212888\0054\m1\us\114-labeling\1141-draft\draft-annotated.pdf

G.2 Label and Labeling Images

Container Labels

- Cabotegravir 600 mg/3 mL and Rilpivirine 900 mg/3 mL

(b) (4)

Carton Labeling

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

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/s/

VALERIE S VAUGHAN
11/09/2020 11:17:49 AM

MISHALE P MISTRY on behalf of SEVAN H KOLEJIAN
11/09/2020 11:20:02 AM

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:	January 3, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 212888
Product Name and Strength:	Cabenuva (cabotegravir; rilpivirine) Extended-Release Injectable Suspensions, cabotegravir 600 mg/3 mL and rilpivirine 900 mg/3 mL cabotegravir 400 mg/2 mL and rilpivirine 600 mg/2 mL
Applicant/Sponsor Name:	ViiV Healthcare Company (ViiV)
OSE RCM #:	2019-910-1
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, carton labeling, and Instructions for Use (IFU) received on December 18, 2019 for Cabenuva. The Division of Antivirals (DAV) requested that we review the revised labels and labeling for Cabenuva (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] and additional comments communicated to the Applicant on December 12, 2019[b].

2 CONCLUSION

Our evaluation of the proposed labels and labeling did not identify areas of vulnerability that may lead to medication errors. We have no additional recommendations at this time.

[a] Purcell J, et. al. Human Factors Study Report, Labels, and Labeling Review for Cabenuva (NDA 212888). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 29. RCM No.: 2019-910 and 2019-912.
[b] Gentles, A. Information Request for "FDA Communication: NDA 212888 - Labeling comments for USPI, Carton, and IFU" Message to Beth Austin. Silver Spring (MD): FDA, CDER, OND, DAV (US); 2019 DEC 12. Available from: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af805305d9&_afrRedirect=1097260191481526

A. APPENDIX A. LABELS AND LABELING REVIEWED

A.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Cabenuva labels and labeling submitted by ViiV Healthcare Company.

- Container label received on December 18, 2019
- Carton labeling received on December 18, 2019
- Information Pack received on December 18, 2019
- Instructions for Use received on December 18, 2019
- Prescribing Information (Image not shown), received on December 18, 2019, available from \\cdsesub1\evsprod\nda212888\0053\m1\us\114-labeling\1141-draft\draft-annotated.pdf

A.2 Label and Labeling Images

Container labels

- Cabotegravir 600 mg/3 mL and Rilpivirine 900 mg/3 mL

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

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VALERIE S VAUGHAN
01/03/2020 08:47:10 AM

LOLITA G WHITE
01/03/2020 08:55:11 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring MD 20993

CLINICAL OUTCOME ASSESSMENT (COA) REVIEW MEMORANDUM

RE: NDA 212888

FROM: Christopher St. Clair, PharmD
Reviewer, Clinical Outcome Assessments Staff

Sarrit Kovacs, PhD
Team Leader, Clinical Outcome Assessments Staff

Elektra Papadopoulos, MD, MPH
Associate Director, Clinical Outcome Assessments Staff

SUBJECT: Division of Antiviral Products consult to Clinical Outcome Assessments Staff requesting review of clinical outcome assessments (b) (4) (DARRTS Reference ID: 4441626)

DRUG: CABENUVA (cabotegravir long-acting + rilpivirine long-acting injection)

This memo serves to close out the clinical outcome assessment (COA) consult C2019185 (filed in DARRTS by the Division of Antiviral Products [DAVP] on May 3, 2019) for NDA 212888 regarding CABENUVA (cabotegravir long-acting injection with rilpivirine long-acting injection) for the treatment of HIV-1 infection in adults. This COA consult is related to review of the Applicant's proposed (b) (4)

COA Staff completed a full review, which is contained in the Patient-Reported Outcomes section of the Integrated Review for NDA 212887-212888.

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/s/

CHRISTOPHER ST. CLAIR
12/10/2019 07:49:50 AM

SARRIT M KOVACS
12/10/2019 08:54:22 AM

ELEKTRA J PAPADOPOULOS
12/10/2019 10:01:44 AM

DNP Consultation Memo ADDENDUM

NDA	212887, 212888
Drug:	cabotegravir/rilpivirine combination product
Proposed Indication:	HIV-1 infection, treatment and prevention
Consultation Requestor:	Yodit Belew, MD Division of Anti-Infective Products
Desired Completion:	09/20/2019
Date Review Completed:	09/16/2019
Date of Addendum:	10/21/2019
Reviewer:	Emily R. Freilich, MD
Team Leader:	Philip Sheridan, MD Division of Neurology Products (DNP)

Addendum

After finalizing our initial review, the Division of Anti-Infective Products requested unblinding of the cases of seizure in the ongoing PrEP trials, which was able to be done without unblinding of the trial sponsors. Furthermore, the sponsor also updated the total number of patients who have been exposed to cabetogravir through the ongoing studies, prompting this addendum.

As previously noted, there were a total of 6 patients with seizures in the CAB studies that are currently under review (phases 1-3b studies for treatment of HIV). There were an additional 6 patients that had seizures in the still ongoing PreP development program for prevention of HIV. However, 5 of these 6 patients remained blinded at the time of my original review.

Of the original 6 patients I noted that had received CAB in the PrEP development program, 1 patient received CAB in the phase 2 completed study, and 5 patients were part of the ongoing blinded studies. One of these patients in Study HPTN084 remains blinded. Of the remaining 4 patients from Study HPTN083, 1 of the 4 patients received CAB, and the other 3 patients received the active comparator.

The results of the unblinding are reassuring given that 3 of the 6 seizures in the ongoing program were in active comparator arm, which is not known to be associated with seizures. There was also an additional patient with a seizure in the blinded Study HTPN084. This results in a total of 6 + 2 + 2 (blinded) potential cases of seizures in development. With the prior estimate of exposed patients, this resulted in a possible incidence rate of (b) (4) incidence. Also noted that many of the cases had possible alternate etiologies and confounding factors. At that time, it was discussed that while the incidence was quite low, there was enough concern for possible association with the treatment, and it was felt that seizure should be added to the label as a rare adverse event.

The sponsor then submitted an updated denominator with the current total patient exposure from the CAB development program to include 5694 total patients, an additional 974 patients from the ongoing HPTN083 and HPTN084 studies. This would leave a crude incidence (worst-case scenario) of (b) (4)%, and an even lower incidence rate if only treatment-related cases were considered.

The higher number of total patient exposure, combined with the unblinding of the 4 patients in Study HTPN083, result in a lower incidence rate at less than (b) (4)%, and weakening the possible association between the treatment and the seizures. However, as previously noted, the studies did exclude patients who were deemed high-risk for seizures, so the incidence in such studies may be underestimated, and close pharmacovigilance should be recommended in the postmarketing space if the drug is approved. We agree with continuing to keep seizure as an Adverse Event of Special Interest, and recommend close pharmacovigilance for any seizure-related events.

_____
Emily R. Freilich, MD
Clinical Reviewer

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EMILY R FREILICH
11/04/2019 03:24:53 PM

PHILIP H SHERIDAN
11/15/2019 08:25:19 PM

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:	November 15, 2019
Requesting Office or Division:	Division of Antivirals
Application Type and Number:	NDA 212887
Product Name and Strength:	Vocabria (cabotegravir) tablets, 30 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	ViiV Healthcare Company (ViiV)
FDA Received Date:	April 29, 2019, October 1, 2019, October 10, 2019, and November 12, 2019
OSE RCM #:	2019-908
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 REASON FOR REVIEW

As part of the approval process for Vocabria (cabotegravir) tablets, 30 mg, the Division of Antivirals (DAV) requested that we review the proposed label and labeling for areas that may 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
Previous DMEPA Reviews	B (N/A)
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 or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below includes identified medication error issues with the submitted patient package insert and container label, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for the Division of Antivirals

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Patient Package Insert (PPI)			
1.	The PPI references only the proprietary name EDURANT when describing how to take VOCABRIA.	Patients may receive prescriptions for generic rilpivirine which does not include the proprietary name EDURANT, which could lead to confusion.	To mitigate confusion and to align with the prescribing information (PI), consider revising the PPI to include the established name rilpivirine when referencing Edurant, for example, consider revising "EDURANT" to "rilpivirine [EDURANT]" throughout the PPI.
2.	The *How should I take Vocabria?* section of the PPI includes additional information about concurrent use of Vocabria with antacid products that is not included in the DOSAGE AND ADMINISTRATION section of the PI.	Section 7 of the PI provides administration instructions to take antacids 2 hours before or 4 hours after taking Vocabria.	We defer to the Division to determine if information about concurrent use of antacids with Vocabria should be included in the DOSAGE AND ADMINISTRATION section of the PI.

Table 3: Identified Issues and Recommendations for ViiV Healthcare Company (entire table to be conveyed to Applicant)

Container Labels, Carton Labeling, and Packaging			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	The principal display panel of the container label does not include a warning about contraindicated medicines.	Section 4 of the Prescribing Information lists several medications in which concurrent Vocabria use is contraindicated.	Include an alert box on the principal display panel of the container label which states, for example:

			Alert: Find out about medicines that should NOT be taken with Vocabria.

4 CONCLUSION

Our evaluation of the proposed patient package insert and container label identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Vocabria received on November 13, 2019 from ViiV Healthcare Company.

Table 3. Relevant Product Information for Vocabria	
Initial Approval Date	N/A
Active Ingredient	cabotegravir
Indication	Indicated in combination with EDURANT, oral rilpivirine, for short-term treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as [see Dosage and Administration (2.1)]: • oral lead-in to assess the tolerability of cabotegravir prior to administration of cabotegravir extended-release injectable suspension, a component of CABENUVA (cabotegravir and rilpivirine) extended-release injectable suspensions. • oral therapy for patients who will miss planned injection dosing with CABENUVA injectable suspensions.
Route of Administration	Oral
Dosage Form	Tablets
Strength	30 mg
Dose and Frequency	Oral Lead-in Dosing to Assess Tolerability of Cabotegravir: • one 30-mg tablet of VOCABRIA in combination with one 25-mg tablet of rilpivirine [EDURANT] once daily, as an oral lead-in for approximately one month (at least 28 days) prior to the initiation of cabotegravir injections, a component of CABENUVA Oral Dosing to Replace Planned Missed Injections of CABENUVA (Up to 2 Consecutive Monthly Injections): • One 30-mg tablet of VOCABRIA [cabotegravir] and one 25-mg tablet of EDURANT [rilpivirine] once daily to replace up to 2 consecutive monthly injection visits. The first dose of oral therapy should be taken approximately 1 month after the last injection dose of CABENUVA and continued until the day injection dosing is restarted.
How Supplied	Bottles of 30 tablets (NDC 49702-248-13)
Storage	Store below 30°C (86°F)
Container Closure	HDPE bottles with (b) (4) child-resistant closures, with a (b) (4) induction heat seal liner.

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,[a] along with postmarket medication error data, we reviewed the following Vocabria labels and labeling submitted by ViiV Healthcare Company.

- Container label received on October 1, 2019
- Prescribing Information and Patient Package Insert (Image not shown) received on April 29, 2019, October 10, 2019, and November 13, 2019, available at: \\cdsesub1\evsprod\nda212887\0001\m1\us\114-labeling\1141-draft\draft-annotated.pdf \\cdsesub1\evsprod\nda212887\0029\m1\us\114-labeling\1141-draft\draft-annotated.pdf \\cdsesub1\evsprod\nda212887\0034\m1\us\114-labeling\1141-draft\draft-annotated.pdf

G.2 Label and Labeling Images

- **Container Label**

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

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/s/

VALERIE S VAUGHAN
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SEVAN H KOLEJIAN
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HUMAN FACTORS STUDY REPORT AND LABELS 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)

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Date of This Review:	October 29, 2019
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 212888
Product Type:	Multi-Ingredient, Co-Packaged Product
Drug Constituent Name and Strength	Cabenuva (cabotegravir; rilpivirine) Extended-Release Injectable Suspensions; cabotegravir 600 mg/3 mL and rilpivirine 900 mg/3 mL cabotegravir 400 mg/2 mL and rilpivirine 600 mg/2 mL
Device Constituent:	Two sterile, single-use vial adapters; two 5-mL single-use syringes; and two sterile, single-use 23-gauge 1.5-inch safety needles
Rx or OTC:	Rx
Applicant/Sponsor Name:	ViiV Healthcare Company (ViiV)
FDA Received Date:	April 29, 2019
OSE RCM #:	2019-910 and 2019-912
DMEPA Human Factors Evaluator:	Janine Purcell, MS
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 212888 for Cabenuva (cabotegravir; rilpivirine) Extended-release injectable suspensions, 200 mg/mL and 300 mg/mL. This is a multi-ingredient, co-packaged product that is intended to treat human immunodeficiency virus type 1 (HIV-1).

1.1 PRODUCT DESCRIPTION

Cabenuva is proposed as a two-drug injectable regimen that requires concomitant dosing of cabotegravir and rilpivirine injectable suspensions via separate intramuscular injections. Cabenuva will be supplied as two co-packaged kits described as "2-mL" and "3-mL" co-packs. Each kit contains the following components:

- 1 vial of cabotegravir extended-release injectable suspension, as either 600 mg/3 mL or 400 mg/2 mL
- 1 vial of rilpivirine extended-release injectable suspension, as either 900 mg/3 mL or 600 mg/ 2 mL
- two sterile, single-use vial adaptors
- two sterile 5-mL single-use syringes; and
- two sterile, single-use 23-gauge 1.5-inch safety needles.

The "3-mL co-pack" (cabotegravir 600 mg/3 mL; rilpivirine 900 mg/3 mL) is intended to be used to initiate injection therapy following oral lead-in therapy. The "2-mL co-pack" (cabotegravir 400 mg/2 mL; rilpivirine 600 mg/2 mL) is intended for once-monthly continuation injection therapy following injection therapy initiation with the "3-mL co-pack." See Appendix A for more product information.

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On December 6, 2016 in the final meeting minutes to a Type B Meeting, ViiV stated that they would submit a human factors study for review.[a]

On January 5, 2018 in the final meeting minutes to a Type C Meeting, ViiV acknowledged preliminary comments from DMEPA on their IFU and anticipated submitting their human factors validation protocol in the second quarter of 2018.[b]

On May 1, 2018, the Applicant submitted a human factors (HF) validation study protocol for Agency review.

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[a] Rivera, L. Final Type B Meeting Minutes for Cabotegravir-Rilpivirine extended release injectable suspension. Silver Spring (MD): FDA, CDER, OPQ, OPRO (US); 2016 DEC 6. IND 109678. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80415e19&_afrRedirect=1706477482609387

[b] Gentles, A. Final Type B Meeting Minutes for Cabotegravir-Rilpivirine extended release injectable suspension. Silver Spring (MD): FDA, CDER, OND, OAP, DAP (US); 2016 2018 6. IND 109678. :https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80476e60&_afrRedirect=1706871561938708

On June 11, 2018 we provided recommendations for the HF validation study protocol and requested that the Applicant address the identified areas of concern prior to commencing the HF validation study.[c]

APPEARS THIS WAY ON ORIGINAL

[c] Shah, M. Human Factors Study Protocol Review for Cabotegravir-Rilpivirine extended release injectable suspension. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 8. RCM No.: 2018-917.

On August 16, 2018 and September 19, 2018, the Applicant submitted updated study protocols in response to the FDA recommendations.

On October 19, 2018, DMEPA provided recommendations for the revised HF validation study protocol and requested that the sponsor address the identified areas of concern prior to commencing the HF validation study. [d]

APPEARS THIS WAY ON ORIGINAL

[d] Wilson, V. Human Factors Study Protocol Review Memo for Cabotegravir-Rilpivirine extended release injectable suspension. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 12. RCM No.: 2018-917-1.

On April 29, 2019, the Applicant submitted a human factors validation study report, which is the subject of this review. We verified that the previous DMEPA recommendations regarding the protocol were followed in the execution of the validation study.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C – N/A
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design and our analysis of the observed use errors and close calls to determine if the validation study results support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

We previously reviewed the HF validation study protocol and note that our recommendations were implemented.[e] We find the study methodology acceptable.

The HF validation study included one user group comprised of 20 registered nurses, 13 with HIV medication experience and seven without. All participants were untrained and use of the IFU was optional and self-directed by the participants.

Each study participant performed a simulation to prepare and administer the two injections that comprise a complete dose of this dual medication product. Next the participant completed a comprehension interview. Finally, the moderator conducted a post- use interview regarding incorrect actions or responses.

3.2 RESULTS AND ANALYSES OF HUMAN FACTORS VALIDATION STUDY DATA

Table 2 describes the study results for critical tasks, the Applicant's analyses of the results, and DMEPA's analyses and recommendations.

[e] Shah, M. Human Factors Study Protocol Review for Cabotegravir-Rilpivirine extended release injectable suspension. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 8. RCM No.: 2018-917.

Wilson, V. Human Factors Study Protocol Review Memo for Cabotegravir-Rilpivirine extended release injectable suspension. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 12. RCM No.: 2018-917-1.

3.2.1 Analysis of human factors validation study results

Table 2: Summary and analyses of errors/close calls/use difficulties with new critical tasks during simulated use testing					
Task Number & Description	Number & Description of Use Errors	Participant's Subjective Feedback	Applicant's Root Cause Analysis	Applicant's discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Tasks 1 & 2 Prepare the dose correctly (Fill the syringe from only 1 vial and check that the correct dose volume is drawn up)	Injection #1 2 use errors Use error 1: The user did not fully expel air prior to drawing up the dose. The syringe contained a significant air bubble that led to the injection of approximately 2.5 mL drug product and 0.5 mL of air. (Participant 02-002).	"I was trying not to make a mess, I would have normally put the syringe more upright to expel all the air if I had not been in this clean setting - I didn't want to make a mess with the product; It would have allowed me to get rid of the air and give the correct amount of medication."	The Applicant attributes this error to study artifact because the participant acknowledged that they did not draw up the dose correctly as it was a simulation.	Because the Applicant attributed this error to study artifact, they did not propose a mitigation strategy.	Based on our analysis of the subjective feedback and the Applicant's root cause analysis, we agree with the Applicant's determination that no mitigation is needed because the use error was attributed to study artifact.
	Injection #1 Use Error 2: Vial adapter was incorrectly used, and as a result the	The participant states "Because that's usually what we do with what we have - I	We requested additional information on how the participant used the vial adapter	The Applicant stated in their URRA that the risk of the incorrect use of the adapter is a single underdose of the	We agree with the Applicant's assessment of the potential clinical harm from this error as a one-time underdose due to

Table 2: Summary and analyses of errors/close calls/use difficulties with new critical tasks during simulated use testing					
Task Number & Description	Number & Description of Use Errors	Participant's Subjective Feedback	Applicant's Root Cause Analysis	Applicant's discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	full dose was not drawn up. The participant lost medication due to incorrect use of the vial adapter and was unable to draw a full dose (~1.5 mL) (Participant 01-003)	probably should have read better - we usually just stick the needle into the vial, using the adaptor was confusing." The participant acknowledged that they typically used needles for aspiration and did not carefully read the instructions on use of a vial adaptor.	incorrect and root cause analysis from the Applicant regarding this error. The Applicant stated the root cause of this error was lack of familiarity with the vial adapter.	medication. The Applicant stated that they believe that the instructions have been appropriately optimized (b) (4) The Applicant stated that errors with the vial adapter dropped from a level of 55 percent in formative testing to 5 percent in the human factors validation study and attributed the improvement to updates made to the IFU.	lost medication when the vial adapter is used incorrectly. We agree with the Applicant's root cause analysis. We acknowledge that the Applicant has iteratively optimized the IFU and that Steps 5 through 10 illustrate and describe how to use the vial adapter to fill the syringe. Additionally, we note the Applicant's plan to mitigate the residual risk of this error (b) (4)

Table 2: Summary and analyses of errors/close calls/use difficulties with new critical tasks during simulated use testing					
Task Number & Description	Number & Description of Use Errors	Participant's Subjective Feedback	Applicant's Root Cause Analysis	Applicant's discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
					(b) (4) [redacted]
	Injection #2 1 use error: The participant incorrectly used the	"Both of these vials - because the medication is white color - you cannot	The applicant stated the participant made this error because they did not follow the IFU.	The Applicant stated that instructions on use of the devices in the IFU is consistent with the	We agree with the Applicant's root cause analysis. (b) (4) [redacted]

Table 2: Summary and analyses of errors/close calls/use difficulties with new critical tasks during simulated use testing					
Task Number & Description	Number & Description of Use Errors	Participant's Subjective Feedback	Applicant's Root Cause Analysis	Applicant's discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	vial adapter (only 2 mL of the 3 mL dose drawn up) (Participant (b) (6)	see how much is really left. The pressure cuff [the vial adapter] built the pressure in the medication, so you may get air. I see it now it this one is not fully [filled]."	They did not carefully read instructions (related to dose volume in the syringe).	manufacturer's intended use and when followed allow for the full dose to be withdrawn. This observation will be used (b) (4)	(b) (4), please see our analysis in the previous error/row above.
	Injection #1 2 Close calls Close call #1: Large bubble - Dose OK (b) (6) Close Call #2: Questioned dose amount, asked if weight based (b) (6)	Close call #1: The participant acknowledged drawing a large bubble into the syringe while ensuring that the whole dose had been drawn up. The bubble was expelled prior to dosing. Close call #2: The participant asked where the information was to	Close call #1: The Applicant stated that the participant acknowledged that the root cause was user error. Close call #2: The Applicant stated that the participant assumed it was a weight-based injection volume based on their experience.	Close call #1: The Applicant assigned no mitigation strategy for this close call because the participant self-corrected and administered the full dose. Close call #2: The Applicant assigned no mitigation strategy for this close call because the participant self-corrected through a more thorough review of the IFU and administered the full dose.	We agree with the Applicant's root cause analyses and do not have additional recommendations.

Table 2: Summary and analyses of errors/close calls/use difficulties with new critical tasks during simulated use testing					
Task Number & Description	Number & Description of Use Errors	Participant's Subjective Feedback	Applicant's Root Cause Analysis	Applicant's discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		adjust the dose based on weight, assuming that it was a weight-based injection volume. The participant re-read the IFU and noted that they were to deliver the full dose.			
	Injection #2 Close call: Splatter (leakage from attaching vial adapter to vial) (Participant (b) (6))	Based on observation, it is believed that the participant used excessive force and/or incorrect technique when attaching the vial adapter to the vial. The participant was able to withdraw the full dose.	The Applicant stated that the participant acknowledged in response to several errors and close calls that they did not thoroughly review the IFU.	The Applicant assigned no mitigation strategy for this close call since the participant acknowledged they did not thoroughly review the IFU and was able to self-correct and administer the full dose.	Our review of the IFU notes there is instruction on technique but no instruction on the amount of force required to attach the vial adaptor. We note the participant was able to self-correct and administer the full dose. We also find it reasonable to expect users to become aware of the force necessary after first time use and then apply that knowledge for

Table 2: Summary and analyses of errors/close calls/use difficulties with new critical tasks during simulated use testing					
Task Number & Description	Number & Description of Use Errors	Participant's Subjective Feedback	Applicant's Root Cause Analysis	Applicant's discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
					subsequent use. Thus, we do not have an additional recommendation.
Task 4: Moved to 2nd injection on their own	Injection #1 4 use errors Four participants (did not initially move on to the second injection on their own. Both injections were completed by all participants.	All four users recognized that the full dosing regimen as dictated by the IFU required delivering of both injections, however they felt that they needed permission from the moderator to move on to the second injection. Subjects either asked if they should move on; or believed, as it was a simulation, that the visit was	The Applicant states that since all participants understood that both injections were necessary, and completed both injections once they understood that the study included both injections, this is considered to be a study artifact.	The Applicant assigned no mitigation strategy for this error.	Based on our analysis of the subjective feedback and the Applicant's root cause analysis, we agree with the Applicant's determination that no mitigation is needed because the use errors were attributed to study artifact.

Table 2: Summary and analyses of errors/close calls/use difficulties with new critical tasks during simulated use testing					
Task Number & Description	Number & Description of Use Errors	Participant's Subjective Feedback	Applicant's Root Cause Analysis	Applicant's discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		concluded after one preparation and administration.			
Knowledge question: Task 6 According to the IFU and/or labelling, can you freeze this pack?	1 Use error (Participant (b) (6)) Answered incorrectly	"It doesn't say. I'm assuming it can only be refrigerated because one of the FAQs ask how long it can be left out of the fridge. I'm not supposed to know that; just how to administer it. You leave a lot of the stuff to pharmacy, you just worry about what happens once it's on your unit."	This error is a study artifact. As storage conditions were not within the responsibility of the user, they did not focus on the long-term storage conditions of the product. They did correctly identify the in-use storage conditions of the product, which were directly within their responsibility.	The Applicant stated assigned no mitigation strategy for this error.	Based on our analysis of the subjective feedback and the Applicant's root cause analysis, we agree with the Applicant's determination that no mitigation is needed because the use error was attributed to study artifact

Table 2: Summary and analyses of errors/close calls/use difficulties with new critical tasks during simulated use testing					
Task Number & Description	Number & Description of Use Errors	Participant's Subjective Feedback	Applicant's Root Cause Analysis	Applicant's discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Knowledge question: Task 7 According to the IFU and/or labelling, at what temperature should this pack be stored?	1 use error "Room temperature and otherwise refrigerated but no more than 77 degrees at room temp for 6 hours." (Participant (b) (6)	"I assume that it has to be refrigerated, and it gives you the exact time and temp it can be left out."	The Applicant stated the participant did understand that there is a long-term storage condition but did not clearly articulate their understanding due to an incomplete read of the IFU.	The Applicant stated assigned no mitigation strategy for this error.	We agree with the Applicant's root cause analysis. Our review of the IFU did not generate any recommendations.
Comprehension question 5a: According to the IFU and/or labeling, what should the medication look like after shaking/ resuspension?	2 Use errors Use error #1: "One should be a brown tint, it doesn't say what the other one should look like." Use error 2: The participant responded with the color of the suspensions rather than	Use error #1: "I see it now. Was not clear to me (was not easy to find)." Upon further inquiry regarding the other injection, the participant acknowledged, after finding the instruction, that they "should have	The Applicant states that the participants did not clearly understand the question and / or read the IFU.	The Applicant noted that the instruction notifying the user that the suspension should look uniform is included as a Note to Step 10. The Applicant assigned no mitigation strategy for this error.	Our review of the root cause analysis and subjective feedback indicate study artifact for the first error and clarity on information about the uniformity of the suspension in both errors. Our heuristic and expert analyses of the study data indicates that changes to the IFU and carton labeling can provide

Table 2: Summary and analyses of errors/close calls/use difficulties with new critical tasks during simulated use testing					
Task Number & Description	Number & Description of Use Errors	Participant's Subjective Feedback	Applicant's Root Cause Analysis	Applicant's discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	stating that the suspension should be uniform.	probably just read better" Use error #2: "That's what it looked like in the vial."			further clarity to assess uniform suspension after shaking the drug product. See Table 4, IFU item 5 below for this specific recommendation. In this instance, we determined that no additional HF validation data is needed to be submitted for Agency's review to support this revision.

3.2.2 Analysis of essential tasks

The HF validation study showed use errors, use difficulties, and close calls with seven essential tasks that are common to other injectable drugs. We have no recommendations for use errors, difficulties, or close calls related to the following tasks:

- Task 6: Wait 15 minutes to allow for medication to come to room temperature
- Task 9: Attach vial adapter
- Task 11: Attach syringe to vial adapter
- Task 12: Unscrew syringe from vial adapter (in correct orientation)
- Task 16: Stretch skin
- Task 17: Fully insert needle
- Task 18: Apply pressure/apply bandage / Do not massage the area

There were use errors associated with the non-critical Task 10, [redacted] (b) (4) ” that according to subjective feedback may have been associated with the design of the IFU. Our review of the participant feedback indicates that the graphic in Step 7 does not visually emphasize drawing up the 1 mL of air. See Table 4, IFU item 7 for our recommendation to improve the instruction for this task. In these particular instances, we determined that no additional HF validation data is needed to be submitted for Agency’s review to support this revision.

3.3 LABELS AND LABELING

Tables 3 and 4 below include the identified medication error issues with the submitted product samples, packaging, label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 3: Identified Issues and Recommendations for Division of Antiviral Products			
	Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information			
1.	The DOSAGE AND ADMINISTRATION section states that the initial injection doses of CABENUVA are a single intramuscular injection of cabotegravir and rilpivirine without specifying upfront that the injections are intended to be administered at gluteal intramuscular sites.	Overlooking the specification that CABENUVA is to be administered via gluteal sites could result in administration errors, for example, administration of CABENUVA into another intramuscular site such as the deltoid.	We recommend specifying "gluteal intramuscular injection" where applicable throughout the DOSAGE AND ADMINISTRATION section.
2.	The STORAGE AND HANDLING section includes important administration instruction which could be missed.	Overlooking important administration instructions could result in administration of deteriorated drug product.	We recommend incorporating the following statements in Section 2.4 (Administration Instructions) of the PI: *Prior to administration, vials should be brought to room temperature (not to exceed 25°C [77°F]). Vials may remain in the carton at room temperature for up to 6 hours. If not used after 6 hours, they must be discarded.*

			Once the suspension has been drawn into the respective syringes, the injections should be administered as soon as possible, but may remain in the syringe for up to 2 hours. If 2 hours are exceeded, the medications, syringes, and needles must be discarded.
3.	The PI expresses the recommended doses as (b) (4) (b) (4)	We are concerned that the presentation of the dosing information could be misinterpreted as 2 mL or 3 mL being the total volume to administer, respectively.	We recommend revising the PI to emphasize the milligram strength of each dose. For example, reformat "X mL (XXX mg)" to read as: "XXX mg (X mL)." Additionally, we recommend revising the descriptor of each kit to read as, "CABENUVA 400 mg/600 mg Kit" and "CABENUVA 600 mg/900 mg Kit," respectively.

Table 4: Identified Issues and Recommendations for ViiV Healthcare Company (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	The IFU does not include disposal instructions for Cabenuva for instances when the product remains at room temperature for more than 6 hours.	The Prescribing Information indicates that cabotegravir and rilpivirine suspensions may remain in the carton at room temperature for up to 6 hours. If not used after 6 hours, they must be discarded.	In the Questions and Answers section of the IFU, revise the response to question 1 (How long can the medicine be left out of the refrigerator?) to indicate that the vials of medicine must be discarded if stored at room temperature for more than 6 hours. Additionally, we recommend you repeat this important information at the beginning of the IFU under the Storage Information section.
2.	The Question and Answers section of the IFU includes important	There is a risk of administration of	We recommend you repeat this important information at the beginning of the IFU under the

	administration/handling information (e.g. vials may sit in the carton for up to 6 hours and medication can remain in the syringe for up to 2 hours…discard if 2 hours exceeded) which could be missed.	deteriorated drug product if end users miss the important information to dispose the product if it sits at room temperature for greater than 6 hours or dispose the product if it remains in the syringe for greater than 2 hours.	Storage Information heading. Alternatively, consider creating an additional heading that appears below the storage information, for example, "Prior to Administration," to list this information.
3.	The IFU includes the statement, "Cabotegravir and rilpivirine are for intramuscular use only."	There is risk that end users could misinterpret this statement to mean that it is acceptable to administer this product via other intramuscular sites such as the deltoid.	To provide clarity and reinforce the proper injection location, we recommend revising the statement to read as: "Cabotegravir and rilpivirine are for gluteal intramuscular use only."
4.	The IFU does not clearly indicate to administer the injections in separate gluteal sites.	The Prescribing Information states to administer each injection at separate gluteal injection sites.	To provide clarity, in the Overview section, we recommend revising the statement, (b) (4) to read as "Each injection must be administered to separate gluteal sites." Additionally, we recommend including additional instruction for the step titled *Repeat for 2nd medicine* to indicate that the second injection must be administered into a separate gluteal intramuscular site. Because these revisions are intended to provide additional clarity, we determined it is not necessary to submit additional human factors validation.
5.	In the HF validation study, two users made errors on the Comprehension	Our heuristic and expert analyses of the study data	We recommend that the second bullet under "Step 3, Shake vigorously" be reworded to: "Invert the vial

	Question 5a, "According to the IFU and/or labeling, what should the medication look like after shaking/ resuspension?"	indicates that changes to the IFU can provide further clarity in the wording and layout of Step 3 in the IFU.	and confirm the suspension is uniform." The next sentence should be made into a new, separate bullet: "If the suspension is not uniform, shake the vial again."
6.	In the HF validation study, there were use errors associated with Task 10, (b) (4) that may have been associated with the design of the IFU .	Our heuristic and expert analyses of the study data indicates that changes to the IFU can provide further clarity. Step 7 does not visually emphasize in the graphic drawing up the 1 mL of air.	We recommend you revise the graphic in Step 7 to include a line and label to clarify the 1 mL of air in the syringe, similar to the graphic in Step 14. For example, 
7.	The co-packaged kits do not contain labels which can be affixed to the syringes once the medications are drawn from the vials into each syringe.	Without labels to identify syringe contents we are concerned for risk of confusion in product identification prior to administration. Cabenuva contains two medications that must be prepared separately and administered in separate gluteal intramuscular injection sites. For instances when the healthcare provider (HCP)	a. We recommend you update the contents listing to include syringe labels. b. We recommend you include a step following Step 11 (Attach needle) to instruct end users to affix the appropriate syringe label to each syringe once the medication has been drawn out of each vial. These revisions are intended to provide additional patient safety mitigation but are not critical to the use of this product, therefore, we determined it is not necessary to submit additional human factors validation.

		chooses to prepare both syringes but not administer the medication immediately, it is important for healthcare providers to be able to easily identify the contents of each syringe once the medications are drawn into the syringes.	
8.	The "(b) (4) descriptors are misleading and could lead to confusion.	We are concerned the (b) (4) descriptors used in the IFU may be misinterpreted as the total volume to be injected collectively between the two vials.	We recommend you replace the (b) (4) descriptors throughout the IFU with "400 mg/600 mg Kit" and "600 mg/900 mg Kit," respectively to serve as a better representation of each kit.
Container Label			
1.	The container labels for the cabotegravir vials do not include the route of administration.	We note that the route of administration is not required to be listed due to the small size of the label, but we recognize the importance of reinforcing the proper route of administration for this product.	We recommend you remove the (b) (4) descriptors. Additionally, move the manufacturer's information to the side panel of the vial to create space to include the route of administration on the cabotegravir vial labels.
2.	The container labels include a (b) (4) descriptor that could lead to confusion.	Each vial contains overfill and the (b) (4) „	We recommend you remove the (b) (4) descriptor from the container labels and consider

		could be misinterpreted to indicate the total vial fill.	including a "discard unused portion" statement on the container labels.
3.	The format of the expiration date is not defined on the container labels.	We are unable to assess whether the proposed format of the container label expiration date reduces the risk of deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Carton Labeling			
1.	As currently presented on the principal display panel, it is unclear which strength correlates with each individual active ingredient. (b) (4)	Lack of clear understanding of the strength for each individual active ingredient could lead to confusion or dosing errors.	To provide clarity for the strength of each active ingredient of this co-packaged product, we recommend listing the active ingredients and correlating strength and dosage form separately. We recommend you reformat the established name, dosage form, and strength for each active ingredient to appear as shown in Figure 1 below. Figure 1.

			(b) (4)  For consistency, the above recommendations should be applied to each area of the cartons, information packs, and IFU where the proprietary name, established names, dosage form, and strengths are listed concurrently. Additionally, box the proprietary name to mitigate misinterpretation, for example, to mitigate interpreting Cabenuva as the proprietary name for cabotegravir only.
2.	The "Discard unused portion" statement is located on a side panel and may be missed.	Each vial of cabotegravir and rilpivirine contains overfill. Overlooking the "discard unused portion" statement could result in overdose errors.	We recommend adding the "Discard unused portion" statement to the principal display panel (PDP) of each carton to appear with the storage information, for example: (b) (4) 
3.	The carton labeling does not include important storage and handling information that is listed in the Prescribing Information.	It is important for end users to understand all aspects of the storage and handling of this product to reduce risk of administration error. For example, the Prescribing	Ensure the storage and handling of this product is clearly communicated on the carton labeling. We recommend placing this information near the storage information located on the principal display panel.

		Information indicates that prior to administration, the vials may remain in the carton at room temperature for up to 6 hours. After 6 hours at room temperature, the vials should be discarded.	
4.	The [redacted] (b) (4) kit descriptors located in the lower right corners of the principal display panel could lead to confusion or misinterpretation.	We are concerned the descriptors could be misinterpreted as the total volume to be injected collectively between both vials.	We recommend you replace the [redacted] (b) (4) descriptors with "400 mg/600 mg Kit" and "600 mg/900 mg Kit" to serve as a better representation of each kit.
5.	Our expert and heuristic review of the carton identified areas on the carton that can be revised. See suggested edits in Figure 2. Please note, Figure 2 incorporates revisions that coincide with carton labeling recommendations #1-4 above, as well as, packaging recommendation #1 below.		Figure 2. Suggested edits for Cabenuva carton labeling

			(b) (4) [redacted]
Packaging			
1.	The co-packaged kits do not contain syringe labels.	Without labels to identify syringe contents we are concerned for risk of confusion in product identification prior to administration. Cabenuva contains two medications, that share a similar milky white appearance. Additionally, each medication must be prepared separately and administered in separate gluteal intramuscular	a. We recommend you include two syringe labels in each kit, one each for cabotegravir and rilpivirine, prominently placed in each carton, which can be affixed to each syringe once the medications are drawn into the syringes. b. For instances where HCPs may prepare both syringes but do not administer immediately, we recommend including a space for the date and time to be written on the label. These revisions are intended to provide additional patient safety mitigation but are not critical to the use of this product, therefore, we determined it is

		injection sites. For instances when the healthcare provider (HCP) chooses to prepare both syringes but not administer immediately, it is important that the HCP is able to easily identify the contents of each syringe.	not necessary to submit additional human factors validation demonstrating the use of these syringe labels.
General Recommendation			
1. (b) (4)			

4 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the HF validation study results identified use errors and close calls on critical tasks. We have provided recommendations to address these use errors and close calls. Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 3 for the Division and Table 4 for the Applicant. We ask that the Division convey Table 4 in its entirety to the applicant so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR VIIV HEALTHCARE COMPANY

Our evaluation of your human factors validation (HF) study results determined submission of additional HF validation is not warranted. However, our evaluation of the proposed packaging, label, and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4, and we recommend that you implement these recommendations prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Cabenuva that ViiV Healthcare Company sent to the Agency on April 29, 2019.

<table>
<tr><th colspan="2">Table 5. Relevant Product Information</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Therapeutic Drug Class or New Drug Class</td><td>Antiviral</td></tr>
<tr><td>Active Ingredient</td><td>Cabotegravir; rilpivirine</td></tr>
<tr><td>Indication</td><td>A complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) and who have no known or suspected resistance to either cabotegravir or rilpivirine</td></tr>
<tr><td>Route of Administration</td><td>Intramuscular</td></tr>
<tr><td>Dosage Form</td><td>Extended-release injectable suspensions</td></tr>
<tr><td>Strength</td><td>cabotegravir 600 mg/3 mL and rilpivirine 900 mg/3 mL
cabotegravir 400 mg/2 mL and rilpivirine 600 mg/2 mL</td></tr>
<tr><td>Dose and Frequency</td><td>
Recommended Dosing Schedule in Adults
<table>
<tr><th>Drug</th><th>Oral
Lead-In[a]
Month 1
(at Least 28 Days)</th><th>IM
Initiation Injections
At Month 2</th><th>IM
Continuation Injections
Month 3 Onwards</th></tr>
<tr><td>Cabotegravir</td><td>30 mg once daily</td><td>3 mL (600 mg)</td><td>2 mL (400 mg) monthly</td></tr>
<tr><td>Rilpivirine</td><td>25 mg once daily</td><td>3 mL (900 mg)</td><td>2 mL (600 mg) monthly</td></tr>
</table>
If a patient plans to miss a scheduled injection visit by more than 7 days, oral therapy (one 30-mg tablet of cabotegravir [VOCABRIA] and one 25-mg tablet of rilpivirine [EDURANT] once daily) may be used to replace up to 2 consecutive monthly injection visits. The first dose of oral therapy should be taken approximately 1 month after the last injection dose of CABENUVA. Injection dosing should be resumed on the day oral dosing completes.
Injection Dosing Recommendations after Missed Injections or Oral Therapy
<table>
<tr><th>Time Since Last Injection</th><th>Recommendation</th></tr>
<tr><td>< 2 months</td><td>Continue with the monthly (b) (4) injection dosing schedule as soon as possible.</td></tr>
<tr><td>≥ 2 months</td><td>Re-initiate the patient on the 3-mL dose, and then continue to follow the (b) (4) injection doing schedule.</td></tr>
</table>
</td></tr>
</table>

How Supplied	(b) (4)
Storage	Store CABENUVA in the refrigerator at 2° to 8°C (36° to 46°F) in the original carton until ready to use. Do not freeze. Do not mix with any other product or diluent. Prior to administration, vials should be brought to room temperature (not to exceed 25°C [77°F]). Vials may remain in the carton at room temperature for up to 6 hours. If not used after 6 hours, they must be discarded. Once the suspension has been drawn into the respective syringes, the injections should be administered as soon as possible, but may remain in the syringe for up to 2 hours. If 2 hours are exceeded, the medications, syringes, and needles must be discarded.
Container Closure	Cabotegravir injectable suspension: • Clear glass vial with a rubber injection stopper and sealed with an aluminum overseal with a removable plastic cap differentiated by labeling and plastic color cap. 2 mL presentation has a dark gray cap and the 3 mL presentation has an orange cap.

	Rilpivirine injectable suspension: • Clear glass vial with a rubber injection stopper and sealed with an aluminum overseal with a removable plastic cap differentiated by labeling and plastic color cap. 2 mL presentation has a mist gray cap and the 3 mL presentation has a yellow cap.
Intended Users	Healthcare Professionals
Intended Use Environment	Community health centers, private practices, and similar facilities

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On June 24, 2019, we searched the L:drive and AIMS using the terms, carbotegravir, rilpivirine, 109678 and 212888 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified two previous reviews. We confirmed that our previous recommendations were implemented in the execution of the HF validation study.

1. Shah, M. Human Factors Study Protocol Review for Cabotegravir-Rilpivirine extended release injectable suspension. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 8. RCM No.: 2018-917.
2. Wilson, V. Human Factors Study Protocol Review Memo for Cabotegravir-Rilpivirine extended release injectable suspension. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 12. RCM No.: 2018-917-1.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in EDR via:

\\cdsesub1\evsprod\ind109678\0278\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv-infection\5354-other-stud-rep\18017\protocol.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

\\cdsesub1\evsprod\nda212888\0001\m3\32-body-data\32r-reg-info\human-factor-validation.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

Date Request Sent	Date Response Received	Accessed in EDR via:
June 26, 2019	July 5, 2019	\\cdsesub1\evsprod\nda212888\0012\m3\32-body-data\32r-reg-info\risk-assess-carla-copack.pdf
July 18, 2019	July 22, 2019	\\cdsesub1\evsprod\nda212888\0018\m1\us\111-information-amendments\cmc-response-22jul2019.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[6] along with postmarket medication error data, we reviewed the following Cabenuva labels and labeling submitted by ViiV Healthcare Company.

- Container labels received on April 29, 2019
- Carton labeling received on April 29, 2019
- Instructions for Use received on April 29, 2019
- Prescribing Information and Patient Information (Image not shown) received on April 29, 2019 and October 10, 2019, accessible in EDR via: \\cdsesub1\evsprod\nda212888\0001\m1\us\114-labeling\1141-draft\draft-clean.docx and

8 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[6] 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JANINE A PURCELL
10/29/2019 09:21:34 AM

VALERIE S VAUGHAN
10/29/2019 12:00:01 PM

LOLITA G WHITE
10/29/2019 12:47:22 PM

QUYNHNHU T NGUYEN
10/30/2019 12:17:36 AM

Clinical Inspection Summary

Date	10/28/2019
From	Karen Bleich, M.D., Reviewer Aisha Johnson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Jacquelyn Rosenberger, Pharm.D, Regulatory Project Manager Mark Needles, M.D., Clinical Reviewer Yuliya Yasinskaya, M.D., Team Leader Division of Anti-Viral Drug Products
NDA/BLA #	NDA 212887 and NDA 212888
Applicant	ViiV Healthcare Co.
Drug	Vocabria (cabotegravir) tablets for oral use (NDA 212887) and Cabenuva (co-packaged cabotegravir and rilpivirine) suspension for IM injection (NDA 212888)
NME (Yes/No)	Yes
Review Classification	Priority
Proposed Indication(s)	Vocabria: For use in combination with rilpivirine for short-term treatment of HIV-1 infection in adults who are virologically suppressed. Cabenuva: For treatment of HIV-1 infection in adults who are virologically suppressed.
Consultation Request Date	5/6/2019
Summary Goal Date	10/29/2019
Action Goal Date	12/29/2019
PDUFA Date	12/29/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study 201584 (FLAIR) and Study 201585 (ATLAS) were submitted to the Agency in support of NDA 212887 and NDA 212888. A total of four clinical investigator sites were selected for audit: Dr. Miguel Gorgolas Hernandez-Morales (Protocol 201584/Site 225283), Dr. Maria Del Mar Masia (Protocol 201584/Site 225120 and Protocol 201585/Site 225163), Dr. Christopher Bettacchi (Protocol 201584/Site 222234 and Protocol 201585/Site 222290), and Dr. Franco Antonia Felizarta (Protocol 201584/Site 222193 and Protocol 201585/Site 222276).

Inspections of selected clinical investigator sites from Studies 201584 and 201585 identified nine unreported adverse events in seven subjects at two of the sites in Spain. Based on the reports of the inspections, communication with the field inspector, and communication with the Sponsor, it was determined that the cause of the underreporting was that the adverse events reports became available to the investigators and the Sponsor after the submission of the NDA. The adverse events were identified upon review of a newly available electronic medical record system that captured primary care visits in Spain. The review of the primary care EMR occurred after the submission of the NDA. The unreported adverse events consisted of events that were reported by study subjects to their care provider and were not also reported by the study subjects to the clinical investigator. The unreported AEs were classified as non-serious and were assessed as unrelated to the study drug by the clinical investigators.

The Sponsor is in the process of evaluating if any additional unreported adverse events exist at other study sites in Spain related to the integration of the primary care EMR after the NDA submission. The Sponsor reports that a final review of the issue and corrective and preventive action plan in expected to be in place by October 31st, 2019.

There was no under reporting of adverse events that were disclosed by subjects to the clinical investigators, which was the primary mechanism for AE reporting in the 201584 and 201585 studies. The unreported AEs do not appear to have been unreported because of any deficiency in study conduct. The inspections demonstrated no additional significant findings related to data integrity or human subject protection.

Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these clinical investigator sites submitted by the sponsor appear acceptable in support of the proposed indication.

II. BACKGROUND

ViiV Healthcare Co. seeks approval to market Vocabria and Cabenuva for the treatment of HIV-1 infection in adults who are virologically suppressed. Vocabria is an oral formulation of cabotegravir, to be taken with oral rilpivarine and is intended for oral lead-in for IM use of Cabenuva. Cabenuva is an IM formulation that consists of co-packaged cabotegravir and rilpivirine and is administered monthly.

The clinical data to support the use of cabotegravir/rilpivarine (as oral tablets or as IM injections) is based on the 48-week results of two Phase 3 studies: Study 201584 (FLAIR) and Study 201585 (ATLAS). Both studies compared the safety and efficacy of monthly IM injections of Cabenuva as compared to standard daily oral triple therapy for HIV-1.

In the FLAIR study, antiretroviral-naïve adults with HIV-1 were enrolled and were given a standard daily oral triple therapy regimen for an induction period. Subjects who achieved viral suppression were subsequently eligible to enter a maintenance phase in which subjects were

randomized to either the IM formulation of the study drug (preceded by an oral lead in) or to continue their oral antiretroviral regimen.

In the ATLAS study, adult subjects with HIV-1 with a suppressed viral load on a stable antiretroviral regiment were eligible for enrollment. Subjects were randomized to either the IM formulation of the study drug (preceded by an oral lead in) or to continue their oral antiretroviral regimen.

In both studies, the primary endpoint was the number of cases of virologic failure at 48 weeks.

The studies are summarized below:

Study 201584 (FLAIR)

Title of Study: "A phase III, randomized, multi-center, parallel-group, open-label study evaluating the efficacy, safety, and tolerability of long-acting intramuscular cabotegravir and rilpivirine for maintenance of virologic suppression following switch from an integrase inhibitor single tablet regimen in HIV-1 infected antiretroviral therapy naïve adult participants: Week 48 – Primary endpoint."
Number of Subjects: 629
Main criteria for inclusion: Anti-retroviral-naïve adults with HIV-1
Treatment administration:
Induction Phase: All subjects received abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) for 20 weeks
Maintenance Phase: Subjects who achieved viral suppression were randomized (1:1) to Arm 1 or Arm 2
Arm 1: Cabotegravir and rilpivirine (daily oral lead in for 4 weeks, followed by monthly IM formulation)
Arm 2: Remain on daily oral induction regiment
Study Sites: 108 sites in 11 countries (Canada, France, Germany, Italy, Japan, Netherlands, Russia, South Africa, Spain, United Kingdom, and U.S).
Study Period: October 27th, 2016 – August 30th, 2018
Primary Objective: To demonstrate the non-inferior antiviral activity of switching to IM cabotegravir + rilpivirine every 4 weeks compared to continuation of continued/current antiretroviral regimen over 48 weeks in HIV-1 antiretroviral naïve subjects
Primary Efficacy Endpoint: Proportion of subjects with a virologic failure endpoint as per FDA Snapshot algorithm at Week 48.

Study 201585 (ATLAS)

Title of Study: "A Phase III, randomized, multicenter, parallel-group, noninferiority, open-label study evaluating the efficacy, safety, and tolerability of switching to long-acting cabotegravir plus long-acting rilpivirine from current INI-, NNRTI-, or PI-based antiretroviral regimen in HIV-1 injected adults who are virologically suppressed."
Number of subjects: 616
Main criteria for inclusion: Adults with HIV-1 on stable antiretroviral regimen with suppressed viral load
Treatment administration: Subjects randomized 1:1 to Arm 1 or Arm 2
Arm 1: Cabotegravir and rilpivirine (daily oral lead in for 4 weeks, followed by monthly IM formulation)
Arm 2: Remain on current antiretroviral therapy (at time of enrollment)
Number of sites: 115 sites in 13 countries (Argentina, Australia, Canada, France, Germany, Italy, Mexico, Korea, Russia, South Africa, Spain, Sweden, and the U.S.)
Study Period: October 28th, 2016 – May 29th, 2018
Primary Objective:
To demonstrate the non-inferior antiviral activity of switching to IM CAB + RPV every 4 weeks (monthly) compared to continuation of CAR over 48 weeks in HIV-1 infected ART-experienced subjects
Primary Efficacy Endpoint:
Proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL per the Snapshot Algorithm at Week 48.

Rationale for Site Selection
Sites were chosen for inspection based primarily upon enrollment of relatively large numbers of subjects and participation in both the FLAIR and ATLAS Studies.

III. RESULTS (by site):

1. Dr Miguel Gorgolas Hernandez-Morales, Madrid, Spain (Protocol 201584 (FLAIR) Site 225283)

The inspection of Dr. Hernandez-Morales' site was conducted from 7/22/19 – 7/26/2019. At the time of the inspection, the study was in long-term follow-up (closed to enrollment). The site screened 21 subjects and enrolled 16 subjects.

The inspection included a review of documents related to the site's training program, Ethics Committee approval and correspondences, informed consent, site monitoring, and financial disclosures. A comprehensive review of the source document records for all enrolled subjects was performed. The data listings submitted in the NDA were verified by comparison with the source data at the site, including protocol deviations, primary efficacy endpoint test results, enrollment criteria, and adverse events.

Adverse events were identified in the source records that were not included in the site data listings provided to the Agency by the Sponsor. The cause of the omission was that the adverse events were identified in primary care electronic medical records and these records became available to the Sponsor and the clinical investigator after the submission of the NDA. The inspector verified that the adverse events in the site's source documents had been entered into the study eCFR retrospectively. The unreported events from Dr. Hernandez-Morales' site are listed in Table 1.

Table 1: Adverse events at Study Site 225283 (FLAIR Study) not included in NDA submission (adapted from Sponsor's Response to Information Request 10/17/2019)

Subject Number	Treatment Assignment	AE Term	Start Date	End Date	AE Severity
(b) (6)	Induction Phase WD	Atopic Eczema	(b) (6)		Mild or Grade 1
	Induction Phase WD	Cold			Mild or Grade 1
	Induction Phase WD	Sinusitis			Mild or Grade 1
(b) (6)	ABC/DTG/3TC	Physical aggression			Mild or Grade 1
	ABC/DTG/3TC	Pediculosis Pubis			Mild or Grade 1

No additional significant deficiencies or inconsistencies between source records and submitted NDA data were identified at the site. No FDA Form 483 was issued at the end of the inspection.

2. Dr. Maria Del Mar Masia, Elche, Spain (Protocol 201584 (FLAIR) Site 225120 and Protocol 201585 (ATLAS) Site 225163)

The inspection of Dr. Masia's site was conducted from 7/29/2019 – 8/2/2019. At the time of the inspection, the FLAIR study was in long-term follow-up (closed to enrollment) and the ATLAS study was completed. The site screened 16 subjects and enrolled 11 subjects for the FLAIR study. For the ATLAS study, the site screened 6 subjects and enrolled 5 subjects.

The inspection included a review of documents for both studies related to the site's training program, Ethics Committee approval and correspondences, site monitoring, investigational product accountability, and financial disclosures.

A comprehensive review of the source document records for all enrolled subjects for both studies was performed. The data listings submitted in the NDA were verified by comparison with the source data at the site, including consent, entry criteria, primary endpoint data, and adverse events.

Adverse events were identified in the source records for both studies that were not included in the site data listings provided to the Agency by the Sponsor. The cause of the omission was that the adverse events were found in primary care electronic medical records and these records became available to the Sponsor and the investigator after the submission of the NDA. The inspector verified that the adverse events in the site's source documents had been entered into the study eCFR retrospectively. The unreported adverse events from Dr. Masia's site for the FLAIR study and for ATLAS study are listed in Tables 2 and 3, respectively.

Table 2: Adverse events at Study Site 225120 (FLAIR Study) not included in NDA submission (adapted from Sponsor's Response to Information Request 10/17/2019)

Subject Number	Treatment Assignment	AE Term	Start Date	End Date	AE Severity
(b) (6)	Cabotegravir and Rilpivirine	Foot pain	(b) (6)		Moderate or Grade 2
	Cabotegravir and Rilpivirine	Proctitis			Moderate or Grade 2
	Cabotegravir and Rilpivirine	bloody exudate			Mild or Grade 1

Table 3: Adverse events at Study Site 225163 (ATLAS Study) not included in NDA submission (adapted from Sponsor's Response to Information Request 10/17/2019)

Subject Number	Treatment Assignment	AE Term	Start Date	End Date	AE Severity
(b) (6)	Cabotegravir and Rilpivirine	Abdominal pain	(b) (6)		Mild or Grade 1

No additional significant deficiencies or inconsistencies between source records and submitted NDA data were identified at the site. No FDA Form 483 was issued at the end of the inspection.

3. Dr. Christopher Bettacchi, Dallas, Texas (Protocol 201584 (FLAIR) Site 222234 and Protocol 201585 (ATLAS) Site 222290)

The inspection of Dr. Bettacchi's site was conducted from 8/5/19 – 8/9/19. At the time of the inspection, the FLAIR study was in long-term follow-up (closed to enrollment) and the ATLAS study was completed. The site screened 24 subjects and enrolled 17 subjects for the FLAIR study. For the ATLAS study, the site enrolled 3 subjects.

The inspection included a review of documents related to the site's training program, IRB approval and correspondences, informed consent, site monitoring, investigational product accountability, protocols, and financial disclosures for both studies.

A comprehensive review of the source document records for all 17 subjects enrolled in FLAIR and all 3 subjects enrolled in ATLAS was performed. The data listings submitted in the NDA were verified by comparison with the source data at the site, including primary efficacy endpoint results, adverse events, protocol deviations, and concomitant medications.

No significant deficiencies were identified at the site and no significant inconsistencies between source records and submitted NDA data were identified. No FDA Form 483 was issued at the end of the inspection.

4. Dr. Franco Antonio Felizarta, Bakersfield, California (Protocol 201584 (FLAIR) Site 222193 and Protocol 201585 (ATLAS) Site 222276)

The inspection of Dr. Felizarta's site was conducted from 6/16/19 – 6/21/19. At the time of the inspection, the FLAIR study was in long-term follow-up (closed to enrollment) and the ATLAS study was completed. The site screened 19 subjects and enrolled 16 subjects for the FLAIR study. For the ATLAS study, the site screened 12 subjects and enrolled 6 subjects.

The inspection included a review of documents related to the site's training programs, IRB approval and correspondences, site monitoring, investigational product accountability, and financial disclosures for both trials. Informed consent documents were reviewed for all enrolled subjects in both trials.

A comprehensive review of the source document records was performed for 6 subjects in the FLAIR study and for 4 subjects in the ATLAS study, including the primary efficacy endpoint test result, adverse events, and eligibility criteria. The data listings submitted in the NDA were verified by comparison to the data in the source documents for the selected subjects.

No significant deficiencies were identified at the site and no significant inconsistencies between source records and submitted NDA data were identified. No FDA Form 483 was issued at the end of the inspection.

{See appended electronic signature page}

Karen Bleich, M.D.
Good Clinical Practice Assessment Branch

Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Aisha Johnson
OSI/DCCE/GCP Reviewer/Karen Bleich
OSI/ GCP Program Analysts/Yolanda Patague/Joseph Peacock
OSI/Database PM/Dana Walters

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

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

Memorandum

Date: October 23, 2019

To: Andrew Gentles, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use

NDA: 212888

In response to DAVP consult request dated May 3, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for CABENUVA (cabtegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use (Cabenuva). The proposed indication of use is as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable regimen with no history of treatment failure on any INSTI-or NNRTI-containing regimen and with no known or suspected resistance to either cabotegravir or rilpivirine.

PI/PPI and IFU: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DAVP (Andrew Gentles) on October 10, 2019, and the IFU received by electronic mail from DAVP (Andrew Gentles) on October 22, 2019. Comments on the PI are provided below. We have no comments on the IFU.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on October 23, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAVP (Andrew Gentles) on October 22 and 23, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov .

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

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

Memorandum

Date: October 23, 2019

To: Andrew Gentles, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for VOCABRIA (cabotegravir) tablets, for oral use

NDA: 212887

In response to DAVP consult request dated May 3, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for VOCABRIA (cabotegravir) tablets, for oral use (Vocabria). The proposed indication of use is in combination with EDURANT (rilpivirine) for short-term use in adults with HIV-1 infection who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) and who have no known or suspected resistance to either cabotegravir or rilpivirine for:

- Oral lead-in to assess the tolerability of cabotegravir prior to administration of long-acting CABENUVA (cabotegravir, rilpivirine) extended-release injectable suspensions.
- Oral therapy for patients who will miss planned injection dosing with CABENUVA extended-release injectable suspensions.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DAVP (Andrew Gentles) on October 10, 2019, and are provided below. A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on October 23, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAVP (Andrew Gentles) on October 22 & 23, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240)402-7721 or wendy.lubarsky@fda.hhs.gov.

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WENDY R LUBARSKY
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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 23, 2019
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)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Wendy Lubarsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension)
Dosage Form and Route:	Co-packaged, for intramuscular use
Application Type/Number:	NDA 212888
Applicant:	ViiV Healthcare Company c/o GlaxoSmithKline LLC

1 INTRODUCTION

On April 28, 2019, GlaxoSmithKline LLC on behalf of ViiV Healthcare Company, submitted for the Agency's review an original New Drug Application (NDA-212888) for CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) co-packaged, for intramuscular use, for the proposed indication of use as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable regimen with no history of treatment failure on any INSTI-or NNRTI-containing regimen and with no known or suspected resistance to either cabotegravir or rilpivirine.

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 May 3, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) co-packaged, for intramuscular use.

2 MATERIAL REVIEWED

- Draft CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) PPI received on April 29, 2019 and received by DMPP and OPDP on October 10, 2019.
- Draft CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) Prescribing Information (PI) received on April 29, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 10, 2019.
- Approved JULUCA (dolutegravir and rilpivirine) comparator labeling dated September 6, 2018.

3 REVIEW METHODS

In our collaborative review of the PPI:

- 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.

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LASHAWN M GRIFFITHS
10/23/2019 02:43:22 PM

DNP Consultation Memo for Division of Anti-Infective Products

NDA	212887, 212888
Drug:	cabotegravir/rilpivirine combination product
Proposed Indication:	HIV-1 infection, treatment and prevention
Consultation Requestor:	Yodit Belew, MD Division of Anti-Infective Products
Desired Completion:	09/20/2019
Date Review Completed	09/16/2019
Reviewer:	Emily R. Freilich, MD
Team Leader:	Philip Sheridan, MD Division of Neurology Products (DNP)

1. Background

The Division of Anti-Infective Products (DAIP) has requested a consultation for the drug cabetogravir (CAB) under NDAs 212887 and 212888. These NDAs are currently under review by DAIP for the treatment of human immunodeficiency virus-1 (HIV-1) infection, in both oral tablet (NDA 212887) and long-acting parenteral injection (212888) dosage forms. The long-acting form is a combination product with rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor (NNRTI) that has previously been approved as oral tablet. There have been a number of patients in development who have had a seizure, and therefore, DAIP has asked DNP to evaluate the association of CAB and seizures.

Alternative HIV treatments are often being developed to help improve patient adherence to treatment, and to prevent the emergence of resistance and transmission of the virus. It is felt that long-acting antiretroviral agents may improve patient compliance and may also allow for reaching underserved patient populations. It may also serve to improve the quality of life for patients with HIV. The parenteral route of administration would also hopefully reduce the gastrointestinal adverse events and eliminate dosing restrictions with regard to food and reduce drug-drug interactions.

The current submissions are for both the oral CAB tablets (proposed tradename VOCABRIA), which will be doses with RPV oral for oral bridging and oral lead-in regimens, and the CAB/RPV long-acting (LA) injection (proposed tradename CABENUVA), to be dosed once a month for maintenance therapy. The development program includes a total of 1590 patients dosed with CAB. This includes the two pivotal Phase 3 studies, two Phase 2 studies, and 509 patients dosed in Phase 1/clinical pharmacology studies. There are also approximately 500 patients enrolled in an ongoing Phase 3B study (ATLAS-2M).

Of note, long-acting CAB in also under development for prevention of HIV infection in at-risk individuals (pre-exposure prophylaxis, PrEP studies), which includes approximately 2600 patients included in the completed Phase 2 studies and the two ongoing Phase 3 studies.

1.1 Cabotegravir

CAB is an NME belonging to the INSTI class, an integrase strand transfer inhibitor. The oral tablet and the long acting injectable (in combination with RPV) are currently under review for the treatment of HIV infection in this submission. As noted above, CAB alone is also under development for prevention of HIV under IND 122744, with two ongoing Phase 3 trials, sponsored by NIH/NIAID/DAIDS.

Of note, the oral CAB has a terminal half-life of approximately 41 hours. The CAB LA has a longer half-life due to absorption rate-limited PK. It is noted that, from PopPK analysis, 47% of patients were predicted to have quantifiable plasma CAB concentrations 1 year after the last IM injection, and 17% were predicted to have quantifiable plasma CAB concentrations 96 weeks after the last injection. In the Phase 2b study outlined below, 4 out of 12 (33%) had quantifiable CAB concentrations at the 12-month follow-up visit.

1.2 Rilpivirine

RPV is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that has been approved in oral form since 2011 for the treatment of HIV infection. The long-acting injectable formulation is an investigational drug currently under review as a combination with CAB for the treatment of HIV infection.

Of note, due to drug-drug interactions that may significantly reduce the exposure of RPV and limit its effectiveness or lead to increased viral resistance, RPV is not to be taken with anti-seizure medications carbamazepine, oxcarbazepine, phenobarbital, and phenytoin, as well as other medications.

There is no mention of seizures as a listed adverse drug reaction in the current prescribing information and seizures were not previously identified as a safety signal in the previous development program of RPV.

1.3 Potential for Neurotoxicity and Class Effects

Both RPV and CAB are both known to penetrate the CSF. The NNRTI class of drugs, including RPV, and the INSTI class (CAB), are known to cause neuropsychiatric adverse events, including depressive disorders, anxiety, insomnia/sleep disorders, and headache. Neither RPV or CAB has a nonclinical signal for seizures.

There was no evidence of a safety signal for seizures in the prior RPV clinical development program. However, older NNRTIs in the same class, such as efavirenz (EFV) and etravirine (ETV) have been associated with convulsions in adult and pediatric patients, generally in the presence of a known medical history of seizures. Risk of convulsions is listed as a warning in the prescribing information for EFV and as an uncommon adverse drug reaction in the prescribing information for ETV.

Reviewer's comment: Of note, the pivotal studies that led to the approval for RPV used efavirenz (EFV) as the active comparator, so it may be important to note if there were any cases of convulsion in the RPV treatment arm that were missed because there was no difference between investigational drug and the active comparator.

In the INSTI class, dolutegravir (DTG) was recently found to be associated with neural tube defects, based on an observational epidemiologic study. *In vitro* data suggests that DTG may be a partial antagonist of the alpha folate 1 receptor, which may be the cause of the neural tube defects. Similar *in vitro* data suggests that CAB may also be a partial antagonist on the alpha folate 1 receptor.

Seizure is not a known or labeled adverse drug reaction for any other drugs in the INSTI class; (b) (4)

Given the nature of the treatment of HIV and need for multiple concomitant retroviral treatments, there are many other treatments used in the CAB development program, either as concomitant treatments or active comparators. There are also many similar drugs with similar mechanisms of action. The prescribing information for the active comparator treatments and other NNRTI and INSTI treatments were reviewed for this consult, including rilpivirine (RPV), dolutegravir (DTG), abacavir (ABC), lamivudine (3TC), efavirenaz (EFV), emtricitabine (FTC), tenofovir disoproxil fumerate (TDF), and etravirine (ETV).

Seizures or convulsions are described in the prescribing information as noted above for ETV and EFV, which are both NNRTIs. Seizures are also included in the prescribing information for the fixed dose combination of DTG with abacavir (ABC) and lamivudine (3TC), which lists seizures as an adverse reaction noted in postmarketing experience. Convulsions are also noted in the prescribing information for lamivudine (3TC) itself, which notes that convulsions were noted in a few neonates treated with 3TC. There are no described seizures in the labels of emtricitabine (FTC), tenofovir (TDF), or the fixed dose combination of the two drugs, which is used as the active comparator in the ongoing and still blinded PrEP trials.

(b) (4)

There were no seizures in the development program for the initial approval of oral DTG. Subsequently there were reports of seizures in the postmarketing experience for Triumeq, which is a fixed dose combination of dolutegravir (DTG), lamivudine (3TC), and abacavir (ABC). (b) (4)

Seizure is already listed in the post-marketing section of label for this fixed dose combination (DTG/3TC/ABC), as noted above.

2. Materials Reviewed

For the completion of this consult, I reviewed the consult request form and the table of cases provided by the applicant. For background material, I also reviewed the submitted Clinical Summary, Clinical Overview, and Summary of Clinical Safety, as well as the protocols for the Phase 3 studies for NDA 212887/212888.

I reviewed the submitted case narratives for the events of seizures, as well as the FAERs database for any additional cases of seizures. I also reviewed the submitted safety reports for IND 122744 for the prevention of HIV-infection (PrEP).

The prescribing information for all the comparator treatments and similar drugs in the NNRTI and INSTI class were also reviewed as noted above.

3. Review of Clinical Data

3.1 Clinical Studies Referenced in Review

- LAI116815 (Phase 1, BA study) – open-label, single-dose parallel study to evaluate the relative bioavailability of 2 new formulations (b) (4) . Given to healthy volunteers, with a 14-day lead in, followed by a single IM dose of 400 mg IM CAB of various particle size

- LAI116482 (LATTE, Phase 2b) – randomized, partially-blind, dose-ranging study with active control comparing oral CAB 10, 30, or 60 mg in combination with RPV and other NRTIs in HIV-infected patients

- 200056 (LATTE-2, Phase 2b) –randomized, parallel-group, open-label study with induction period of 20 weeks oral CAB followed by IM CAB/RPV maintenance every 4 or 8 weeks or oral CAB plus alternative NRTI medications

- 201584 (FLAIR, Phase 3)- multi-center, randomized, parallel-group, open-label, non-inferiority study with induction phase for 20 weeks of standard treatment (ABC/DTG/3TC) fixed dose combination followed by switch to oral CAB 30 mg/RPV 25 mg x 4 weeks then IM CAB LA/RPV LA 600/900 x 1 and 400/600 mg q4 weeks vs continued oral antiretroviral regimen

- 201585 (ATLAS, Phase 3) – multi-center, randomized, parallel-group, open-label, non-inferiority study with comparison of continued antiretroviral treatment to oral CAB 30 mg and RPV 25 mg x 4 weeks followed by IM CAB/RPV LQ every 4 weeks

- 207966 (ATLAS 2M, Phase 3b) – randomized, multicenter, parallel-group, non-inferiority, open-label study in HIV patients who are virologically suppressed with CAB/RPV LA 400/600 mg IM every 4 weeks compared to CAB/RPV LA 600/900 mg IM every 8 weeks

- 201103 (HPTN 077, Phase 2a) – multi-center, double-blind, 2-arm, randomized, placebo-controlled trial of the safety, tolerability and acceptability of CAB LA in HIV un-infected men and women at low to minimal risk for acquiring HIV infection, using daily oral CAB 30 mg or placebo x 4 weeks followed by 1 week wash out, and then CAB LA 800 mg IM injection every 12 weeks

- 201738 (HPTN 083, Phase 2b/3) – randomized, multicenter, double-blind, double-dummy, non-inferiority study in men at high risk for HIV acquisition with daily lead-in of oral CAB or oral TDF/FTC (300/200 mg fixed-dose combination) x 5 weeks, then CAB LA 600 mg IM q 4 weeks x 1, then q8 weeks vs continued daily oral TDF/FTC

- 201739 (HPTN 084, Phase 2b/3)- randomized, multicenter, double-blind, superiority study in African women at risk of HIV acquisition with an oral lead-in phase of oral CAB x 4 weeks vs daily TDF/FTC followed by CAB LA 600 mg IM q4 weeks x 1 then q8 weeks vs continued daily oral TDF/FTC

3.2 Seizure and seizure-like events

In the development program of CAB/RPV for treatment of HIV, there were reports of 6 patients who had seizures in the treatment arm and 2 seizures reported in the comparator treatment arm. The reported seizures with treatment are described in detail below in Table 1. Also, in the Phase 3 program, there was one seizure reported in a patient in the

comparator arm for Study 201585 that was not serious and did not lead to study drug discontinuation.

Table 1. Reported Events of Seizures in CAB Development Program

Study/ Subject ID	**Dose/exposure**	**Age**	**Time to Onset**	**Event Details**	**Risk Factors**
(b) (6) (FLAIR, Phase 3) Subj ID (b) (6)	ABC/3TC/DTG daily x 6 months (induction) CAB oral 30 mg and RPV oral 25 mg daily x 5 weeks Then CAB/RPV 600/900 injection x 1, then monthly 400/600 mg injections. Withdrew from study (b) (6) due to injection site reaction (last dose (b) (6))	59-year-old male	26 weeks and 2 days from first oral dose (2 months after last dose of CAB/RPV)	+ GTC at home and in ambulance, with subsequent confusion, nystagmus. + viral prodrome, found to have + flu A, treated with multiple antivirals/antibiotics, given pabrinex (thiamine, riboflavin, pyridoxine nicotinamide, ascorbic acid) for h/o ETOH consumption = diagnosis of influenza meningoencephalitis. 3 months later also diagnosed with b/l chronic subdural hematomas requiring evacuation.	+ influenza Meningoencephalitis + multiple concomitant medications that lower seizure threshold (oseltamivir, teicoplanin, acyclovir + chronic ETOH use + bilateral subdural hematomas
LAI (b) (6) (LATTE, Phase 2b)	30 mg CAB oral plus ABC/3TC for 24 weeks, then CAB 30 mg oral + RPV 25 mg oral	38-year-old male	191 weeks and 1 day	Virologically suppressed on CAB for 3.7 years. Partner witnessed possible seizure-like event of flailing in sleep with saliva from mouth/nose and difficult to arouse, no recollection the following day. + history of GHB and crystal meth use, and had used “morphine” on the day of the event.	Long latency period + illicit drug use (? Morphine) on day of event
LAI (b) (6) (Phase 1, BA single dose IM study)	30 mg CAB oral for 4 weeks followed by single dose 400 mg IM CAB	20-30-year-old male	42 weeks and 5 days	42.5 weeks after initial dose, had myoclonus followed by full GTC in the morning, after drinking large amounts of ETOH night.	h/o seizure (likely JME diagnosis) + alcohol night before *note: Patient had no detectable CAB levels in blood 6

				EEG c/w history of JME, had history of seizure activity at age 13.	months prior to event
(b) (6) (ATLAS 2M)	30 mg CAB and 25 mg RPV oral x 4 weeks followed by loading dose CAB/RPV LA 600/900 mg x 1, then monthly CAB/RPV LA 400 /600 mg injections	60-70-year old	23 weeks and 5 days	Four days prior to presentation reported headaches and visual symptoms, then collapsed at home with witnessed GTC. Given Dexamethasone and oral levetiracetam (LEV) in ER. MRI showed large R Fronto-temporal tumor, with mass effect, suggestive of glial tumor or metastatic lesion. Had surgery 3 days later.	+ new diagnosis brain tumor No prior neurologic symptoms
(b) (6) (ATLAS 2M) SID: (b) (6)	30 mg oral CAB and 25 mg RPV oral x 4 weeks, then CAB/RPV LA 600/900 mg x 1, then monthly 400/600 CAB/PRV LA, then q8 weeks CAB/RPV 600/900 mg	45-year-old male	74 weeks and 3 days (last dose (b) (6), pancreatitis (b) (6), seizure (b) (6))	Patient presented with severe abdominal pain and was diagnosed with acute severe pancreatitis. Was admitted to ICU on (b) (6) and experienced cardiopulmonary arrest on (b) (6) requiring CPR with continued impairment in consciousness. Imaging showed b/l cerebral infracts and PRES. EEG showed slow waves and low brain activity, CSF was normal. Developed multiple complications, then 2 months later, on (b) (6) had focal seizure for several minutes treated with levetiracetam (LEV) and diazepam. Another episode a few days later, continued LEV. At the time of seizure was on multiple	S/p cardiac arrest with bilateral strokes and PRES Concomitant medication at time of seizure included meropenem which lowers seizure threshold

				medications. Patient died.	
(b) (6) (LATTE-2, Phase 2b) SID (b) (6)	30 mg CAB plus ABC/3TC oral x 20 weeks 25 mg RPV oral added x 4 weeks, then IM CAB/RPV LA 800/600 mg x 1, then monthly CAB/RPV LA 400/600 mg	37-year-old male	49 weeks and 6 days	Developed acute-onset status epilepticus for presumed 6 hours w/o medical attention which resulted in anoxic brain injury and death. Found unresponsive and unconscious and seizing, MRI with diffuse cerebral edema, + papaverine on urine/serum spect and social history + for recreational drug use. + DNR and family withdrew care, but denied autopsy	+ papaverine in urine although initial tox screen negative (indicates heroin use) + long latency from initiation of investigational product + recreational drug use on social history

Reviewer's comment: The above 6 cases occurred during the clinical development of CAB and RPV for treatment of HIV. Most of the cases had confounding variables which are more likely to be the etiology of the seizures. However, there are at least two cases that occurred after a long time on CAB which had a simultaneous exposure to illicit drugs, but no other clear cause for the seizure activity. The possibility that exposure to CAB contributed to lowering the seizure threshold in otherwise high-risk patients cannot be excluded.
Furthermore, it should also be noted that patients who were at risk for seizures or had a known history of seizures were excluded from the Phase 3 studies. It is possible that there may have been more events had those patients not been excluded. These cases warrant a minimum of further surveillance, and potentially a mention in the labeling as a rare but possible adverse event.

(b) (4)

Table 2. Reports of Seizure in the CAB PrEP Development Program

(b) (4)

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(b) (4)

Reviewer's comment: The above 6 cases were reported to the IND for the use of CAB for the prevention of HIV in high-risk patients (PrEP). These cases have fewer confounding variables than those in the current NDA submission. However, many of these patients are still blinded. It would be helpful to know which treatment they were receiving, or if there is an uneven distribution between the treatment arms. If all of these patients, or the majority of them, were indeed receiving CAB, it would appear that the exposure to CAB may be a contributing factor in the cause of the seizure or to lowering the seizure threshold in patients already at risk for seizures. See conclusions below.

3.3 Other Reported Neurologic Adverse Events

Neuropsychiatric adverse events were considered an AE of special interest because they are common in this population, INSTI inhibitors have previously been associated with reports of mood disorders, suicidal ideation and sleep disorders, and RPV is associated with depression as an adverse drug reaction.

Overall, neuropsychiatric events occurred with low frequency, and were similar between the treatment groups in the Phase 3 clinical studies. There were no serious neuropsychiatric events reported, and 2 neuropsychiatric AEs led to withdrawal (1 patient with suicidal ideation, and 1 with anxiety). The incidence of sleep disorders, especially insomnia, were higher in the CAB/RPV treatment group compared to the comparator arm, and there was a higher incidence for mood disorders. The events of mood disorders did not include any SAEs or any AEs that led to study withdrawal. The incidence of anxiety and suicidal ideation were higher only in those patients with prior history of psychiatric illness.

4. Summary and Reviewer Conclusions

The crude incidence of acute symptomatic seizures or single, unprovoked seizures is estimated to be between 0.02-0.06% per year.[1] The incidence of seizures in patients with HIV is estimated to be significantly higher, approximately 6% per year[2]. However, this number comes from early studies of HIV prior to the development of antiretroviral therapy, when many patients had advanced disease or AIDs, and may have been having seizures because of invasion of the CNS by the virus, primary CNS opportunistic infections, or other seizure risk factors (i.e., polysubstance abuse, etc.). The incidence of seizures in the CAB development program would not be expected to have been quite so high, as the patients were all virologically suppressed on antiretroviral therapy at the time of enrollment, and those patients in the ongoing PrEP studies are HIV negative. Furthermore, because seizures were noted early in CAB development, patients who were considered high risk for seizures or had a history of seizures were excluded from the Phase 3 studies, which may have led to an underestimating of the incidence of such events.

The calculated crude incidence of seizures in the development program for this submission is 6 patients out of 2,090 patients enrolled in studies for the treatment of HIV, which is approximately (b) (4)%. If all 5 of the patients in the ongoing blinded PrEP studies did receive CAB, the incidence would be (b) (4)%. While not a high number, it is higher than the overall estimated annual incidence of single, unprovoked seizures, although potentially not higher than the incidence in patients with HIV.

I also reviewed the labels for other medications that have been shown to lower the seizure threshold, bupropion and meropenem. The prescribing information for bupropion describes an increased relative risk for seizures of 0.4% in the clinical studies, which

[1] Ssentongo P. Prevalence and Incidence of New-Onset Seizures and Epilepsy in Patients with Human Immunodeficiency Virus (HIV): Systematic Review and Meta-analysis. Epilepsy & Behavior 2019; 93:49-55.

[2] Kotsopoulous IAW, Van Merode T, Kessels FGH, de Krom MC, Knottnerus JA. Systematic Review and Meta-analysis of Incidence Studies of Epilepsy and Unprovoked Seizures. Epilepsia 2002: 43(11): 1402-1409.

clearly increased with higher dose. Meropenem had a 0.7% incidence of seizures in the overall clinical development program.

While many of the cases in the current clinical development program are not convincing for a causal relationship to the drug, there are a few cases that do not have an identifiable etiology for the seizures, and it cannot be ruled out that the exposure to CAB may have lowered the seizure threshold in these patients. Furthermore, if the patients outlined above in Table 2 are indeed in the CAB treatment arm, then that would confirm a safety signal for seizures. Without the blinded treatment arm information, it is difficult to draw a formal conclusion or make a determination regarding labeling.

As noted above, patients who were high risk for seizures were excluded from the Phase 3 studies, which may have led to a decreased incidence of such events. (b) (4) Taken together, it appears that there is a probable safety signal, pending more information about CAB exposure in the ongoing studies.

5. Consult Questions

DAIP has asked for DNP's assessment of the case reports related to seizures.

1. Do you believe CAB use may be associated with seizure events?

Reviewer's comment:

As noted above, it is hard to make a formal determination given the unknown exposure in the patients listed in Table 2. However, even if only a few of those patients were receiving CAB, it appears that here is likely an association with CAB and the lowering of the seizure threshold, particularly in patients that are already high-risk for seizures.

2. If so, please provide labeling recommendations.
3. If the cases do not support the above conclusion, do you have any additional recommendations beyond routine post-market pharmacovigilance?

Labeling recommendations:

At a minimum, I believe seizures should be listed as a rare but uncommon side effect occurring in (b) (4)% of patients in clinical development. If the majority of the PrEP cases are found to be in the CAB treatment arm, or there is a very uneven distribution of cases, then a warning similar to that in efavirenz would be warranted. Potential language would be:

(b) (4)

(b) (4)

Emily R. Freilich, MD
Clinical Reviewer

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/s/

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