CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	212887 and 212888
PDUFA Goal Date	January 28, 2021
OSE RCM #	2019-909, 2019-911, 2019-913, 2019-1650
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	January 8, 2021
Subject	Evaluation of Need for a REMS
Established Name	cabotegravir and cabotegravir and rilpivirine
Trade Name	Vocabria and Cabenuva
Name of Applicant	ViiV Healthcare Company
Therapeutic Class	integrase strand transfer inhibitor, non-nucleoside reverse transcriptase inhibitor
Formulation(s)	cabotegravir 30 mg tablet (NDA 212887) cabotegravir 200 mg/mL extended-release injectable suspension and rilpivirine 300 mg/mL extended-release injectable suspension, co-packaged (NDA 212888)
Dosing Regimen	Oral lead-in dosing: cabotegravir 30 mg orally once daily with rilpivirine 25 mg orally once daily for approximately 1 month (at least 28 days) IM initiation injections dosing: cabotegravir 600 mg IM single injection and rilpivirine 900 mg IM single injection on the last day of oral lead-in dosing (at month 2). IM continuation injections dosing: cabotegravir 400 mg IM single injection and rilpivirine 600 mg IM single injection once monthly (month 3 onwards)

This is an addendum to the review by the Division of Risk Management (DRM) submitted in DARRTS on December 17, 2019 that evaluated whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Vocabria (cabotegravir) and Cabenuva (cabotegravir and rilpivirine) was necessary to ensure the benefits outweigh its risks.[a] ViiV Healthcare Company submitted a New Drug Application (NDA) 212887 for cabotegravir with the proposed indication 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 Cabenuva extended-release injectable suspensions and oral therapy for patients who will miss planned injection dosing with Cabenuva. ViiV Healthcare Company also submitted a NDA 212888 for cabotegravir and rilpivirine with the proposed indication 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 antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. This application is under review in the Division of Antivirals (DAV). The applicant did not submit a proposed REMS with this application but submitted a risk management plan.

Vocabria (cabotegravir) is an integrase strand transfer inhibitor (INSTI). The proposed dosing regimen is cabotegravir 30 mg orally once daily with rilpivirine 25 mg orally once daily for approximately 1 month (at least 28 days). Cabenuva (cabotegravir and rilpivirine) is a combination of an INSTI and non-nucleoside reverse transcriptase inhibitor (NNRTI). Cabenuva must be administered by a healthcare professional. The proposed dosing regimen for intramuscular (IM) initiation injections is cabotegravir 600 mg IM single injection and rilpivirine 900 mg IM single injection on the last day of oral lead-in dosing (at month 2) and for IM continuation injections is cabotegravir 400 mg IM single injection and rilpivirine 600 mg IM single injection once monthly (month 3 onwards).

The original NDA 212887 and NDA 212888 was submitted on 04/29/2019. The agency issued a complete response letter on 12/19/2019 due to product quality/facility inspections deficiencies. The Drug Master File for rilpivirine was also found inadequate to support this application. The sponsor resubmitted the NDA application on 7/28/2020. The sponsor addressed the deficiencies that were identified in the complete response letter issued on 12/19/2019. There were no new safety issues that arose with this resubmission.[b] The clinical review team recommends approval based on the corrective action on the Office of Pharmaceutical Quality (OPQ) issues, as well the efficacy and safety results analyzed in the original NDA 212887 and NDA 212888 submission on 4/29/2019.

[a] Moriyama, B. Division of Risk Management NME review for cabotegravir and cabotegravir and rilpivirine, December 18, 2019.

[b] Cabotegravir and cabotegravir and rilpivirine draft integrated review. Accessed December 23, 2020.

The DRM and the DAV agree that a REMS is not necessary to ensure the benefits of cabotegravir and cabotegravir and rilpivirine outweigh its risks. The efficacy of cabotegravir and rilpivirine for the treatment of HIV-1 infection was supported by the FLAIR and ATLAS clinical trials that indicated that cabotegravir and rilpivirine was noninferior to current three drug antiretroviral regimen for the treatment of patients with HIV-1 infection who were virologically suppressed. The serious risks associated with cabotegravir and rilpivirine including hypersensitivity reactions, post-injection reactions, hepatotoxicity, depressive disorders, risk of adverse reactions or loss of virological response due to drug interactions; these risks as well as long-acting properties and potential associated risks with Cabenuva will be addressed in the warnings and precautions section of the label. The likely prescribers will be internal medicine practitioners and infectious diseases specialists who should have experience prescribing antiretroviral drugs for the treatment of HIV-1 infection.

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
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Application Type	NDA
Application Number	212887 and 212888
PDUFA Goal Date	December 29, 2019
OSE RCM #	2019-909, 2019-911, 2019-913, 2019-1650
Reviewer Name(s)	Brad Moriyama, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	December 17, 2019
Subject	Evaluation of Need for a REMS
Established Name	cabotegravir and cabotegravir and rilpivirine
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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Vocabria (cabotegravir) and Cabenuva (cabotegravir and rilpivirine) is necessary to ensure the benefits outweigh its risks. ViiV Healthcare Company submitted a New Drug Application (NDA) 212887 for cabotegravir with the proposed indication 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 Cabenuva extended-release injectable suspensions and oral therapy for patients who will miss planned injection dosing with Cabenuva. ViiV Healthcare Company also submitted a New Drug Application (NDA) 212888 for cabotegravir and rilpivirine with the proposed indication 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 antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. The serious risks associated with cabotegravir and rilpivirine include hypersensitivity reactions, post-injection reactions, hepatotoxicity, depressive disorders, risk of adverse reactions or loss of virological response due to drug interactions, and long-acting properties and potential associated risks with Cabenuva. The applicant did not submit a proposed REMS but submitted a risk management plan with this application.

The recommended regulatory action at this time per the clinical review team is a complete response. This recommendation is based on Office of Pharmaceutical Quality (OPQ) issues of deficiencies observed at the manufacturing facility of NDA 212888, including (b) (4) in the cabotegravir drug product. The Drug Master File for rilpivirine was also found inadequate to support this application. Because of the OPQ issues and that the applicant (b) (4) DRM is unable to formulate recommendations for risk management, specifically the need for a REMS at this time.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Vocabria (cabotegravir) and Cabenuva (cabotegravir and rilpivirine) is necessary to ensure the benefits outweigh its risks. ViiV Healthcare Company submitted NDA 212887 for cabotegravir with the proposed indication 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 Cabenuva extended-release injectable suspensions and oral therapy for patients who will miss planned injection dosing with Cabenuva.[1] ViiV Healthcare

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

Company also submitted a NDA 212888 for cabotegravir and rilpivirine with the proposed indication 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 antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.[2] This application is under review in the Division of Antiviral Products (DAVP). The applicant did not submit a proposed REMS with this application but submitted a risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Vocabria (cabotegravir), a NME, is an integrase strand transfer inhibitor (INSTI), proposed in combination with Edurant (rilpivirine) 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 oral lead-in to assess the tolerability of cabotegravir prior to administration of Cabenuva extended-release injectable suspensions and oral therapy for patients who will miss planned injection dosing with Cabenuva. Cabotegravir is supplied as a 30 mg tablet. The proposed dosing regimen is cabotegravir 30 mg orally once daily with rilpivirine 25 mg orally once daily for approximately 1 month (at least 28 days).[b]

Cabenuva (cabotegravir and rilpivirine), a NME, is a combination of an INSTI and non-nucleoside reverse transcriptase inhibitor (NNRTI), proposed 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 antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. Cabotegravir is a NME and rilpivirine (Edurant) is a 505(b)(2) submission.[3] Cabenuva is supplied as cabotegravir 200 mg/mL extended-release injectable suspension and rilpivirine 300 mg/mL extended-release injectable suspension, co-packaged. Cabenuva must be administered by a healthcare professional. The proposed dosing regimen for intramuscular (IM) initiation injections is cabotegravir 600 mg IM single injection and rilpivirine 900 mg IM single injection on the last day of oral lead-in dosing (at month 2) and for IM continuation injections is cabotegravir 400 mg IM single injection and rilpivirine 600 mg IM single injection once monthly (month 3 onwards).[b] Cabotegravir and cabotegravir and rilpivirine will primarily be used in both inpatient and outpatient settings. The likely prescribers will be internal medicine practitioners and infectious diseases specialists. Cabotegravir and cabotegravir and rilpivirine are not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

The following is a summary of the regulatory history for cabotegravir NDA 212887 and cabotegravir and rilpivirine NDA 212888 relevant to this review:

- 04/29/2019: NDA 212887 submission in combination with Edurant (rilpivirine) 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 oral lead-in to assess the tolerability of cabotegravir prior to administration of Cabenuva extended-release injectable suspensions and oral therapy for patients who will miss planned injection dosing with Cabenuva received.

  NDA 212888 submission 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 antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine received.

- 08/06/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for cabotegravir and cabotegravir and rilpivirine.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

The case definition of HIV infection, as defined by the CDC in 2014, includes laboratory evidence, by multitest algorithms or stand-alone virologic tests, or clinical evidence.[4] Acquired immunodeficiency syndrome (AIDS) is defined by HIV infection with a $CD4^+$ cell count < 200 cells/millimeter^3, and/or the presence of an AIDS-defining clinical condition.[5] The estimated number of people ≥ 13 years of age with HIV infection in the United States at the end of 2016 was 1,140,400.[6,c] In addition, the number of people diagnosed with HIV infection in the United States in 2017 was 38,281.[7] Although HIV infection is currently not curable, patients that are appropriately treated for HIV infection may live a near normal lifespan.[8,9] The number of deaths in people with HIV infection in the United States and 6 dependent areas in 2016 was 15,807.[7,d]

3.2 Description of Current Treatment Options

The Department of Health and Human Services guideline for the Use of Antiretroviral Agents in Adults and Adolescent with HIV recommend antiretroviral therapy in all patients with HIV infection.[9]

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[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Treatment with antiretroviral drugs decreases the morbidity and mortality associated with HIV infection. Since 1987, a large number of antiretroviral drugs have been approved by the FDA for the treatment of HIV infection, with over 30 drugs in 7 mechanistic classes. The Department of Health and Human Services guidelines recommend an initial regimen for most people with HIV of an INSTI plus 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). These regimens include bictegravir/tenofovir alafenamide/emtricitabine, dolutegravir/abacavir/lamivudine, dolutegravir plus tenofovir/emtricitabine, and raltegravir plus tenofovir/emtricitabine.

Four integrase strand transfer inhibitors including raltegravir, dolutegravir, elvitegravir, and bictegravir have been approved by the FDA for the treatment of HIV-1 infection.[10,11,12,13,14] The antiretroviral drugs raltegravir and dolutegravir do not have a boxed warning in their respective labels or have required a REMS for approval. Bictegravir is approved in a combination tablet with emtricitabine and tenofovir alafenamide (Biktarvy). Elvitegravir is approved in a combination tablet with cobicistat, emtricitabine, and tenofovir alafenamide (Genvoya) and in a combination tablet with cobicistat, emtricitabine, and tenofovir disoproxil fumarate (Stribild). Biktarvy, Genvoya, and Stribild have a boxed warning for post treatment acute exacerbation of hepatitis B which may be occur with discontinuation of emtricitabine and/or tenofovir in patients coinfected with HIV-1 and chronic hepatitis B virus.

4 Benefit: Risk Assessment[e]

The efficacy and safety of cabotegravir and rilpivirine for the treatment of HIV-1 infection was demonstrated in two Phase 3 studies (NCT 02938520, NCT 02951052).[2,15] The two studies were similar in design: multicenter, randomized, open-label, parallel-arm, noninferiority, and active-controlled. Both studies had the same primary efficacy endpoint of the proportion of subjects with plasma HIV-1 RNA ≥ 50 copies/mL at week 48. Patients who were randomized to cabotegravir and rilpivirine received oral lead-in dosing of cabotegravir 30 mg orally once daily and rilpivirine 25 mg orally once daily for at least 4 weeks followed by cabotegravir IM injection and rilpivirine IM injection every 4 weeks for an additional 44 weeks.

In study NCT 02938520 (trial 201584, FLAIR), patients that were HIV-1 infected and antiretroviral treatment naive received a dolutegravir INSTI containing regimen for 20 weeks. Patients that were virologically suppressed (HIV-1 RNA < 50 copies/mL) (N=566) were randomized to cabotegravir and rilpivirine (N=283) or their current antiretroviral regimen (N=283). The success rate for the primary efficacy endpoint was 2.1% in the cabotegravir and rilpivirine group and 2.5% in the current antiretroviral regimen group (difference, -0.4%; 95% confidence interval -2.8% to 2.1%). In study NCT 02951052 (trial 201585, ATLAS), patients that were HIV-1 infected, antiretroviral treatment experienced, and virologically-suppressed (HIV-1 RNA < 50 copies/mL) (N=616) for at least 6 months were randomized to cabotegravir and rilpivirine (N=308) or their current antiretroviral regimen (N=308). The success rate

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

for the primary efficacy endpoint was 1.6% in the cabotegravir and rilpivirine group and 1% in the current antiretroviral regimen group (difference, 0.7%; 95% confidence interval -1.2% to 2.5%). The FDA clinical reviewer concluded that the two trials indicated that cabotegravir and rilpivirine was noninferior to current three drug antiretroviral regimen for the treatment of patients with HIV-1 infection who were virologically suppressed.[f]

The safety of cabotegravir and rilpivirine was evaluated in two Phase 3 clinical trials for the treatment of HIV-1 infection (NCT 02938520, NCT 02951052).[2,15] In the combined safety population from NCT 02938520 (FLAIR) and NCT 02951052 (ATLAS), 591 patients received cabotegravir and rilpivirine and 591 patients remained on their current antiretroviral regimen. Discontinuation from treatment due to an adverse event occurred in 4% in the cabotegravir and rilpivirine group and 2% in the current antiretroviral regimen group. Common adverse reactions reported with cabotegravir and rilpivirine included injection site reactions, pyrexia, fatigue, headache, musculoskeletal pain, nausea, sleep disorders, dizziness, and rash.

The serious risk[g] associated with cabotegravir and rilpivirine include hypersensitivity reactions, post-injection reactions, hepatotoxicity, depressive disorders, risk of adverse reactions or loss of virological response due to drug interactions, and long-acting properties and potential associated risks with Cabenuva. Post-injection reactions including dyspnea, agitation, abdominal cramps, flushing, sweating, oral numbness, and changes in blood pressure have been reported with rilpivirine injection. These reactions may have been due to inadvertent intravenous administration. In addition, hepatotoxicity has been reported with cabotegravir or rilpivirine. An adverse event of increased alanine aminotransferase (Grade 3 to 4) occurred in 2% of the cabotegravir and rilpivirine group and < 1% of the current antiretroviral regimen group. An adverse event of increased aspartate aminotransferase (Grade 3 to 4) occurred in 2% of the cabotegravir and rilpivirine group and < 1% of the current antiretroviral regimen group. The FDA clinical reviewer did not identify any cases of drug induced liver injury in the Phase 3 clinical trials.[15] Furthermore, depressive disorders including depressed mood, depression, major depression, mood altered, mood swings, dysphoria, negative thoughts, suicidal ideation or attempt have occurred in patients receiving cabotegravir and rilpivirine or the individual drug products.

Selection of appropriate patients to be treated with cabotegravir and rilpivirine is important as non-adherence to monthly injections or missed doses may lead to the loss of virologic response and the

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[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

development of resistance. The proposed label contains recommendations for planned missed injections and unplanned missed injections. In addition, an alternative, fully suppressive antiretroviral regimen should be started no later than 1 month after the final dose of cabotegravir and rilpivirine injection to minimize the risk of developing viral resistance.

The clinical reviewer of this application has determined that the benefit/risk assessment favors approval. (b) (4) .[16] However, late in the review cycle OPQ issues of deficiencies observed at the manufacturing facility of NDA 212888, including (b) (4) in the cabotegravir drug product were identified.[15] The Drug Master File for rilpivirine was also found inadequate to support this application. A complete response will be issued due to these product quality review issues.

5 Conclusion & Recommendations

DAVP recommends a complete response on the basis of OPQ issues of deficiencies observed at the manufacturing facility of NDA 212888, including (b) (4) in the cabotegravir drug product. The Drug Master File for rilpivirine was also found inadequate to support this application. (b) (4) Based on the currently available data, there were no safety issues that require a REMS for cabotegravir and cabotegravir and rilpivirine; however due to the complete response, DRM is deferring final comments on the need for a REMS at this time.

6 Appendices

6.1 REFERENCES

[1] Proposed prescribing information for cabotegravir as currently edited by FDA, Accessed December 6, 2019.

[2] Proposed prescribing information for cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension as currently edited by FDA, Accessed December 6, 2019.

[3] Edurant (rilpivirine) package insert. Titusville, NJ: Janssen Therapeutics, Division of Janssen Products, LP; 2019 May.

[4] Centers for Disease Control and Prevention (CDC). Revised surveillance case definition for HIV infection--United States, 2014. MMWR Recomm Rep 2014;63(RR-03):1-10.

[5] Refer to Guidance for Industry Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment for more information (https://www.fda.gov/media/86284/download)

[6] Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2010–2016. HIV Surveillance Supplemental Report 2019;24(No. 1).

[7] Centers for Disease Control and Prevention. HIV Surveillance Report, 2017; vol. 29.

[8] Fauci AS, Redfield RR, Sigounas G, Weahkee MD, Giroir BP. Ending the HIV Epidemic: A Plan for the United States. JAMA. 2019;321(9):844-845.

[9] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at https://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Last accessed November 9, 2019.

[10] Isentress (raltegravir) package insert. Whitehouse Station, NJ: Merck Sharp and Dohme Corp., a subsidiary of Merck and Co., Inc.; 2018 March.

[11] Tivicay (dolutegravir) package insert. Research Triangle Park, NC: ViiV Healthcare; 2019 October.

[12] Biktarvy (bictegravir, emtricitabine, and tenofovir alafenamide) package insert. Foster City, CA: Gilead Sciences, Inc.; 2019 August.

[13] Genvoya (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) package insert. Foster City, CA: Gilead Sciences, Inc.; 2019 February.

[14] Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) package insert. Foster City, CA: Gilead Sciences, Inc.; 2019 January.

[15] Cabotegravir and cabotegravir and rilpivirine integrated review. Accessed December 12, 2019.

[16] Division of Antiviral Products (DAVP). Cabotegravir and rilpivirine IND 109678 internal meeting. December 2, 2019.

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