

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CABENUVA safely and effectively. See full prescribing information for CABENUVA.

CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use

Initial U.S. Approval: 2021

RECENT MAJOR CHANGES

Dosage and Administration, Administration Instructions for Injections (2.9) 12/2023

INDICATIONS AND USAGE

CABENUVA, a 2-drug co-packaged product of cabotegravir, an HIV-1 integrase strand transfer inhibitor (INSTI), and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents 12 years of age and older and weighing at least 35 kg to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA <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. (1)

DOSAGE AND ADMINISTRATION

- Refer to full prescribing information for detailed information on dosage and administration recommendations. (2)
- Prior to initiating treatment with CABENUVA, oral lead-in dosing may be considered to assess the tolerability of cabotegravir and rilpivirine with the recommended dosage used for approximately 1 month. (2.3)
- For gluteal intramuscular injection only. (2.4, 2.5, 2.9)
- Recommended Monthly Dosing Schedule: Initiate injections of CABENUVA (600 mg of cabotegravir and 900 mg of rilpivirine) on the last day of current antiretroviral therapy or oral lead-in and continue with injections of CABENUVA (400 mg of cabotegravir and 600 mg of rilpivirine) every month thereafter. (2.4)
- Recommended Every-2-Month Dosing Schedule: Initiate injections of CABENUVA (600 mg of cabotegravir and 900 mg of rilpivirine) on the last day of current antiretroviral therapy or oral lead-in for 2 consecutive months and continue with injections of CABENUVA every 2 months thereafter. (2.5)

DOSAGE FORMS AND STRENGTHS

Injection:

- Kit of single-dose vials of 400 mg/2 mL (200 mg/mL) of cabotegravir extended-release injectable suspension and 600 mg/2 mL (300 mg/mL) of rilpivirine extended-release injectable suspension. (3)
- Kit of single-dose vials of 600 mg/3 mL (200 mg/mL) of cabotegravir extended-release injectable suspension and 900 mg/3 mL (300 mg/mL) of rilpivirine extended-release injectable suspension. (3)

CONTRAINDICATIONS

- Previous hypersensitivity reaction to cabotegravir or rilpivirine. (4)

- Coadministration with drugs where significant decreases in cabotegravir and/or rilpivirine plasma concentrations may occur, which may result in loss of virologic response. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions have been reported with rilpivirine-containing regimens and in association with integrase inhibitors. Discontinue CABENUVA immediately if signs or symptoms of hypersensitivity reactions develop. (5.1)
- Serious post-injection reactions with rilpivirine were reported. Monitor and treat as clinically indicated. (5.2)
- Hepatotoxicity has been reported in patients receiving cabotegravir or rilpivirine. Monitoring of liver chemistries is recommended. Discontinue CABENUVA if hepatotoxicity is suspected. (5.3)
- Depressive disorders have been reported with CABENUVA. Prompt evaluation is recommended for depressive symptoms. (5.4)
- Residual concentrations of cabotegravir and rilpivirine may remain in the systemic circulation of patients up to 12 months or longer. It is essential to initiate an alternative, fully suppressive antiretroviral regimen no later than 1 month after the final injections of CABENUVA when dosed monthly and no later than 2 months after the final injections when dosed every 2 months. If virologic failure is suspected, prescribe an alternative regimen as soon as possible. (5.6)

ADVERSE REACTIONS

The most common adverse reactions (Grades 1 to 4) observed in ≥2% of subjects receiving CABENUVA were injection site reactions, pyrexia, fatigue, headache, musculoskeletal pain, nausea, sleep disorders, dizziness, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Refer to the full prescribing information for important drug interactions with CABENUVA. (4, 5.5, 7)
- Because CABENUVA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. (7.1)
- Drugs that induce uridine diphosphate glucuronosyltransferase (UGT)1A1 or cytochrome P450 (CYP)3A4 may decrease the plasma concentrations of the components of CABENUVA. (4, 7.3, 7.4)
- CABENUVA should be used with caution in combination with drugs with a known risk of Torsade de Pointes. (7.3, 7.4)

USE IN SPECIFIC POPULATIONS

- Pregnancy: After oral use of rilpivirine, exposures were generally lower during pregnancy compared with the postpartum period. (8.1)

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

Revised: 12/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CABENUVA is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents 12 years of age and older and weighing at least 35 kg to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA <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 *[see Microbiology (12.4), Clinical Studies (14.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration Overview

- CABENUVA contains cabotegravir extended-release injectable suspension in a single-dose vial and rilpivirine extended-release injectable suspension in a single-dose vial *[see Dosage Forms and Strengths (3)]*.
- CABENUVA must be administered by a healthcare provider by gluteal intramuscular injection *[see Dosage and Administration (2.9)]*.
- CABENUVA may be initiated with oral cabotegravir and oral rilpivirine prior to the intramuscular injections or the patient may proceed directly to injection of CABENUVA without an oral lead-in *[see Dosage and Administration (2.3)]*.
- CABENUVA can be injected monthly or every 2 months *[see Dosage and Administration (2.4, 2.5)]*. Healthcare providers should discuss these 2 dosing options with the patient prior to starting CABENUVA and decide which injection dosing frequency would be the most appropriate option for the patient *[see Adverse Reactions (6.1), Microbiology (12.4), Clinical Studies (14.1)]*.

2.2 Adherence to CABENUVA

Prior to starting CABENUVA, healthcare providers should carefully select patients who agree to the required monthly or every-2-month injection dosing schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance with missed doses *[see Dosage and Administration (2.1), Warnings and Precautions (5.6), Microbiology (12.4)]*.

2.3 Optional Oral Lead-In Dosing to Assess Tolerability of CABENUVA in Adults and Adolescents 12 Years of Age and Older and Weighing at Least 35 kg

The healthcare provider and patient may decide to use an oral lead-in with oral cabotegravir and oral rilpivirine prior to the initiation of CABENUVA to assess the tolerability of cabotegravir and rilpivirine, or the healthcare provider and patient may proceed directly to injection of CABENUVA without the use of an oral lead-in.

If oral lead-in is used, the recommended oral lead-in daily dose is one 30-mg tablet of VOCABRIA (cabotegravir) and one 25-mg tablet of EDURANT (rilpivirine) taken with a meal for approximately 1 month (at least 28 days), followed by intramuscular initiation injections of CABENUVA. See Tables 1 and 2 for recommended oral lead-in and monthly or every-2-month intramuscular injection dosing schedule for CABENUVA [*see Dosage and Administration (2.4, 2.5)*].

2.4 Recommended Monthly Gluteal Intramuscular Injection Dosing with CABENUVA in Adults and Adolescents 12 Years of Age and Older and Weighing at Least 35 kg

Initiation Injections (CABENUVA 600-mg/900-mg Kit)

Initiate injections on the last day of current antiretroviral therapy or oral lead-in, if used [*see Dosage and Administration (2.3)*]. The recommended initiation injection doses of CABENUVA are a single 600-mg (3-mL) intramuscular injection of cabotegravir and a single 900-mg (3-mL) intramuscular injection of rilpivirine. Administer cabotegravir and rilpivirine at separate gluteal injection sites (on opposite sides or at least 2 cm apart) during the same visit [*see Dosage and Administration (2.9)*]. 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 are a single 400-mg (2-mL) intramuscular injection of cabotegravir and a single 600-mg (2-mL) intramuscular injection of rilpivirine at each visit (Table 1). Administer cabotegravir and rilpivirine at separate gluteal injection sites (on opposite sides or at least 2 cm apart) during the same visit [*see Dosage and Administration (2.9)*]. 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 Dosing Schedule with Optional Oral Lead-In or Direct to Injection for Monthly Injection

Drug	Optional Oral Lead-In^a (at Least 28 Days)	Intramuscular (Gluteal) Initiation Injections (One-Time Dosing)	Intramuscular (Gluteal) Continuation Injections (Once-Monthly Dosing)
	Month (at Least 28 Days) Prior to Starting Injections	Initiate Injections at Month 1^b	One Month after Initiation Injection and Monthly 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)

^a The optional oral therapy should be continued until the day the first injection is administered.

^b Given on the last day of current antiretroviral therapy or oral lead-in if used.

2.5 Recommended Every-2-Month Gluteal Intramuscular Injection Dosing with CABENUVA in Adults and Adolescents 12 Years of Age and Older and Weighing at Least 35 kg

Initiation Injections (CABENUVA 600-mg/900-mg Kit)

Initiate injections on the last day of current antiretroviral therapy or oral lead-in, if used [*see Dosage and Administration (2.3)*]. The recommended initiation injection doses of CABENUVA are a single 600-mg (3-mL) intramuscular injection of cabotegravir and a single 900-mg (3-mL) intramuscular injection of rilpivirine 1 month apart for 2 consecutive months (Table 2).

Administer cabotegravir and rilpivirine at separate gluteal injection sites (on opposite sides or at least 2 cm apart) during the same visit [*see Dosage and Administration (2.9)*]. Patients may be given CABENUVA up to 7 days before or after the date the patient is scheduled to receive the second initiation injections.

Continuation Injections (CABENUVA 600-mg/900-mg Kit)

After the 2 initiation doses given consecutively 1 month apart (Months 1 and 2), the recommended continuation injection doses (Month 4 onwards) of CABENUVA are a single 600-mg (3-mL) intramuscular injection of cabotegravir and a single 900-mg (3-mL) intramuscular injection of rilpivirine administered every 2 months (Table 2). Administer cabotegravir and rilpivirine at separate gluteal injection sites (on opposite sides or at least 2 cm apart) during the same visit [*see Dosage and Administration (2.9)*]. Patients may be given CABENUVA up to 7 days before or after the date the patient is scheduled to receive the injections.

Table 2. Recommended Dosing Schedule with Optional Oral Lead-In or Direct to Injection for Every-2-Month Injection

Drug	Optional Oral Lead-In^a (at Least 28 Days)	Intramuscular (Gluteal) Injections^b
	Month (at Least 28 Days) Prior to Starting Injections	Initiate Injections^c at Month 1, Month 2, and then Every 2 Months Onwards (Starting at Month 4)
Cabotegravir	30 mg once daily with a meal	600 mg (3 mL)
Rilpivirine	25 mg once daily with a meal	900 mg (3 mL)

^a The optional oral therapy should be continued until the day the first injection is administered.

^b For the every-2-month injection dosing schedule in adults, Initiation Injections are injections administered at Month 1 and Month 2 and Continuation Injections are injections administered every 2 months onwards (starting Month 4).

^c Given on the last day of current antiretroviral therapy or oral lead-in if used.

2.6 Dosing Recommendations When Switching from Monthly to Every-2-Month Intramuscular Injections

Patients switching from a monthly continuation injection schedule (a single 400-mg [2-mL] gluteal intramuscular injection of cabotegravir and a single 600-mg [2-mL] intramuscular injection of rilpivirine) to an every-2-month continuation injection dosing schedule should receive a single 600-mg (3-mL) intramuscular injection of cabotegravir and a single 900-mg (3-mL) intramuscular injection of rilpivirine administered 1 month after the last monthly continuation injections and then every 2 months thereafter. Cabotegravir and rilpivirine injections should be administered at separate gluteal injection sites (on opposite sides or at least 2 cm apart) during the same visit [*see Dosage and Administration (2.9)*].

2.7 Dosing Recommendations When Switching from Every-2-Month to Monthly Intramuscular Injections

Patients switching from an every-2-month continuation injection schedule (a single 600-mg [3-mL] intramuscular injection of cabotegravir and a single 900-mg [3-mL] intramuscular injection of rilpivirine) to a monthly continuation dosing schedule should receive a single 400-mg (2-mL) intramuscular injection of cabotegravir and a single 600-mg (2-mL) intramuscular injection of rilpivirine 2 months after the last every-2-month continuation injection and then monthly thereafter. Cabotegravir and rilpivirine injections should be administered at separate gluteal injection sites (on opposite sides or at least 2 cm apart) during the same visit [*see Dosage and Administration (2.9)*].

2.8 Recommended Dosing Schedule for Missed Injections

Adherence to the injection dosing schedule is strongly recommended [see *Dosage and Administration* (2.2)]. Patients who miss a scheduled injection visit should be clinically reassessed to ensure resumption of therapy remains appropriate. Refer to Table 3 for dosing recommendations after missed injections.

Planned Missed Injections for Patients on the Monthly Dosing Schedule

If a patient plans to miss a scheduled injection visit by more than 7 days, VOCABRIA in combination with EDURANT once daily may be used for up to 2 months to replace missed injection visits, or any other fully suppressive oral antiretroviral regimen may be used until injections are resumed. 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 1 month (+/-7 days) after the last injection dose of CABENUVA and continued until the day injection dosing is restarted. Refer to Table 3 for injection dosing recommendations. For oral therapy with VOCABRIA and EDURANT of durations greater than 2 months, an alternative oral regimen is recommended.

Unplanned Missed Injections for Patients on the Monthly Dosing Schedule

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 [see *Warnings and Precautions* (5.6)]. If injection dosing will be continued, see Table 3 for dosing recommendations.

Table 3. Injection Dosing Recommendations after Missed Injections for Patients on the Monthly Dosing Schedule^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 gluteal 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 gluteal intramuscular injections then continue to follow the 400-mg (2-mL) cabotegravir and 600-mg (2-mL) rilpivirine gluteal intramuscular monthly injection dosing schedule.

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

Planned Missed Injections for Patients on the Every-2-Month Dosing Schedule

If a patient plans to miss a scheduled injection visit by more than 7 days, VOCABRIA in combination with EDURANT once daily may be used for up to 2 months to replace 1 missed

injection visit, or any other fully suppressive oral antiretroviral regimen may be used until injections are resumed. 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 2 months after the last injection dose of CABENUVA and continued until the day injection dosing is restarted. Refer to Table 4 for injection dosing recommendations. For oral therapy with VOCABRIA and EDURANT of durations greater than 2 months, an alternative oral regimen is recommended.

Unplanned Missed Injections for Patients on the Every-2-Month Dosing Schedule

If a scheduled every-2-month injection visit is 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 [see *Warnings and Precautions (5.6)*]. If the every-2-month dosing schedule will be continued, see Table 4 for dosing recommendations.

Table 4. Injection Dosing Recommendations after Missed Injections for Patients on the Every-2-Month Dosing Schedule

Missed Injection Visit	Time since Last Injection	Recommendation
Injection 2 (Month 2)	Less than or equal to 2 months	Resume with 600-mg (3-mL) cabotegravir and 900-mg (3-mL) rilpivirine intramuscular injections as soon as possible, then continue to follow the every-2-month injection dosing schedule.
	Greater than 2 months	Re-initiate the patient with 600-mg (3-mL) cabotegravir and 900-mg (3-mL) rilpivirine intramuscular injections, followed by the second initiation injection dose 1 month later. Then continue to follow the every-2-month injection dosing schedule thereafter.
Injection 3 or later (Month 4 onwards)	Less than or equal to 3 months	Resume with 600-mg (3-mL) cabotegravir and 900-mg (3-mL) rilpivirine intramuscular injections as soon as possible and continue with the every-2-month injection dosing schedule.
	Greater than 3 months	Re-initiate the patient with 600-mg (3-mL) cabotegravir and 900-mg (3-mL) rilpivirine intramuscular injections, followed by the second initiation injection dose 1 month later. Then continue with the every-2-month injection dosing schedule thereafter.

2.9 Administration Instructions for Injections

Refer to the Instructions for Use for complete administration instructions with illustrations. Carefully follow these instructions and ensure that the vial adaptor is used correctly when preparing the suspension for injection to avoid leakage.

A complete dose requires 2 injections: 1 injection of cabotegravir and 1 injection of rilpivirine [*see Dosage and Administration (2.4, 2.5)*].

Cabotegravir and rilpivirine are suspensions for gluteal intramuscular injection that do not need further dilution or reconstitution.

Administer each injection at separate gluteal injection sites (on opposite sides or at least 2 cm apart) during the same visit. The ventrogluteal site is recommended. A dorsogluteal approach (upper outer quadrant) is acceptable, if preferred by the healthcare professional. Do not administer by any other route or anatomical site. Consider the body mass index (BMI) of the patient to ensure that the needle length is sufficient to reach the gluteus muscle. Longer needle lengths (not included in the dosing kit) may be required for patients with higher BMI (example: $>30 \text{ kg/m}^2$) to ensure that injections are administered intramuscularly as opposed to subcutaneously. The administration order of cabotegravir and rilpivirine injections is not important.

Before preparing the injections, remove CABENUVA from the refrigerator and wait at least 15 minutes to allow the medicines to come to room temperature. The vials may remain in the carton at room temperature for up to 6 hours; do not put back into the refrigerator. If not used within 6 hours, the medication must be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The cabotegravir vial has a brown tint to the glass that may limit visual inspection. Discard CABENUVA if either medicine exhibits particulate matter or discoloration.

Shake each vial of CABENUVA vigorously so that the suspensions look uniform before injecting. Small air bubbles are expected and acceptable.

Once the suspensions have been drawn into the respective syringes, the injections should be administered as soon as possible, but may remain in the syringes for up to 2 hours. The filled syringes should not be placed in the refrigerator. If the medicine remains in the syringes for more than 2 hours, the filled syringes and needles must be discarded [*see How Supplied/Storage and Handling (16)*].

3 DOSAGE FORMS AND STRENGTHS

Injection:

- Kit of single-dose vials of 400 mg/2 mL (200 mg/mL) of cabotegravir extended-release injectable suspension and 600 mg/2 mL (300 mg/mL) of rilpivirine extended-release

injectable suspension. (3)

- Kit of single-dose vials of 600 mg/3 mL (200 mg/mL) of cabotegravir extended-release injectable suspension and 900 mg/3 mL (300 mg/mL) of rilpivirine extended-release injectable suspension. (3)

4 CONTRAINDICATIONS

CABENUVA is contraindicated in patients:

- with previous hypersensitivity reaction to cabotegravir or rilpivirine [*see Warnings and Precautions (5.1)*].
- receiving the following coadministered drugs for which significant decreases in cabotegravir and/or rilpivirine plasma concentrations may occur due to uridine diphosphate glucuronosyltransferase (UGT)1A1 and/or cytochrome P450 (CYP)3A enzyme induction, which may result in loss of virologic response [*see Drug Interactions (7), Clinical Pharmacology (12.3)*]:
 - Anticonvulsants: Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
 - Antimycobacterials: Rifabutin, rifampin, rifapentine
 - Glucocorticoid (systemic): Dexamethasone (more than a single-dose treatment)
 - Herbal product: St John's wort (*Hypericum perforatum*)

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious or severe hypersensitivity reactions have been reported in association with other integrase inhibitors and during postmarketing experience with rilpivirine-containing regimens where reactions include cases of drug reaction with eosinophilia and systemic symptoms (DRESS) [*see Adverse Reactions (6.1, 6.2)*]. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries. Serious or severe hypersensitivity reactions have been reported in association with other integrase inhibitors and could occur with CABENUVA [*see Adverse Reactions (6.1)*]. Administration of cabotegravir and rilpivirine oral lead-in dosing was used in clinical studies to help identify patients who may be at risk of a hypersensitivity reaction [*see Dosage and Administration (2.3), Contraindications (4)*]. Remain vigilant and discontinue CABENUVA if a hypersensitivity reaction is suspected [*see Contraindications (4), Adverse Reactions (6)*].

Discontinue CABENUVA immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, mucosal involvement [oral blisters or lesions],

conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver transaminases, should be monitored and appropriate therapy initiated. For information regarding the long-acting properties of CABENUVA, *[see Warnings and Precautions (5.6)]*. Administer oral lead-in dosing prior to administration of CABENUVA to help identify patients who may be at risk of a hypersensitivity reaction *[see Dosage and Administration (2.3), Contraindications (4)]*.

5.2 Post-Injection Reactions

In clinical trials, serious post-injection reactions were reported within minutes after the injection of rilpivirine. These events included symptoms such as dyspnea, bronchospasm, agitation, abdominal cramping, rash/urticaria, dizziness, flushing, sweating, oral numbness, changes in blood pressure, and pain (e.g., back and chest). These events were reported in <1% of subjects and began to resolve within minutes after the injection, with some patients receiving supportive care. These events may have been associated with accidental intravenous administration during the intramuscular injection procedure *[see Adverse Reactions (6.1)]*.

Carefully follow the Instructions for Use when preparing and administering CABENUVA. The suspensions should be injected slowly via intramuscular injection, and care should be taken to avoid accidental intravenous administration *[see Dosage and Administration (2.9)]*. Observe patients briefly (approximately 10 minutes) after the injection. If a patient experiences a post-injection reaction, monitor and treat as clinically indicated.

5.3 Hepatotoxicity

Hepatotoxicity has been reported in patients receiving cabotegravir or rilpivirine with or without known pre-existing hepatic disease or identifiable risk factors *[see Adverse Reactions (6.1)]*.

Patients with underlying liver disease or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations.

Monitoring of liver chemistries is recommended and treatment with CABENUVA should be discontinued if hepatotoxicity is suspected. For information regarding the long-acting properties of CABENUVA, *[see Warnings and Precautions (5.6)]*.

5.4 Depressive Disorders

Depressive disorders (including depressed mood, depression, major depression, mood altered, mood swings, dysphoria, negative thoughts, suicidal ideation, suicide attempt) have been reported with CABENUVA or the individual drug products *[see Adverse Reactions (6.1)]*.

Promptly evaluate patients with depressive symptoms to assess whether the symptoms are related to CABENUVA and to determine whether the risks of continued therapy outweigh the benefits.

5.5 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of CABENUVA and other drugs may result in known or potentially significant drug interactions, some of which may lead to adverse events, loss of virologic

response of CABENUVA, and possible development of viral resistance [see *Contraindications (4)*, *Drug Interactions (7.4)*].

Rilpivirine 75-mg and 300-mg once-daily oral doses (3 and 12 times, respectively, the recommended oral dosage) in healthy adults prolonged the QTc interval with mean steady-state C_{\max} values 4.4- and 11.6-fold, respectively, higher than C_{\max} values associated with the recommended 600-mg monthly dose of rilpivirine extended-release injectable suspension and 4.1- and 10.7-fold, respectively, higher than C_{\max} values associated with the recommended 900-mg every-2-month dose of rilpivirine extended-release injectable suspension [see *Clinical Pharmacology (12.2)*]. CABENUVA should be used with caution in combination with drugs with a known risk of Torsade de Pointes [see *Drug Interactions (7.3, 7.4)*].

See Table 8 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with, and after discontinuation of, CABENUVA; review concomitant medications during therapy with CABENUVA [see *Drug Interactions (7.4)*].

5.6 Long-Acting Properties and Potential Associated Risks with CABENUVA

Residual concentrations of both cabotegravir and rilpivirine may remain in the systemic circulation of patients for prolonged periods (up to 12 months or longer). It is important to carefully select patients who agree to the required monthly or every-2-month injection dosing schedule because non-adherence to monthly or every-2-month injections or missed doses could lead to loss of virologic response and development of resistance [see *Dosage and Administration (2.2)*, *Adverse Reactions (6.1)*, *Drug Interactions (7.4)*].

To minimize the potential risk of developing viral resistance, it is essential to initiate an alternative, fully suppressive antiretroviral regimen no later than 1 month after the final injections of CABENUVA when dosed monthly and no later than 2 months after the final injections of CABENUVA when dosed every 2 months. If virologic failure is suspected, switch the patient to an alternative regimen as soon as possible.

6 ADVERSE REACTIONS

The following adverse reactions are described below and in other sections of the labeling:

- Hypersensitivity reactions [see *Warnings and Precautions (5.1)*]
- Post-injection reactions [see *Warnings and Precautions (5.2)*]
- Hepatotoxicity [see *Warnings and Precautions (5.3)*]
- Depressive disorders [see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

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

Clinical Trials Experience in Adults

The safety assessment of CABENUVA is based on the analysis of pooled 48-week data from 1,182 virologically suppressed subjects with HIV-1 infection in 2 international, multicenter, open-label pivotal trials, FLAIR and ATLAS, and 1,045 virologically suppressed subjects from the ATLAS-2M trial [see *Clinical Studies (14.1)*]. Additional safety information from other ongoing or earlier clinical trials in the cabotegravir and rilpivirine program have been considered in assessing the overall safety profile of CABENUVA.

Adverse reactions were reported following exposure to CABENUVA extended-release injectable suspensions (median time exposure at the time of analysis: 54 weeks in FLAIR and ATLAS, and 64 weeks in ATLAS-2M) and data from VOCABRIA (cabotegravir) tablets and EDURANT (rilpivirine) tablets administered in combination as oral lead-in therapy (median time exposure: 5.3 weeks in FLAIR and ATLAS, and 5.6 weeks in ATLAS-2M). Adverse reactions included those attributable to both the oral and injectable formulations of cabotegravir and rilpivirine administered as a combination regimen. Refer to the prescribing information for EDURANT (rilpivirine) for other adverse reactions associated with oral rilpivirine.

The most common adverse reactions regardless of severity reported in $\geq 2\%$ of adult subjects from FLAIR and ATLAS at Week 48 are presented in Table 5. Selected laboratory abnormalities are included in Table 7. At Week 96, the overall safety profile for FLAIR was consistent with that observed at Week 48, with no new safety findings identified.

In the extension phase of the FLAIR study at Week 124, the overall safety profile was consistent with that observed at Week 48 and when injection therapy with CABENUVA was initiated directly without the oral lead-in phase.

Overall, 4% of subjects in the group receiving CABENUVA and 2% of subjects in the control group in FLAIR and ATLAS discontinued due to adverse events. Non-injection-site-related adverse events leading to discontinuation and occurring in more than 1 subject were headache, diarrhea, hepatitis A, and acute hepatitis B (all with an incidence $<1\%$). In ATLAS-2M, 2% of subjects in both treatment groups discontinued due to adverse events. Non-injection-site-related adverse events leading to discontinuation and occurring in more than 1 subject in ATLAS-2M were fatigue, pyrexia, headache, presyncope, acute hepatitis B, hyperhidrosis, and abnormal dreams that occurred with an incidence of $\leq 1\%$ in either treatment group.

Table 5. Adverse Reactions^a (Grades 1 to 4) Reported in at Least 2% of Subjects with HIV-1 Infection in FLAIR and ATLAS Trials (Week 48 Pooled Analyses)

Adverse Reactions	Cabotegravir plus Rilpivirine Once Monthly (n = 591)		Current Antiretroviral Regimen (n = 591)	
	All Grades	At Least Grade 2	All Grades	At Least Grade 2
Injection site reactions ^b	83%	37%	0	0
Pyrexia ^c	8%	2%	0	0
Fatigue ^d	5%	1%	<1%	<1%
Headache	4%	<1%	<1%	<1%
Musculoskeletal pain ^e	3%	1%	<1%	0
Nausea	3%	<1%	1%	<1%
Sleep disorders ^f	2%	<1%	<1%	0
Dizziness	2%	<1%	<1%	0
Rash ^g	2%	<1%	0	0

^a Adverse reactions defined as “treatment-related” as assessed by the investigator.

^b See Injection-Associated Adverse Reactions for additional information.

^c Pyrexia: includes pyrexia, feeling hot, chills, influenza-like illness, body temperature increased.

^d Fatigue: includes fatigue, malaise, asthenia.

^e Musculoskeletal pain: includes musculoskeletal pain, musculoskeletal discomfort, back pain, myalgia, pain in extremity.

^f Sleep disorders: includes insomnia, poor quality sleep, somnolence.

^g Rash: includes erythema, pruritus, pruritus generalized, purpura, rash, rash- erythematous, generalized, macular.

In ATLAS-2M, the type and frequency of adverse reactions reported in subjects receiving CABENUVA once monthly or CABENUVA once every 2 months for 48 weeks were similar. Differences between treatment arms were reported for the types of injection-associated adverse reactions (see Injection-Associated Adverse Reactions for additional information).

Injection-Associated Adverse Reactions: Local Injection Site Reactions (ISRs): In the 3 Phase 3 studies, FLAIR, ATLAS, and ATLAS-2M, the most frequent adverse reactions associated with the intramuscular administration of CABENUVA were ISRs.

In the pooled analysis of FLAIR and ATLAS, 83% of subjects reported any injection site reaction with the monthly dosing regimen, with 1% of subjects who discontinued treatment with CABENUVA because of ISRs. After 14,682 injections, 3,663 ISRs were reported. The severity of ISRs was generally mild (Grade 1: 75% of subjects) or moderate (Grade 2: 36% of subjects). Four percent (4%) of subjects experienced severe (Grade 3) ISRs, and no subject experienced Grade 4 ISRs. The median duration of overall ISR events was 3 days. The most commonly

reported ISR in FLAIR and ATLAS was pain/discomfort, with 79% reported in the group receiving CABENUVA.

In ATLAS-2M, 75% of subjects reported any injection site reaction in both the monthly and every-2-month dosing regimens, with <1% of subjects who discontinued treatment with CABENUVA because of ISRs. When dosing monthly, after 15,711 injections, 3,152 ISRs were reported. When dosing every 2 months, after 8,470 injections, 2,507 ISRs were reported. The severity of ISRs was generally mild (Grade 1: 70% and 71% of subjects) or moderate (Grade 2: 28% and 27% of subjects) in monthly and every-2-month dosing regimens, respectively. Four percent (4%) of subjects in the monthly group and 3% of subjects in the every-2-month group experienced severe (Grade 3) ISRs, and no subject experienced Grade 4 ISRs. The median duration of overall ISR events was 3 days for both dosing regimens. The most commonly reported ISR in ATLAS-2M was pain/discomfort, with 71% and 73% reported in the monthly and every-2-month dosing regimens, respectively. The severity and duration of ISRs, including pain/discomfort, were similar for both dosing regimens and in subjects without prior exposure to CABENUVA.

The most commonly reported ISR (Grades 1 to 3) in at least 1% of adult subjects in the pooled analyses from FLAIR and ATLAS, and from ATLAS-2M, are presented in Table 6. The side-by-side tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trials.

Table 6. Injection Site Reactions (Grades 1 to 3) Reported in at Least 1% of Subjects in FLAIR and ATLAS (Pooled Analysis) and ATLAS-2M Trials (Week 48 Analysis)

Injection Site Reactions	FLAIR and ATLAS	ATLAS-2M	
	Cabotegravir plus Rilpivirine Once Monthly (n = 591)	Cabotegravir plus Rilpivirine Once Every 2 Months (n = 522)	Cabotegravir plus Rilpivirine Once Monthly (n = 523)
Any injection site reaction	83%	75%	75%
Pain/discomfort	79%	73%	71%
Nodules	14%	10%	17%
Induration	12%	8%	7%
Swelling	8%	6%	5%
Erythema	4%	2%	3%
Pruritus	4%	5%	5%
Bruising/discoloration	3%	2%	2%
Warmth	2%	1%	2%
Hematoma	2%	<1%	3%

Anesthesia, abscess, cellulitis, and hemorrhage at the injection site were each reported in <1% of subjects.

Other Injection-Associated Adverse Reactions: In the ATLAS and FLAIR clinical trials, an increased incidence of pyrexia (8%) was reported by subjects receiving cabotegravir plus rilpivirine injections compared with no events among subjects receiving current antiretroviral regimen. In ATLAS and FLAIR, no cases were serious or led to withdrawal and the occurrences of pyrexia may represent a response to administration of CABENUVA via intramuscular injection. In ATLAS-2M, 1 subject in each arm reported pyrexia that led to withdrawal.

In ATLAS and FLAIR, reports of musculoskeletal pain (3%) and less frequently, sciatica, were also more common in subjects receiving cabotegravir plus rilpivirine compared with the current antiretroviral regimen and some events had a temporal association with injection.

Vasovagal or pre-syncope reactions were reported in <1% of subjects after injection with rilpivirine or cabotegravir.

Less Common Adverse Reactions: The following select adverse reactions (regardless of severity) occurred in <2% of subjects receiving cabotegravir plus rilpivirine.

Gastrointestinal Disorders: Abdominal pain (including upper abdominal pain), gastritis, dyspepsia, vomiting, diarrhea, and flatulence.

Hepatobiliary Disorders: Hepatotoxicity.

Investigations: Weight increase (*see below*).

Psychiatric Disorders: Anxiety (including anxiety and irritability), depression, abnormal dreams; suicidal ideation, and suicide attempt (these events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness).

Skin and Hypersensitivity Reactions: Hypersensitivity reactions.

Weight Increase: At Week 48, subjects in FLAIR and ATLAS who received cabotegravir plus rilpivirine had a median weight gain of 1.5 kg; those in the current antiretroviral regimen group had a median weight gain of 1.0 kg (pooled analysis). In the FLAIR trial, the median weight gain in subjects receiving cabotegravir plus rilpivirine or a dolutegravir-containing regimen was 1.3 kg and 1.5 kg, respectively, compared with 1.8 kg and 0.3 kg, respectively, in the ATLAS trial in subjects receiving either cabotegravir plus rilpivirine or a protease inhibitor-, non-nucleoside reverse transcriptase inhibitor (NNRTI)-, or integrase strand transfer inhibitor (INSTI)-containing regimen, respectively. At Week 48, subjects in ATLAS-2M who received cabotegravir plus rilpivirine in both the monthly and every-2-month treatment arms had a median weight gain of 1.0 kg.

Laboratory Abnormalities: Selected laboratory abnormalities with a worsening grade from baseline and representing the worst-grade toxicity are presented in Table 7. The side-by-side

tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trials.

Table 7. Selected Laboratory Abnormalities (Grades 3 to 4, Week 48) in FLAIR and ATLAS (Pooled Analyses) and ATLAS-2M Trials

Laboratory Parameter	FLAIR and ATLAS		ATLAS-2M	
	Cabotegravir plus Rilpivirine Once Monthly (n = 591)	Current Antiretroviral Regimen (n = 591)	Cabotegravir plus Rilpivirine Once Every 2 Months (n = 522)	Cabotegravir plus Rilpivirine Once Monthly (n = 523)
ALT ($\geq 5.0 \times \text{ULN}$)	2%	<1%	<1%	<1%
AST ($\geq 5.0 \times \text{ULN}$)	2%	<1%	<1%	1%
Total bilirubin ($\geq 2.6 \times \text{ULN}$)	<1%	<1%	<1%	<1%
Creatine phosphokinase ($\geq 10.0 \times \text{ULN}$)	8%	4%	3%	4%
Lipase ($\geq 3.0 \times \text{ULN}$)	5%	3%	3%	2%

ALT = Alanine aminotransferase, ULN = Upper limit of normal, AST = Aspartate transaminase.

Changes in Total Bilirubin: Small, non-progressive increases in total bilirubin (without clinical jaundice) were observed with cabotegravir plus rilpivirine. These changes are not considered clinically relevant as they likely reflect competition between cabotegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1) [see *Clinical Pharmacology* (12.3)].

Serum Cortisol: In pooled Phase 3 trials of EDURANT (rilpivirine), the overall mean change from baseline in basal cortisol was -0.69 (-1.12, 0.27) mcg/dL in the group receiving EDURANT compared with -0.02 (-0.48, 0.44) mcg/dL in the control group. Abnormal responses to ACTH stimulation tests were also higher in the group receiving EDURANT. The clinical significance of the higher abnormal rate of ACTH stimulation tests in the group receiving EDURANT is not known. Refer to the prescribing information for EDURANT for additional information.

Clinical Trial Experience in Adolescents

Based on data from the Week 16 analysis of the MOCHA study in 23 adolescents (aged 12 to younger than 18 years and weighing ≥ 35 kg) receiving background antiretroviral therapy, the safety profile in adolescents with the addition of either oral cabotegravir followed by injectable cabotegravir (n = 8) or oral rilpivirine (n = 15) followed by injectable rilpivirine (n = 13) was consistent with the safety profile established with cabotegravir plus rilpivirine in adults. Adverse

reactions were reported in 61% of adolescent subjects receiving either cabotegravir or rilpivirine. The majority of these subjects (86%) had a Grade 1 or Grade 2 adverse reaction. The adverse reactions reported by more than one subject (regardless of severity) were injection site pain (n = 13) and insomnia (n = 2). Two subjects had Grade 3 adverse reactions of hypersensitivity (n = 1) and insomnia (n = 1). The Grade 3 adverse reaction of drug hypersensitivity led to discontinuation of rilpivirine during oral lead-in. Sixty-two percent of subjects who received at least 1 injection of cabotegravir or rilpivirine reported at least 1 ISR. All ISRs were Grade 1 or Grade 2.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving cabotegravir- or oral-rilpivirine-containing regimens. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders

Hypersensitivity reactions (including angioedema and urticaria) [*see Warnings and Precautions (5.1)*].

Renal and Genitourinary Disorders

Nephrotic syndrome.

Skin and Subcutaneous Tissue Disorders

Severe skin and hypersensitivity reactions, including DRESS [*see Warnings and Precautions (5.1)*].

7 DRUG INTERACTIONS

7.1 Concomitant Use with Other Antiretroviral Medicines

Because CABENUVA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended [*see Indications and Usage (1)*].

7.2 Use of Other Antiretroviral Drugs after Discontinuation of CABENUVA

Residual concentrations of cabotegravir and rilpivirine may remain in the systemic circulation of patients for prolonged periods (up to 12 months or longer). These residual concentrations are not expected to affect the exposures of antiretroviral drugs that are initiated after discontinuation of CABENUVA [*see Warnings and Precautions (5.6), Drug Interactions (7.4), Clinical Pharmacology (12.3)*].

7.3 Potential for Other Drugs to Affect CABENUVA

Refer to the prescribing information for VOCABRIA (cabotegravir) and EDURANT (rilpivirine) for additional drug interaction information related to oral cabotegravir and oral rilpivirine, respectively.

Cabotegravir

Cabotegravir is primarily metabolized by UGT1A1 with some contribution from UGT1A9. Drugs that are strong inducers of UGT1A1 or UGT1A9 are expected to decrease cabotegravir plasma concentrations and may result in loss of virologic response; therefore, coadministration of CABENUVA with these drugs is contraindicated [see *Contraindications (4)*].

Rilpivirine

Rilpivirine is primarily metabolized by CYP3A. Coadministration of CABENUVA and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs [see *Contraindications (4)*, *Drug Interactions (7.4)*]. Coadministration of CABENUVA and drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine [see *Drug Interactions (7.4)*, *Clinical Pharmacology (12.3)*].

QT-Prolonging Drugs: At mean steady-state C_{\max} values 4.4- and 11.6-fold higher than those with the recommended 600-mg dose of rilpivirine extended-release injectable suspension, rilpivirine may prolong the QTc interval [see *Clinical Pharmacology (12.2)*]. CABENUVA should be used with caution in combination with drugs with a known risk of Torsade de Pointes [see *Warnings and Precautions (5.5)*, *Drug Interactions (7.4)*].

7.4 Established and Other Potentially Significant Drug Interactions

Refer to the prescribing information for VOCABRIA (cabotegravir) and EDURANT (rilpivirine) for additional drug interaction information related to oral cabotegravir and oral rilpivirine, respectively.

Information regarding potential drug interactions with cabotegravir and rilpivirine is provided in Table 8. These recommendations are based on either drug interaction trials following oral administration of cabotegravir or rilpivirine or predicted interactions due to the expected magnitude of the interaction and potential for loss of virologic response [see *Contraindications (4)*, *Warnings and Precautions (5.5)*, *Clinical Pharmacology (12.3)*]. Table 8 includes potentially significant interactions but is not all inclusive.

Table 8. Drug Interactions with CABENUVA

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Anticonvulsants: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	↓Cabotegravir ↓Rilpivirine	Coadministration is contraindicated with CABENUVA due to potential for loss of virologic response and development of resistance [see <i>Contraindications (4)</i>].
Antimycobacterials: Rifampin ^a Rifapentine	↓Cabotegravir ↓Rilpivirine	
Antimycobacterial: Rifabutin ^a	↓Cabotegravir ↔Rifabutin ↓Rilpivirine	
Glucocorticoid (systemic): Dexamethasone (more than a single-dose treatment)	↓Rilpivirine	
Herbal product: St John's wort (<i>Hypericum perforatum</i>)	↓Rilpivirine	
Macrolide or ketolide antibiotics: Azithromycin Clarithromycin Erythromycin	↔Cabotegravir ↑Rilpivirine	Macrolides are expected to increase concentrations of rilpivirine and are associated with a risk of Torsade de Pointes [see <i>Warnings and Precautions (5.5)</i>]. Where possible, consider alternatives, such as azithromycin, which increases rilpivirine concentrations less than other macrolides.
Narcotic analgesic: Methadone ^a	↔Cabotegravir ↓Methadone ↔Rilpivirine	No dose adjustment of methadone is required when starting coadministration of methadone with CABENUVA. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.

↑ = Increase, ↓ = Decrease, ↔ = No change.

^a See *Clinical Pharmacology (12.3)* for magnitude of interaction.

7.5 Drugs without Clinically Significant Interactions

Cabotegravir

Based on drug interaction study results, the following drugs can be coadministered with cabotegravir (non-antiretrovirals and rilpivirine) or given after discontinuation of cabotegravir (antiretrovirals and non-antiretrovirals) without a dose adjustment: etravirine, midazolam, oral contraceptives containing levonorgestrel and ethinyl estradiol, and rilpivirine [*see Clinical Pharmacology (12.3)*].

Rilpivirine

Based on drug interaction study results, the following drugs can be coadministered with rilpivirine (non-antiretrovirals and cabotegravir) or given after discontinuation of rilpivirine (antiretrovirals and non-antiretrovirals): acetaminophen, atorvastatin, cabotegravir, chlorzoxazone, dolutegravir, ethinyl estradiol, norethindrone, raltegravir, ritonavir-boosted atazanavir, ritonavir-boosted darunavir, sildenafil, tenofovir alafenamide, and tenofovir disoproxil fumarate [*see Clinical Pharmacology (12.3)*]. Rilpivirine did not have a clinically significant effect on the pharmacokinetics of digoxin or metformin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to CABENUVA during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

There are insufficient human data on the use of CABENUVA during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage. While there are insufficient human data to assess the risk of neural tube defects (NTDs) with exposure to CABENUVA during pregnancy, NTDs were associated with dolutegravir, another integrase inhibitor. Discuss the benefit-risk of using CABENUVA with individuals of childbearing potential or during pregnancy.

Cabotegravir and rilpivirine are detected in systemic circulation for up to 12 months or longer after discontinuing injections of CABENUVA; therefore, consideration should be given to the potential for fetal exposure during pregnancy [*see Warnings and Precautions (5.6), Drug Interactions (7.2)*].

Cabotegravir use in pregnant individuals has not been evaluated. Available data from the APR show no difference in the overall risk of birth defects for rilpivirine compared with the

background rate for major birth defects of 2.7% in a United States (U.S.) reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) (*see Data*).

The rate of miscarriage is not reported in the APR. The background risk for major birth defects and miscarriage for the indicated population is unknown. The background rate for major birth defects in a U.S. reference population of the MACDP is 2.7%. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates mothers and infants from a limited geographic area and does not include outcomes for births that occurred at <20 weeks' gestation.

In animal reproduction studies with oral cabotegravir, a delay in the onset of parturition and increased stillbirths and neonatal deaths were observed in a rat pre- and postnatal development study at >28 times the exposure at the recommended human dose (RHD). No evidence of adverse developmental outcomes was observed with oral cabotegravir in rats or rabbits (>28 times or similar to the exposure at the RHD, respectively) given during organogenesis (*see Data*).

No adverse developmental outcomes were observed when rilpivirine was administered orally at exposures 15 (rats) and 70 (rabbits) times the exposure in humans at the RHD (*see Data*).

Clinical Considerations

Lower exposures with oral rilpivirine were observed during pregnancy. Viral load should be monitored closely if the patient remains on CABENUVA during pregnancy. Cabotegravir and rilpivirine are detected in systemic circulation for up to 12 months or longer after discontinuing injections of CABENUVA; therefore, consideration should be given to the potential for fetal exposure during pregnancy [*see Warnings and Precautions (5.6)*].

Data

Human Data: Cabotegravir: Data from a birth outcome surveillance study in Botswana showed that dolutegravir, another integrase inhibitor, was associated with increased risk of NTDs when administered at the time of conception and in early pregnancy. Data from clinical trials are insufficient to address this risk with cabotegravir.

Rilpivirine: Based on prospective reports to the APR of over 580 exposures to oral rilpivirine-containing regimens during the first trimester of pregnancy and over 200 during second/third trimester of pregnancy, the prevalence of birth defects in live births was 1.5% (95% CI: 0.7% to 2.9%) and 1.5% (95% CI: 0.3% to 4.2%) following first and second/third trimester exposures, respectively, compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. In a clinical trial, total oral rilpivirine exposures were generally lower during pregnancy compared with the postpartum period. Refer to the prescribing information for EDURANT (rilpivirine) for additional information on rilpivirine.

Animal Data: Cabotegravir: Cabotegravir was administered orally to pregnant rats at 0, 0.5, 5, or 1,000 mg/kg/day from 15 days before cohabitation, during cohabitation, and from Gestation Days 0 to 17. There were no effects on fetal viability when fetuses were delivered by caesarean, although a minor decrease in fetal body weight was observed at 1,000 mg/kg/day (>28 times the exposure in humans at the RHD). No drug-related fetal toxicities were observed at 5 mg/kg/day (approximately 13 times the exposure in humans at the RHD), and no drug-related fetal malformations were observed at any dose.

Cabotegravir was administered orally to pregnant rabbits at 0, 30, 500, or 2,000 mg/kg/day from Gestation Days 7 to 19. No drug-related fetal toxicities were observed at 2,000 mg/kg/day (approximately 0.7 times the exposure in humans at the RHD).

In a rat pre- and postnatal development study, cabotegravir was administered orally to pregnant rats at 0, 0.5, 5, or 1,000 mg/kg/day from Gestation Day 6 to Lactation Day 21. A delay in the onset of parturition and increases in the number of stillbirths and neonatal deaths by Lactation Day 4 were observed at 1,000 mg/kg/day (>28 times the exposure in humans at the RHD); there were no alterations to growth and development of surviving offspring. In a cross-fostering study, similar incidences of stillbirths and early postnatal deaths were observed when rat pups born to cabotegravir-treated mothers were nursed from birth by control mothers. There was no effect on neonatal survival of control pups nursed from birth by cabotegravir-treated mothers. A lower dose of 5 mg/kg/day (13 times the exposure at the RHD) was not associated with delayed parturition or neonatal mortality in rats. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in fetal tissue.

Rilpivirine: Rilpivirine was administered orally to pregnant rats (40, 120, or 400 mg/kg/day) and rabbits (5, 10, or 20 mg/kg/day) through organogenesis (on Gestation Days 6 through 17 and 6 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with rilpivirine in rats and rabbits at exposures 15 (rats) and 70 (rabbits) times the exposure in humans at the RHD. In a pre- and postnatal development study, rilpivirine was administered orally up to 400 mg/kg/day through lactation. No adverse effects were noted in the offspring at maternal exposures up to 63 times the exposure in humans at the RHD.

8.2 Lactation

Risk Summary

Based on limited data after oral administration, rilpivirine is present in human breast milk. The data do not allow determination of the amount of rilpivirine that is transferred to milk. There are no data on the presence of cabotegravir in human milk. Cabotegravir is present in animal milk (*see Data*). When a drug is present in animal milk, it is likely that the drug will be present in human milk. It is not known if the components of CABENUVA affect human milk production or have effects on the breastfed infant. Residual exposures in human milk of cabotegravir (if

present) and rilpivirine may remain for 12 months or longer after the last injections have been administered [see *Warnings and Precautions* (5.6)].

Potential risks of breastfeeding include: (1) HIV-1 transmission (in HIV-1–negative infants), (2) developing viral resistance (in HIV-1–positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults.

Data

Cabotegravir: Animal lactation studies with cabotegravir have not been conducted. However, cabotegravir was detected in the plasma of nursing pups on Lactation Day 10 in the rat pre- and postnatal development study.

8.4 Pediatric Use

The safety and effectiveness of CABENUVA have been established in adolescents aged 12 to younger than 18 years and weighing at least 35 kg, which is supported by the following:

- Trials in adults [see *Clinical Studies* (14.1)]
- MOCHA (NCT03497676) trial in adolescents

MOCHA Trial

The safety, tolerability, and pharmacokinetics of oral and injectable cabotegravir and oral and injectable rilpivirine are being assessed in an ongoing Phase 1/2 multicenter, open-label, non-comparative study, MOCHA (IMPAACT 2017). Data are available from the Week 16 interim analysis from MOCHA. The primary objective at Week 16 was to confirm the use of the adult dose, through the evaluation of safety and pharmacokinetics, for oral and injectable cabotegravir and injectable rilpivirine in HIV-1–infected virologically suppressed adolescents.

Twenty-three HIV-1–infected and virologically suppressed adolescents aged 12 to younger than 18 years and weighing at least 35 kg were assigned to 1 of 2 cohorts, 1C or 1R, based on their background antiretroviral regimen. In cohort 1C, participants (n = 8) received one 30-mg cabotegravir tablet daily for 1 month, followed by monthly cabotegravir injections (Month 1: 600-mg injection, Months 2 and 3: 400-mg injection) for an additional 3 months, while continuing background antiretroviral therapy. In cohort 1R, participants received one 25-mg rilpivirine tablet (n = 15) daily for 1 month, followed by monthly rilpivirine injections (n = 13) (Month 1: 900-mg injection, Months 2 and 3: 600-mg injection) for an additional 3 months, while continuing background antiretroviral therapy.

At baseline, in cohort 1C, the median age of participants was 14.5 years; the median weight was 57.2 kg (range: 43.0, 73.5); 25% were female; 100% were non-White; and no participant had a CD4+ cell count <350 cells per mm³. At baseline, median CD4+ cell count was 725 cells per mm³ (range: 629 to 924). In cohort 1R, the median age of participants was 17 years; the median weight was 63.0 kg (range: 44.1, 98.5); 53% were female; 73% were non-White; and no

participant had a CD4+ cell count <350 cells per mm³. At baseline, median CD4+ cell count was 827 cells per mm³ (range: 439 to 1,509).

The safety of CABENUVA in adolescents is expected to be similar to adults, as there was no clinically significant difference in drug exposure for the components of CABENUVA [see *Adverse Reactions (6.1)*]. The efficacy of CABENUVA in adolescents is extrapolated from adults with support from pharmacokinetic analyses showing similar drug exposure [see *Clinical Pharmacology (12.3)*].

The safety, efficacy, and pharmacokinetics of CABENUVA have not been established in pediatric patients younger than 12 years of age or weighing <35 kg.

8.5 Geriatric Use

Clinical trials of CABENUVA did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in administration of CABENUVA in elderly patients, reflecting greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy [see *Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

Based on studies with oral cabotegravir and population pharmacokinetic analyses of oral rilpivirine, no dosage adjustment of CABENUVA is necessary for patients with mild (creatinine clearance ≥60 to <90 mL/min) or moderate renal impairment (creatinine clearance ≥30 to <60 mL/min). In patients with severe renal impairment (creatinine clearance 15 to <30 mL/min) or end-stage renal disease (creatinine clearance <15 mL/min), increased monitoring for adverse effects is recommended [see *Clinical Pharmacology (12.3)*]. In patients with end-stage renal disease not on dialysis, effects on the pharmacokinetics of cabotegravir or rilpivirine are unknown. As cabotegravir and rilpivirine are >99% protein bound, dialysis is not expected to alter exposures of cabotegravir or rilpivirine.

8.7 Hepatic Impairment

Based on separate studies with oral cabotegravir and oral rilpivirine, no dosage adjustment of CABENUVA is necessary for patients with mild or moderate hepatic impairment (Child-Pugh A or B). The effect of severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of cabotegravir or rilpivirine is unknown [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

There is no known specific treatment for overdose with cabotegravir or rilpivirine. If overdose occurs, monitor the patient and apply standard supportive treatment as required, including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient. As both cabotegravir and rilpivirine are highly bound to plasma proteins, it is unlikely that either would be significantly removed by dialysis. Consider the prolonged exposure

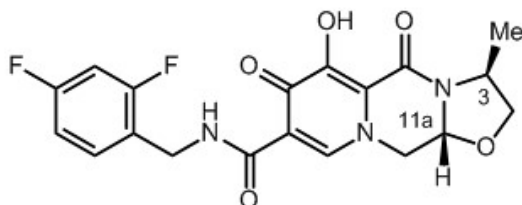
to cabotegravir and rilpivirine (components of CABENUVA) following an injection when assessing treatment needs and recovery [see *Warnings and Precautions* (5.6)].

11 DESCRIPTION

CABENUVA contains cabotegravir extended-release injectable suspension, an HIV INSTI, co-packaged with rilpivirine extended-release injectable suspension, an HIV NNRTI.

Cabotegravir

The chemical name for cabotegravir is (3*S*,11*aR*)-N-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11*a*-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide. The empirical formula is C₁₉H₁₇F₂N₃O₅ and the molecular weight is 405.35 g/mol. It has the following structural formula:

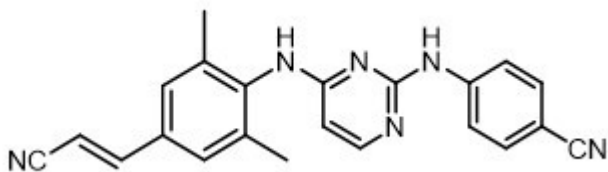


Cabotegravir extended-release injectable suspension is a white to light pink free-flowing suspension for intramuscular injection in a sterile single-dose vial. Each vial contains 2 mL or 3 mL of the following: cabotegravir 200 mg/mL and the inactive ingredients mannitol (35 mg/mL), polyethylene glycol (PEG) 3350 (20 mg/mL), polysorbate 20 (20 mg/mL), and Water for Injection.

The vial stoppers are not made with natural rubber latex.

Rilpivirine

The chemical name for rilpivirine is 4-[[4-[[4-[(*E*)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile. Its molecular formula is C₂₂H₁₈N₆ and its molecular weight is 366.42. Rilpivirine has the following structural formula:



Rilpivirine extended-release injectable suspension is a white to off-white suspension for intramuscular injection. Each sterile single-dose vial contains 2 mL or 3 mL of the following: rilpivirine 300 mg/mL and the following inactive ingredients: citric acid monohydrate (1 mg/mL), poloxamer 338 (50 mg/mL), Water for Injection, glucose monohydrate to ensure isotonicity, sodium dihydrogen phosphate monohydrate, and sodium hydroxide to adjust pH.

The vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CABENUVA contains 2 long-acting HIV-1 antiretroviral drugs, cabotegravir and rilpivirine [see *Microbiology (12.4)*].

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose of cabotegravir 150 mg orally every 12 hours (10 times the recommended total daily oral lead-in dosage of CABENUVA), the QT interval is not prolonged to any clinically relevant extent. Administration of 3 doses of cabotegravir 150 mg orally every 12 hours resulted in a geometric mean C_{max} approximately 2.8-, 5.4-, and 5.6-fold above the geometric mean steady-state C_{max} associated with the recommended 30-mg dose of oral cabotegravir, the recommended 400-mg dose given monthly, and the recommended 600-mg dose given every 2 months of cabotegravir extended-release injectable suspension, respectively.

At the recommended dose of rilpivirine 25 mg orally once daily, the QT interval is not prolonged to any clinically relevant extent. The rilpivirine 25-mg once-daily mean steady-state C_{max} was 247 ng/mL, which is 1.7-fold higher than the mean steady-state C_{max} observed with the recommended 600-mg dose of rilpivirine extended-release injectable suspension given monthly and 1.6-fold higher than the mean steady-state C_{max} observed with the recommended 900-mg dose of rilpivirine extended-release injectable suspension given every 2 months.

When rilpivirine 75-mg and 300-mg once-daily oral doses (3 and 12 times, respectively, the recommended oral lead-in dosage) were studied in healthy adults, the maximum mean time-matched (95% upper confidence bound) differences in QTcF interval were 10.7 (15.3) and 23.3 (28.4) msec, respectively, after baseline and placebo adjustment. Steady-state administration of rilpivirine 75 mg once daily and 300 mg once daily resulted in a mean steady-state C_{max} approximately 4.4- and 11.6-fold, respectively, higher than the mean steady-state C_{max} observed with the recommended 600-mg dose of rilpivirine extended-release injectable suspension given monthly and approximately 4.1- and 10.7-fold, respectively, higher than the mean steady-state C_{max} observed with the recommended 900-mg dose of rilpivirine extended-release injectable suspension given every 2 months. The corresponding C_{max} ratios are 2.6 and 6.7 when compared with the recommended oral rilpivirine dosage [see *Warnings and Precautions (5.5)*].

12.3 Pharmacokinetics

Absorption, Distribution, and Elimination

The pharmacokinetic properties of the components of CABENUVA are provided in Table 9. The multiple-dose pharmacokinetic parameters are provided in Table 10. For the pharmacokinetic

properties of oral cabotegravir and oral rilpivirine, refer to the full prescribing information for VOCABRIA (cabotegravir) and EDURANT (rilpivirine), respectively.

Table 9. Pharmacokinetic Properties of the Components of CABENUVA

	Cabotegravir	Rilpivirine
Absorption^a		
T _{max} (days), median	7	3 to 4
Distribution		
% Bound to human plasma proteins	>99.8	99.7
Blood-to-plasma ratio	0.52	0.7
CSF-to-plasma concentration ratio (median [range]) ^b	0.003 (0.002 to 0.004)	0.01 (BLQ to 0.02)
Elimination		
t _{1/2} (weeks), mean ^c	5.6 to 11.5	13 to 28
<i>Metabolism</i>		
Metabolic pathways	UGT1A1 UGT1A9 (minor)	CYP3A
<i>Excretion</i>		
Major route of elimination	Metabolism	Metabolism
% of dose excreted as total ¹⁴ C (unchanged drug) in urine ^d	27 (0)	6 (<1)
% of dose excreted as total ¹⁴ C (unchanged drug) in feces ^d	59 (47)	85 (26)

CSF = Cerebrospinal fluid, BLQ = Below limit of quantification.

^a When taken orally with a high-fat meal versus fasted, the AUC_(0-inf) (geometric mean ratio [90% CI] of cabotegravir and rilpivirine are 1.14 [1.02, 1.28] and 1.72 [1.36, 2.16]), respectively.

^b The clinical relevance of CSF-to-plasma concentration ratios is unknown. Concentrations were measured at steady-state 1 week after intramuscular administration of cabotegravir and rilpivirine extended-release injectable suspensions given monthly or every 2 months.

^c Elimination half-life driven by slow absorption rate from the intramuscular injection site.

^d Dosing in mass balance studies: single-dose oral administration of [¹⁴C] cabotegravir; single-dose oral administration of [¹⁴C] rilpivirine.

Table 10. Pharmacokinetic Parameters following Once-Daily Oral Cabotegravir and Rilpivirine and following Initiation and Monthly and Every-2-Month Continuation Intramuscular Injections of the Components of CABENUVA in Adults

Drug	Dosing Phase	Dosage Regimen	Geometric Mean (5 th , 95 th Percentile) ^a		
			AUC _(0-tau) ^b (mcg•h/mL)	C _{max} (mcg/mL)	C _{tau} ^b (mcg/mL)
Cabotegravir	Oral lead-in ^c	30 mg once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
	Initial injection (after oral lead-in) ^d	600 mg IM initial dose	1,591 (714; 3,245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
	Initial injection (direct to injection) ^e	600 mg IM initial dose	—	1.89 (0.438, 5.69)	1.43 (0.403, 3.90)
	Monthly injection ^f	400 mg IM monthly	2,415 (1,494; 3,645)	4.2 (2.5, 6.5)	2.8 (1.7, 4.6)
	Every-2-month injection ^f	600 mg IM every 2 months	3,764 (2,431; 5,857)	4.0 (2.3, 6.8)	1.6 (0.8, 3.0)
Drug	Dosing Phase	Dosage Regimen	Geometric Mean (5 th , 95 th Percentile) ^a		
			AUC _(0-tau) ^b (ng•h/mL)	C _{max} (ng/mL)	C _{tau} ^b (ng/mL)
Rilpivirine	Oral lead-in ^{c,g}	25 mg once daily	2,083 (1,125; 3,748)	116 (48.6, 244)	79.4 (31.8, 177)
	Initial injection (after oral lead-in) ^d	900 mg IM initial dose	44,842 (21,712; 87,575)	144 (93.9, 221)	41.9 (21.7, 78.9)
	Initial injection (direct to injection) ^e	900 mg IM initial dose	—	68 (27.5, 220)	48.9 (17.7, 138)
	Monthly injection ^f	600 mg IM monthly	68,324 (39,042; 118,111)	121 (68.1, 210)	85.8 (49.6, 147)
	Every-2-month injection ^f	900 mg IM every 2 months	132,450 (76,638; 221,783)	138 (80.6, 228)	68.9 (38.0, 119)

IM = Intramuscular.

- ^a Pharmacokinetic parameter values were based on individual post-hoc estimates from separate cabotegravir and rilpivirine population pharmacokinetic models (cabotegravir: pooled FLAIR and ATLAS for the oral, initial, and monthly injection dosing schedule and ATLAS-2M [subjects with no prior exposure to cabotegravir plus rilpivirine] for the every-2-month injection dosing schedule; rilpivirine: pooled FLAIR, ATLAS, and ATLAS-2M [subjects with no prior exposure], except for initial injection (direct to injection) [see footnote e] and for oral rilpivirine [see footnote g]).
- ^b tau is dosing interval: 24 hours for oral cabotegravir and rilpivirine, 1 month for cabotegravir and rilpivirine extended-release injectable suspensions given monthly, 2 months for cabotegravir and rilpivirine extended-release injectable suspensions given every 2 months.
- ^c Oral lead-in pharmacokinetic parameter values represent steady-state.
- ^d Initial injection C_{\max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, $AUC_{(0-\tau)}$ and the C_{τ} values reflect the initial injections for cabotegravir and rilpivirine.
- ^e Pharmacokinetic parameters for initial injection (direct to injection) based on observed data from FLAIR Extension Phase (n = 110), AUC not calculated based on observed data, C_{\max} = 1 week following initial injection, C_{τ} = 1 month following initial injection.
- ^f Monthly and every-2-month injection pharmacokinetic parameter values represent Week 48 data.
- ^g Oral rilpivirine: $AUC_{(0-\tau)}$ based on population pharmacokinetic estimates of rilpivirine 25 mg once daily from pooled Phase 3 trials with EDURANT (rilpivirine); C_{τ} based on observed data from FLAIR, ATLAS, and ATLAS-2M; C_{\max} based on observed data for rilpivirine 25 mg once daily from a pharmacokinetic substudy in pooled Phase 3 trials with EDURANT (rilpivirine).

Specific Populations

No clinically significant differences in the pharmacokinetics of cabotegravir or rilpivirine were observed based on age, sex, race/ethnicity, BMI, or UGT1A1 polymorphisms.

Cabotegravir and rilpivirine concentrations in subjects who were hepatitis C virus antibody positive at baseline were similar to those in the overall study population. The effect of hepatitis B virus co-infection on the pharmacokinetics of cabotegravir is unknown. No clinically relevant differences in the pharmacokinetics of oral rilpivirine have been observed with hepatitis B and/or C virus co-infection.

Patients with Renal Impairment: With oral cabotegravir, no clinically significant differences in the pharmacokinetics of cabotegravir are expected in patients with mild, moderate, or severe renal impairment. Cabotegravir has not been studied in patients with end-stage renal disease not on dialysis. As cabotegravir is >99% protein bound, dialysis is not expected to alter exposures of cabotegravir [see *Use in Specific Populations* (8.6)].

Population pharmacokinetic analyses indicated that mild renal impairment had no clinically relevant effect on the exposure of oral rilpivirine. There is limited or no information regarding the pharmacokinetics of rilpivirine in patients with moderate or severe renal impairment or end-stage renal disease not on dialysis. As rilpivirine is >99% protein bound, dialysis is not expected to alter exposures of rilpivirine [see *Use in Specific Populations* (8.6)].

Patients with Hepatic Impairment: No clinically significant differences in the pharmacokinetics of cabotegravir are expected in mild to moderate (Child-Pugh A or B) hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of cabotegravir has not been studied [see *Use in Specific Populations* (8.7)].

No clinically significant differences in the pharmacokinetics of rilpivirine were observed in mild to moderate (Child-Pugh A or B) hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) has not been studied [see *Use in Specific Populations* (8.7)].

Geriatric Patients: The pharmacokinetics of cabotegravir (oral or injectable) and of injectable rilpivirine have not been studied and data are limited in subjects aged 65 years or older [see *Use in Specific Populations* (8.5)].

Pediatric Patients: Population pharmacokinetic analyses revealed no clinically relevant differences in exposure between HIV-1–infected adolescent (weighing ≥ 35 kg and aged at least 12 years) and HIV-1–infected and –uninfected adult participants from the cabotegravir or rilpivirine development program.

Table 11. Predicted Pharmacokinetic Parameters following Cabotegravir and Rilpivirine Orally Once Daily, and Initiation, Monthly, and Every-2-Months Continuation Intramuscular Injections in Adolescents Aged 12 to Younger than 18 Years (≥ 35 kg)

Drug	Dosing Phase	Dosage Regimen	Geometric Mean (5 th , 95 th Percentile) ^a		
			AUC _(0-tau) ^b (mcg•h/mL)	C _{max} (mcg/mL)	C _{tau} ^b (mcg/mL)
Cabotegravir	Oral lead-in ^c	30 mg once daily	193 (106, 346)	14.4 (8.02, 25.5)	5.79 (2.48, 12.6)
	Initial injection ^d	600 mg IM initial dose	2,123 (881; 4,938)	11.2 (5.63, 21.5)	1.84 (0.64, 4.52)
	Every-1-month injection ^e	400 mg IM every 1 month	3,222 (1,879; 5,406)	7.88 (4.41, 13.8)	3.65 (1.63, 7.49)
	Every-2-months injection ^e	600 mg IM every 2 months	4,871 (2,827; 8,232)	7.23 (3.76, 14.1)	2.01 (0.64, 4.73)

Drug	Dosing Phase	Dosage Regimen	Geometric Mean (5 th , 95 th Percentile)		
			AUC _(0-tau) ^b (ng•h/mL)	C _{max} (ng/mL)	C _{tau} ^b (ng/mL)
Rilpivirine	Oral lead-in ^c	25 mg PO once daily	2,389 (1,259; 4,414)	144 (80.8, 234)	82.5 (37.5, 167)
	Initial injection ^d	900 mg IM initial dose	41,515 (19,301; 82,646)	156 (93.4, 246)	39.7 (20.0, 78.2)
	Every-1-month injection ^e	600 mg IM every month	74,717 (40,243; 136,114)	128 (67.8, 233)	97.3 (51.1, 175)
	Every-2-months injection ^e	900 mg IM every 2 months	114,139 (61,432; 206,214)	111 (57.6, 212)	63.1 (32.9, 117)

IM = intramuscular, PO = by mouth.

^a Pharmacokinetic parameter values were based on population pharmacokinetic model simulations in a virtual HIV-1–infected adolescent population weighing 35 to 156 kg.

^b tau is dosing interval: 24 hours for oral administration, 1 month for the initial injection and monthly intramuscular injections, and 2 months for every-2-months intramuscular injections of extended-release injectable suspension.

^c Oral lead-in pharmacokinetic parameter values represent steady-state.

^d Initial injection C_{max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, the AUC_(0-tau) and C_{tau} values reflect the initial injection.

^e Monthly and every-2-month injection pharmacokinetic parameter values represent Week 48 data.

Drug Interaction Studies

Cabotegravir is not a clinically relevant inhibitor of the following enzymes and transporters: CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4; UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B15, and 2B17; P-glycoprotein (P-gp); breast cancer resistance protein (BCRP); bile salt export pump (BSEP); organic cation transporter (OCT)1, OCT2; organic anion transporter polypeptide (OATP)1B1, OATP1B3; multidrug and toxin extrusion transporter (MATE) 1, MATE 2-K; and multidrug resistance protein (MRP)2 or MRP4.

In vitro, cabotegravir inhibited renal OAT1 (IC₅₀ = 0.81 microM) and OAT3 (IC₅₀ = 0.41 microM). Based on physiologically based pharmacokinetic (PBPK) modeling, cabotegravir may increase the AUC of OAT1/3 substrates up to approximately 80%.

In vitro, cabotegravir did not induce CYP1A2, CYP2B6, or CYP3A4.

Simulations using PBPK modeling show that no clinically significant interaction is expected during coadministration of cabotegravir with drugs that inhibit UGT1A1.

In vitro, cabotegravir was not a substrate of OATP1B1, OATP1B3, OATP2B1, or OCT1.

Cabotegravir is a substrate of P-gp and BCRP in vitro; however, because of its high permeability, no alteration in cabotegravir absorption is expected with coadministration of P-gp or BCRP inhibitors.

Rilpivirine is not likely to have a clinically relevant effect on the exposure of drugs metabolized by CYP enzymes.

Drug interaction studies were not conducted with injectable cabotegravir or injectable rilpivirine. Drug interaction studies with oral cabotegravir or oral rilpivirine are summarized in Tables 12, 13, 14, and 15.

Table 12. Effect of Coadministered Drugs on the Pharmacokinetics of Cabotegravir

Coadministered Drug(s) and Dose(s)	Dose of Cabotegravir	n	Geometric Mean Ratio (90% CI) of Cabotegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C _{max}	AUC	C _{tau} or C ₂₄
Etravirine 200 mg twice daily	30 mg once daily	12	1.04 (0.99, 1.09)	1.01 (0.96, 1.06)	1.00 (0.94, 1.06)
Rifabutin 300 mg once daily	30 mg once daily	12	0.83 (0.76, 0.90)	0.77 (0.74, 0.83)	0.74 (0.70, 0.78)
Rifampin 600 mg once daily	30-mg single dose	15	0.94 (0.87, 1.02)	0.41 (0.36, 0.46)	0.50 (0.44, 0.57)
Rilpivirine 25 mg once daily	30 mg once daily	11	1.05 (0.96, 1.15)	1.12 (1.05, 1.19)	1.14 (1.04, 1.24)

n = Maximum number of subjects with data, CI = Confidence Interval.

Table 13. Effect of Coadministered Drugs on the Pharmacokinetics of Rilpivirine

Coadministered Drug(s) and Dose(s)	Dose of Rilpivirine	n	Geometric Mean Ratio (90% CI) of Rilpivirine Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C _{max}	AUC	C _{min}
Acetaminophen 500-mg single dose	150 mg once daily ^a	16	1.09 (1.01 to 1.18)	1.16 (1.10 to 1.22)	1.26 (1.16 to 1.38)
Atorvastatin 40 mg once daily	150 mg once daily ^a	16	0.91 (0.79 to 1.06)	0.90 (0.81 to 0.99)	0.90 (0.84 to 0.96)

Chlorzoxazone 500-mg single dose taken 2 hours after rilpivirine	150 mg once daily ^a	16	1.17 (1.08 to 1.27)	1.25 (1.16 to 1.35)	1.18 (1.09 to 1.28)
Darunavir/ritonavir 800/100 mg once daily	150 mg once daily ^a	14	1.79 (1.56 to 2.06)	2.30 (1.98 to 2.67)	2.78 (2.39 to 3.24)
Didanosine 400 mg once daily delayed-release capsules taken 2 hours before rilpivirine	150 mg once daily ^a	21	1.00 (0.90 to 1.10)	1.00 (0.95 to 1.06)	1.00 (0.92 to 1.09)
Ethinyl estradiol/ norethindrone 0.035 mg once daily/ 1 mg once daily	25 mg once daily	15	↔ ^b	↔ ^b	↔ ^b
Ketoconazole 400 mg once daily	150 mg once daily ^b	15	1.30 (1.13 to 1.48)	1.49 (1.31 to 1.70)	1.76 (1.57 to 1.97)
Lopinavir/ritonavir 400/100 mg twice daily (soft gel capsule)	150 mg once daily ^a	15	1.29 (1.18 to 1.40)	1.52 (1.36 to 1.70)	1.74 (1.46 to 2.08)
Methadone 60 to 100 mg once daily, individualized dose	25 mg once daily	12	↔ ^b	↔ ^b	↔ ^b
Raltegravir 400 mg twice daily	25 mg once daily	23	1.12 (1.04 to 1.20)	1.12 (1.05 to 1.19)	1.03 (0.96 to 1.12)
Rifabutin 300 mg once daily	25 mg once daily	18	0.69 (0.62 to 0.76)	0.58 (0.52 to 0.65)	0.52 (0.46 to 0.59)
Rifabutin 300 mg once daily	50 mg once daily	18	1.43 (1.30 to 1.56)	1.16 (1.06 to 1.26)	0.93 (0.85 to 1.01)
			(reference arm for comparison was 25 mg once-daily rilpivirine administered alone)		
Rifampin 600 mg once daily	150 mg once daily ^a	16	0.31 (0.27 to 0.36)	0.20 (0.18 to 0.23)	0.11 (0.10 to 0.13)
Sildenafil 50-mg single dose	75 mg once daily ^a	16	0.92 (0.85 to 0.99)	0.98 (0.92 to 1.05)	1.04 (0.98 to 1.09)
Tenofovir disoproxil fumarate 300 mg once daily	150 mg once daily ^a	16	0.96 (0.81 to 1.13)	1.01 (0.87 to 1.18)	0.99 (0.83 to 1.16)

n = Maximum number of subjects with data, CI = Confidence Interval, ↔ = No change.

^a This interaction study has been performed with a dose higher than the recommended dose for rilpivirine (25 mg once daily) assessing the maximal effect on the coadministered drug.

^b Comparison based on historic controls.

Table 14. Effect of Cabotegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	Dose of Cabotegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Cabotegravir No Effect = 1.00		
			C _{max}	AUC	C _{tau} or C ₂₄
Ethinyl estradiol 0.03 mg once daily	30 mg once daily	19	0.92 (0.83, 1.03)	1.02 (0.97, 1.08)	1.00 (0.92, 1.10)
Levonorgestrel 0.15 mg once daily	30 mg once daily	19	1.05 (0.96, 1.15)	1.12 (1.07, 1.18)	1.07 (1.01, 1.15)
Midazolam 3 mg	30 mg once daily	12	1.09 (0.94, 1.26)	1.10 (0.95, 1.26)	NA
Rilpivirine 25 mg once daily	30 mg once daily	11	0.96 (0.85, 1.09)	0.99 (0.89, 1.09)	0.92 (0.79, 1.07)

n = Maximum number of subjects with data, CI = Confidence Interval, NA = Not available.

Table 15. Effect of Rilpivirine on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	Dose of Rilpivirine	n	Geometric Mean Ratio (90% CI) of Coadministered Drug Pharmacokinetic Parameters with/without EDURANT No Effect = 1.00		
			C _{max}	AUC	C _{min}
Acetaminophen 500-mg single dose	150 mg once daily ^a	16	0.97 (0.86 to 1.10)	0.91 (0.86 to 0.97)	NA
Atorvastatin 40 mg once daily 2-hydroxy-atorvastatin 4-hydroxy-atorvastatin	150 mg once daily ^a	16	1.35 (1.08 to 1.68) 1.58 (1.33 to 1.87) 1.28 (1.15 to 1.43)	1.04 (0.97 to 1.12) 1.39 (1.29 to 1.50) 1.23 (1.13 to 1.33)	0.85 (0.69 to 1.03) 1.32 (1.10 to 1.58) NA
Chlorzoxazone	150 mg	16	0.98	1.03	NA

500-mg single dose taken 2 hours after rilpivirine	once daily ^a		(0.85 to 1.13)	(0.95 to 1.13)	
Darunavir/ritonavir 800/100 mg once daily	150 mg once daily ^a	15	0.90 (0.81 to 1.00)	0.89 (0.81 to 0.99)	0.89 (0.68 to 1.16)
Didanosine 400 mg once daily delayed-release capsules taken 2 hours before rilpivirine	150 mg once daily ^a	13	0.96 (0.80 to 1.14)	1.12 (0.99 to 1.27)	NA
Digoxin 0.5-mg single dose	25 mg once daily	22	1.06 (0.97 to 1.17)	0.98 (0.93 to 1.04) ^c	NA
Ethinyl estradiol 0.035 mg once daily Norethindrone 1 mg once daily	25 mg once daily	17	1.17 (1.06 to 1.30) 0.94 (0.83 to 1.06)	1.14 (1.10 to 1.19) 0.89 (0.84 to 0.94)	1.09 (1.03 to 1.16) 0.99 (0.90 to 1.08)
Ketoconazole 400 mg once daily	150 mg once daily ^a	14	0.85 (0.80 to 0.90)	0.76 (0.70 to 0.82)	0.34 (0.25 to 0.46)
Lopinavir/ritonavir 400/100 mg twice daily (soft gel capsule)	150 mg once daily ^a	15	0.96 (0.88 to 1.05)	0.99 (0.89 to 1.10)	0.89 (0.73 to 1.08)
Methadone 60 to 100 mg once daily, individualized dose R(-) methadone S(+) methadone	25 mg once daily	13	 0.86 (0.78 to 0.95) 0.87 (0.78 to 0.97)	 0.84 (0.74 to 0.95) 0.84 (0.74 to 0.96)	 0.78 (0.67 to 0.91) 0.79 (0.67 to 0.92)
Metformin 850-mg single dose	25 mg once daily	20	1.02 (0.95 to -1.10)	0.97 (0.90 to 1.06) ^b	NA
Raltegravir 400 mg twice daily	25 mg once daily	23	1.10 (0.77 to 1.58)	1.09 (0.81 to 1.47)	1.27 (1.01 to 1.60)
Rifampin 600 mg once daily 25-desacetyl rifampin	150 mg once daily ^a	16	1.02 (0.93 to 1.12) 1.00 (0.87 to 1.15)	0.99 (0.92 to 1.07) 0.91 (0.77 to 1.07)	NA NA
Sildenafil	75 mg	16	0.93	0.97	NA

50-mg single dose	once daily ^a		(0.80 to 1.08)	(0.87 to 1.08)	
<i>N</i> -desmethyl-sildenafil			0.90 (0.80 to 1.02)	0.92 (0.85 to 0.99) ^c	NA
Tenofovir disoproxil fumarate 300 mg once daily	150 mg once daily ^a	16	1.19 (1.06 to 1.34)	1.23 (1.16 to 1.31)	1.24 (1.10 to 1.38)

n = Maximum number of subjects with data, CI = Confidence Interval, NA = Not available.

^a This interaction study has been performed with a dose higher than the recommended dose for rilpivirine (25 mg once daily) assessing the maximal effect on the coadministered drug.

^b n = (maximum number of subjects with data) for AUC_(0-∞) = 15.

^c AUC_(0-last).

12.4 Microbiology

Mechanism of Action

Cabotegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration that is essential for the HIV replication cycle. The mean 50% inhibitory concentration (IC₅₀) value of cabotegravir in a strand transfer assay using purified recombinant HIV-1 integrase was 3.0 nM.

Rilpivirine is a diarylpyrimidine NNRTI of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular DNA polymerases α , β , and γ .

Antiviral Activity in Cell Culture

Cabotegravir exhibited antiviral activity against laboratory strains of HIV-1 (subtype B, n = 4) with mean 50 percent effective concentration (EC₅₀) values of 0.22 to 1.7 nM in peripheral blood mononuclear cells (PBMCs) and 293 cells. Cabotegravir demonstrated antiviral activity in PBMCs against a panel of 24 HIV-1 clinical isolates (3 in each of group M subtypes A, B, C, D, E, F, and G and 3 in group O) with a median EC₅₀ value of 0.19 nM (range: 0.02 to 1.06 nM, n = 24). The median EC₅₀ value against subtype B clinical isolates was 0.05 nM (range: 0.02 to 0.50 nM, n = 3). Against clinical HIV-2 isolates, the median EC₅₀ value was 0.12 nM (range: 0.10 to 0.14 nM, n = 3).

Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC₅₀ value for HIV-1_{IIIB} of 0.73 nM (0.27 ng/mL). Rilpivirine demonstrated antiviral activity against a broad panel of HIV-1 group M (subtypes A, B, C, D, F, G, and H) primary isolates with EC₅₀ values ranging from 0.07 nM to 1.01 nM (0.03 to 0.37 ng/mL) and was less active against group O primary isolates with EC₅₀ values ranging from 2.88 nM to 8.45 nM (1.06 to 3.10 ng/mL).

In cell culture, cabotegravir was not antagonistic in combination with the NNRTI rilpivirine, or the nucleoside reverse transcriptase inhibitors (NRTIs) emtricitabine (FTC), lamivudine (3TC), or tenofovir disoproxil fumarate (TDF).

The antiviral activity of rilpivirine was not antagonistic when combined with the NNRTIs efavirenz, etravirine, or nevirapine; the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine; the protease inhibitors amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir; the fusion inhibitor enfuvirtide; the CCR5 co-receptor antagonist maraviroc, or the INSTI raltegravir.

Resistance

Cell Culture: Cabotegravir-resistant viruses were selected during passage of HIV-1 strain IIIB in MT-2 cells in the presence of cabotegravir. Amino acid substitutions in integrase that emerged and conferred decreased susceptibility to cabotegravir included Q146L (fold change: 1.3 to 4.6), S153Y (fold change: 2.8 to 8.4), and I162M (fold change: 2.8). The integrase substitution T124A also emerged alone (fold change: 1.1 to 7.4 in cabotegravir susceptibility), in combination with S153Y (fold change: 3.6 to 6.6 in cabotegravir susceptibility) or I162M (2.8-fold change in cabotegravir susceptibility). Cell culture passage of virus harboring integrase substitutions Q148H, Q148K, or Q148R selected for additional substitutions (C56S, V72I, L74M, V75A, T122N, E138K, G140S, G149A, and M154I), with substituted viruses having reduced susceptibility to cabotegravir of 2.0- to 410-fold change. The combinations of E138K+Q148K and V72I+E138K+Q148K conferred the greatest reductions of 53- to 260-fold change and 410-fold change, respectively.

Rilpivirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes as well as NNRTI-resistant HIV-1. The frequently observed amino acid substitutions that emerged and conferred decreased phenotypic susceptibility to rilpivirine included L100I; K101E; V106I and A; V108I; E138K and G, Q, R; V179F and I; Y181C and I; V189I; G190E; H221Y; F227C; and M230I and L.

Clinical Trials: In the pooled Phase 3 FLAIR (Week 124) and ATLAS (Week 96) analysis, there were 8 confirmed virologic failures (2 consecutive HIV-1 RNA \geq 200 copies/mL) on cabotegravir plus rilpivirine (8/591, 1.4%) and 8 confirmed virologic failures on current antiretroviral regimen (8/591, 1.4%). Of the 8 confirmed virologic failures in the cabotegravir plus rilpivirine arm, 7 (88%) had treatment-emergent NNRTI resistance-associated substitutions K101E, V106V/A, V108I, E138A, E138G, E138K, H221H/L, or M230L in reverse transcriptase, and 6 of them showed reduced phenotypic susceptibility to rilpivirine (range: 2- to 27-fold). One additional subject in the ATLAS Extension Switch on cabotegravir plus rilpivirine had emergent NNRTI resistance substitution E138A at Week 80 with HIV-1 RNA >50 copies/mL and <200 copies/mL.

Additionally, 5 of the 8 (63%) cabotegravir plus rilpivirine confirmed virologic failures had treatment-emergent INSTI resistance-associated substitutions and reduced phenotypic

susceptibility to cabotegravir: Q148R (n = 2; 5- and 9-fold decreased susceptibility to cabotegravir), G140R (n = 1; 7-fold decreased susceptibility to cabotegravir), N155H (n = 1; 3-fold decreased susceptibility to cabotegravir), or N155H+R263K (n = 1; 9-fold decreased susceptibility to cabotegravir).

There was another confirmed virologic failure subject at Week 112 in FLAIR who had switched to cabotegravir plus rilpivirine direct to injection at Week 100; there were no INSTI resistance-associated substitutions detected at failure.

In comparison, in the current antiretroviral regimen arm with 8 confirmed virologic failures, 2 of 7 (29%) who had post-baseline resistance data had treatment-emergent resistance substitutions and phenotypic resistance to their antiretroviral drugs; both had treatment-emergent NRTI substitutions, M184V or I, which conferred resistance to emtricitabine or lamivudine in their regimen, and one of them also had the treatment-emergent NNRTI resistance substitution G190S, which conferred resistance to efavirenz in their regimen.

In the ATLAS-2M trial, there were 11 confirmed virologic failures (2 consecutive HIV-1 RNA ≥ 200 copies/mL) through Week 48: 9 subjects (1.7%) in the every-2-month treatment arm and 2 subjects (0.4%) in the monthly treatment arm. Of note, 8 of the 11 (73%) subjects met confirmed virologic failure criteria at or before the Week 24 injection visit.

Four of the 9 confirmed virologic failure subjects in the every-2-month arm transitioned from the oral current antiretroviral regimen arm of ATLAS into this trial.

In the every-2-month treatment arm, 8 of 9 (89%) confirmed virologic failure subjects had NNRTI resistance-associated substitutions (E138E/K+V179V/I, K101E+E138A, A98G+K103N, E138K, V179I+Y188L+P225H, Y188L, K103N+E138A, or K101E) at virologic failure. Decreases in rilpivirine susceptibility for these 8 subject isolates ranged from 2- to 30-fold. Six of the 8 subjects with NNRTI resistance-associated substitutions also had INSTI resistance-associated substitutions (L74I+Q148Q/R+N155N/H (n = 2), L74I+T97A+N155H, L74I+N155H, N155H, or L74I+Q148R) at failure with cabotegravir fold changes ranging from 1- to 9-fold. The INSTI polymorphism L74I was detected at baseline in 5 of the virologic failure subjects by a HIV-1 proviral DNA assay.

In the monthly treatment arm, both of the confirmed virologic failure subjects had NNRTI resistance-associated substitutions (K101E+M230L or Y188F+G190Q) at virologic failure with decreased susceptibility to rilpivirine of 17- and >119.2 -fold, respectively. Both subjects also had INSTI resistance-associated substitutions (N155N/H or Q148R+E138E/K) at failure with decreased susceptibility to cabotegravir of 2- and 5-fold, respectively. Neither subject had the L74I integrase polymorphism at baseline.

Genotypic Baseline Factors Associated with Virologic Failure

An increased risk of cabotegravir plus rilpivirine confirmed virologic failure is associated with baseline virological factors: HIV-1 subtype A1, the presence of baseline integrase L74I polymorphism, and archived NNRTI resistance-associated substitutions.

Association of Subtype A1 and Baseline L74I Polymorphism in Integrase with Cabotegravir plus Rilpivirine Virologic Failure

Eight of the 18 (44%) cabotegravir plus rilpivirine confirmed virologic failures in FLAIR, ATLAS, and ATLAS-2M had HIV-1 subtype A1 with 7 of the 8 subtype A1 failures having the integrase polymorphism L74I detected at baseline and failure timepoints (Table 16). There was no detectable phenotypic resistance to cabotegravir conferred by the presence of L74I at baseline. Subtype A1 is uncommon in the U.S.

The presence of the integrase polymorphism L74I in subtype B commonly seen in the U.S. was not associated with virologic failure. In contrast to FLAIR and ATLAS, where all virologic failures were subtype A, A1, or AG, subtypes of the cabotegravir plus rilpivirine virologic failures in ATLAS-2M included A (n = 1), A1 (n = 3), B (n = 4), C (n = 2), and complex/A1 (n = 1).

Association of Archived Baseline NNRTI Substitutions with Cabotegravir plus Rilpivirine Virologic Failure

The presence of archived NNRTI resistance-associated substitutions at baseline detected using an exploratory HIV-1 proviral DNA assay was associated with a higher virologic failure rate in the every-2-month arm of ATLAS-2M and in the cabotegravir plus rilpivirine arm (monthly) of ATLAS compared to without archived NNRTI resistance-associated substitutions (Table 16). However, in clinical practice, it is unlikely baseline resistance testing will be performed on virologically suppressed patients (HIV-1 RNA <50 copies/mL). Thus, in patients with an incomplete or uncertain NNRTI treatment history, consideration should be given before starting cabotegravir plus rilpivirine treatment.

Table 16. Rate of Confirmed Virologic Failure in FLAIR, ATLAS, and ATLAS-2M: Baseline^a Analysis (Subtype A1, Presence of Integrase Polymorphism L74I, and Presence of Archived NNRTI Resistance-Associated Substitutions)

	FLAIR CAB+RPV N = 283	FLAIR CAR N = 283	ATLAS CAB+RPV N = 308	ATLAS CAR N = 308	ATLAS-2M Q4W N = 523	ATLAS-2M Q8W N = 522
Total confirmed virologic failures	5	4	3	4	2	9
Subtype A1^b	4/8 (50%)	1/4 (25%)	1/17 (6%)	0/21 (0%)	0/30 (0%)	4/31 (13%)
+L74I^c	4/5 (80%)	1/3 (33%)	1/16 (6%)	0/19 (0%)	2/28 (0%)	3/26 (12%)
-L74I	0/3 (0%)	0/1 (0%)	0/1 (0%)	0/2 (0%)	0/2 (0%)	1/5 (20%)
Other subtypes	2/268 (0.7%)	3/272 (1%)	2/240 (0.8%)	4/252 (1.6%)	2/409 (0.5%)	5/415 (1.2%)
+L74I^c	0/49 (0%)	1/43 (2.3%)	1/29 (3%)	1/39 (2.6%)	0/42 (0%)	2/48 (4%)
-L74I	0/219 (2.5%)	2/229 (0.9%)	1/211 (0.5%)	3/213 (1.4%)	2/367 (0.5%)	3/367 (0.8%)
Missing data	7	7	51	35	84	76
With NNRTI RAS^d	NA	NA	3/78 (4%)	2/83 (2%)	1/128 (0.8%)	7/117 (6%)
Without NNRTI RAS	NA	NA	0/179 (0%)	2/190 (1%)	1/310 (0.3%)	2/327 (0.6%)
Missing data	NA	NA	51	35	84	76

NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor, CAB+RPV = Cabotegravir + Rilpivirine, CAR = Current Antiretroviral Regimen, RAS = resistance-associated substitutions, NA = Not available.

^a Baseline and/or Screening result used.

^b Per Standard Monogram Nomenclature Reports. Based on June 2020 Los Alamos National Library panel, the majority of HIV-1 subtype A1 was reclassified as HIV-1 subtype A6.

^c L74I and L74L/I mixture.

^d Baseline/Screening NNRTI substitutions at L100, K101, K103, V106, V108, E138, V179, Y181, Y188, G190, H221, P225, M230.

Cross-Resistance

Virologic failure isolates from cabotegravir plus rilpivirine treatment in FLAIR, ATLAS, and ATLAS-2M exhibited cross-resistance to INSTIs and NNRTIs. All confirmed virologic isolates with genotypic evidence of cabotegravir resistance had cross-resistance to elvitegravir and

raltegravir but retained phenotypic susceptibility to dolutegravir and when tested bictegravir. Virologic failure isolates with rilpivirine resistance had cross-resistance with NNRTIs delavirdine, doravirine, efavirenz, etravirine, and nevirapine.

Cabotegravir: Cross-resistance has been observed among INSTIs. Cabotegravir had reduced susceptibility (>5-fold change) to recombinant HIV-1 strain NL432 viruses harboring the following integrase amino acid substitutions: G118R, Q148K, Q148R, T66K+L74M, E92Q+N155H, E138A+Q148R, E138K+Q148K/R, G140C+Q148R, G140S+Q148H/K/R, Y143H+N155H, and Q148R+N155H (range: 5.1- to 81-fold). The substitutions E138K+Q148K and Q148R+N155H conferred the greatest reductions in susceptibility of 81- and 61-fold, respectively.

Cabotegravir was active against viruses harboring the NNRTI substitutions K103N or Y188L, or the NRTI substitutions M184V, D67N/K70R/T215Y, or V75I/F77L/F116Y/Q151M.

Rilpivirine: Cross-resistance has been observed among NNRTIs. The single NNRTI substitutions K101P, Y181I, and Y181V conferred 52-, 15-, and 12-times fold change to rilpivirine, respectively. The K103N substitution did not show reduced susceptibility to rilpivirine by itself. Combinations of 2 or 3 NNRTI resistance-associated substitutions gave 3.7- to 554-fold change to rilpivirine in 38% and 66% of substitutions, respectively. Considering all available cell culture and clinical data, any of the following amino acid substitutions, when present at baseline, are likely to decrease the antiviral activity of rilpivirine: K101E and P; E138A, G, K, R, and Q; V179L; Y181C, I, and V; Y188L; H221Y; F227C; M230I and L, and the combination of L100I/K103N.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies in mice and rats were conducted with cabotegravir. In mice, no drug-related increases in tumor incidence were observed at cabotegravir exposures (AUC) up to approximately 8 times (males) and 7 times (females) higher than those in humans at the RHD. In rats, no drug-related increases in tumor incidence were observed at cabotegravir exposures up to approximately 26 times higher than those in humans at the RHD.

Two-year carcinogenicity studies in mice and rats were conducted with rilpivirine. In mice, rilpivirine was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific. At the lowest tested dose in the mouse carcinogenicity study, the systemic exposure to rilpivirine was 21 times that observed in humans at the RHD. In rats, no drug-related neoplasms were observed at exposures 3 times those observed in humans at the RHD.

Mutagenesis

Cabotegravir and rilpivirine were not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

Impairment of Fertility

In rats, no effects on fertility were observed at cabotegravir exposures (AUC) >20 times (male) and 28 times (female) the exposure in humans at the RHD. Similarly, no effects on fertility were observed in rats at rilpivirine exposures (AUC) >36 times (male) and 40 times (female) the exposure in humans at the RHD.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adults

Monthly Dosing Trials

The efficacy of CABENUVA has been evaluated in 2 Phase 3 randomized, multicenter, active-controlled, parallel-arm, open-label, non-inferiority trials:

- Trial 201584 (FLAIR [NCT02938520]), (n = 629): HIV-1–infected, antiretroviral treatment (ART)-naïve subjects received a dolutegravir INSTI-containing regimen for 20 weeks (either dolutegravir/abacavir/lamivudine or dolutegravir plus 2 other NRTIs if subjects were HLA-B*5701 positive). Subjects who were virologically suppressed (HIV-1 RNA <50 copies/mL, n = 566) were then randomized (1:1) to receive either a cabotegravir plus rilpivirine regimen or remain on the current antiretroviral regimen. Subjects randomized to receive cabotegravir plus rilpivirine initiated treatment with daily oral lead-in dosing with one 30-mg VOCABRIA (cabotegravir) tablet plus one 25-mg EDURANT (rilpivirine) tablet for at least 4 weeks followed by monthly injections with CABENUVA for an additional 44 weeks [*see Dosage and Administration (2.2, 2.3)*].
- Trial 201585 (ATLAS [NCT02951052]), (n = 616): HIV-1–infected, ART-experienced, virologically-suppressed (for at least 6 months; median prior treatment duration was 4.3 years) subjects (HIV-1 RNA <50 copies/mL) were randomized and received either a cabotegravir plus rilpivirine regimen or remained on their current antiretroviral regimen. Subjects randomized to receive cabotegravir plus rilpivirine initiated treatment with daily oral lead-in dosing with one 30-mg VOCABRIA (cabotegravir) tablet plus one 25-mg EDURANT (rilpivirine) tablet for at least 4 weeks followed by monthly injections with CABENUVA for an additional 44 weeks [*see Dosage and Administration (2.2, 2.3)*].

The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the trial prematurely.

At baseline, in FLAIR and ATLAS the median age was 34 years and 40 years, 22% and 32% were female, and 24% and 31% were non-White, respectively. In both studies, 7% had CD4+ cell count <350 cells/mm³; these characteristics were similar between treatment arms. In

ATLAS, subjects received an NNRTI (50%), integrase inhibitor (33%), or protease inhibitor (17%) as their baseline third-agent class prior to randomization; this was similar between treatment arms. Subjects with hepatitis B co-infection were excluded from the trial.

The primary endpoint of FLAIR and ATLAS was the proportion of subjects with plasma HIV-1 RNA ≥ 50 copies/mL at Week 48.

The primary endpoint and other Week 48 outcomes, including outcomes by key baseline factors, for FLAIR and ATLAS are shown in Tables 17 and 18.

Table 17. Virologic Outcomes of Randomized Treatment in FLAIR and ATLAS Trials at Week 48

Virologic Outcomes	FLAIR Monthly Dosing		ATLAS Monthly Dosing	
	CAB plus RPV (n = 283)	CAR (n = 283)	CAB plus RPV (n = 308)	CAR (n = 308)
HIV-1 RNA ≥ 50 copies/mL^a	2%	2%	2%	1%
Treatment difference	-0.4% (95% CI: -2.8%, 2.1%)		0.7% (95% CI: -1.2%, 2.5%)	
HIV-1 RNA <50 copies/mL	94%	93%	93%	95%
No virologic data at Week 48 window	4%	4%	6%	4%
Discontinued due to adverse event or death	3%	<1%	4%	2%
Discontinued for other reasons	1%	4%	2%	2%
Missing data during window but on study	0	0	0	0

CAB = Cabotegravir, RPV = Rilpivirine, CAR = Current Antiretroviral Regimen, n = Number of subjects in each treatment group, CI = Confidence interval.

^a Includes subjects who discontinued for lack of efficacy and discontinued while not suppressed.

Adjusted for study and randomization stratification factors, treatment difference of HIV-1 RNA ≥ 50 copies/mL for the pooled data was 0.2% with 95% CI (-1.4%, 1.7%).

Table 18. Proportion of Subjects in FLAIR and ATLAS Trials with Plasma HIV-1 RNA ≥ 50 copies/mL at Week 48 for Key Baseline Factors

Baseline Factors	FLAIR Monthly Dosing		ATLAS Monthly Dosing	
	CAB plus RPV (N = 283) n/N (%)	CAR (N = 283) n/N (%)	CAB plus RPV (N = 308) n/N (%)	CAR (N = 308) n/N (%)
Baseline CD4+ (cells/mm³)				
<350	0/19	1/27 (4%)	0/23	1/27 (4%)
≥ 350 to <500	3/64 (5%)	0/60	2/56 (4%)	0/60
≥ 500	3/200 (2%)	6/196 (3%)	3/299 (1%)	2/224 (<1%)
Gender				
Male	3/220 (1%)	6/219 (3%)	3/209 (1%)	3/204 (1%)
Female	3/63 (5%)	1/64 (2%)	2/99 (2%)	0/104
Race				
White	6/216 (3%)	5/201 (2%)	3/214 (1%)	2/207 (<1%)
African American/African Heritage	0/47	2/56 (4%)	2/62 (3%)	1/77 (1%)
Asian/Other	0/20	0/24	0/32	0/24
Body mass index				
<30 kg/m ²	3/243 (1%)	7/246 (3%)	3/248 (1%)	1/242 (<1%)
≥ 30 kg/m ²	3/40 (8%)	0/37	2/60 (3%)	2/66 (3%)
Age (years)				
<50	5/250 (2%)	6/254 (2%)	4/242 (2%)	2/212 (<1%)
≥ 50	1/33 (3%)	1/29 (3%)	1/66 (2%)	1/96 (1%)
Baseline antiviral therapy at randomization				
Protease inhibitor-containing regimen	0	0	1/51 (2%)	0/54
Integrase inhibitor-containing regimen	6/283 (2%)	7/283 (2%)	0/102	2/99 (2%)
Non-nucleoside reverse transcriptase inhibitor-containing regimen	0	0	4/155 (3%)	1/155 (<1%)

CAB = Cabotegravir, RPV = Rilpivirine, CAR = Current Antiretroviral Regimen.

Subjects in both the FLAIR and ATLAS trials were virologically suppressed prior to Day 1 or at study entry, respectively, and no clinically relevant change from baseline in CD4+ cell counts was observed.

In FLAIR at Week 96, the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL was 3.2 % for both the cabotegravir plus rilpivirine (n = 283) and current antiretroviral regimen (n = 283) treatment arms; adjusted treatment difference was 0.0% with 95% CI (-2.9%, 2.9%). The proportion of subjects with HIV-1 RNA <50 copies/mL was 87% and 89% for the cabotegravir plus rilpivirine and the current antiretroviral regimen arms, respectively; adjusted treatment difference was -2.8% with 95% CI (-8.2%, 2.5%).

Optional Oral Lead-In: FLAIR Extension Phase

In the FLAIR study during the Extension Phase (Week 100 to Week 124), the efficacy of CABENUVA was evaluated in patients who switched (at Week 100) from their current antiretroviral regimen to CABENUVA, with and without an oral lead-in phase. A total of 121 subjects chose to start the treatment with oral lead-in and 111 subjects chose direct to injection. Subjects were not randomized during the Extension Phase. At Week 124, the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL was 0.8% and 0.9% for the oral lead-in and direct to injection groups, respectively. The rates of virologic suppression (HIV-1 RNA <50 copies/mL) were similar in both the oral lead-in (93%) and direct to injection (99%) groups.

Every-2-Month Dosing Trial

The efficacy of CABENUVA dosed every 2 months has been evaluated in 1 Phase 3b randomized, multicenter, parallel-arm, open-label, non-inferiority trial:

- Trial 207966 (ATLAS-2M [NCT03299049]), (n = 1,045): HIV-1–infected, ART-experienced, virologically suppressed subjects, including 504 subjects from the ATLAS trial (randomized to CAB plus RPV [n = 253] or CAR [n = 251]; prior exposure to cabotegravir plus rilpivirine [n = 391]), were randomized and received a cabotegravir plus rilpivirine regimen administered as injection doses of cabotegravir 400 mg plus rilpivirine 600 mg either monthly or cabotegravir 600 mg plus rilpivirine 900 mg every 2 months. Subjects without prior exposure to cabotegravir plus rilpivirine initiated treatment with daily oral lead-in dosing with one 30-mg VOCABRIA (cabotegravir) tablet plus one 25-mg EDURANT (rilpivirine) tablet for at least 4 weeks followed by monthly or every-2-month injections with CABENUVA for an additional 44 weeks.

The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the study prematurely.

At baseline, the median age was 42 years, 27% were female, 27% were non-White, and 6% had a CD4+ cell count <350 cells per mm³; these characteristics were similar between the treatment arms. Subjects received either an NNRTI (29%), an integrase inhibitor besides cabotegravir plus rilpivirine (26%), a protease inhibitor (7%), or cabotegravir plus rilpivirine (37%) as their baseline third-agent class prior to randomization.

The primary endpoint of ATLAS-2M was the proportion of subjects with a plasma HIV-1 RNA ≥ 50 copies/mL at Week 48.

The primary endpoint and other Week 48 outcomes, including outcomes by key baseline factors, for ATLAS-2M are shown in Tables 19 and 20.

Table 19. Virologic Outcomes of Randomized Treatment in ATLAS 2-M Trial at Week 48

Virologic Outcomes	Cabotegravir plus Rilpivirine	
	Every-2-Month Dosing n = 522	Monthly Dosing n = 523
HIV-1 RNA ≥ 50 copies/mL^a	2%	1%
Treatment difference	0.8 (95% CI: -0.6%, 2.2%)	
HIV-1 RNA <50 copies/mL	94%	94%
No virologic data at Week 48 window	4%	6%
Discontinued study due to adverse event or death	2%	3%
Discontinued for other reasons	2%	3%
Missing data during window but on study	0	0

^a Includes subjects who discontinued for lack of efficacy, discontinued while not suppressed.
n = Number of subjects in each treatment group, CI = Confidence interval.

Table 20. Proportion of Subjects in ATLAS 2-M Trial with Plasma HIV-1 RNA ≥ 50 copies/mL at Week 48 for Key Baseline Factors

Baseline Factors	Cabotegravir plus Rilpivirine	
	Every-2-Month Dosing (N = 522) n/N (%)	Monthly Dosing (N = 523) n/N (%)
Baseline CD4+ (cells/mm³)		
<350	1/35 (3%)	1/27 (4%)
≥ 350 to <500	1/96 (1%)	0/89
≥ 500	7/391 (2%)	4/407 (1%)
Gender		
Male	4/385 (1%)	5/380 (1%)
Female	5/137 (4%)	0/143
Race		
White	5/370 (1%)	5/393 (1%)
Black/African American	4/101 (4%)	0/90
Asian/Other	0/51	0/40
Body mass index		
<30 kg/m ²	3/409 (1%)	3/425 (1%)
≥ 30 kg/m ²	6/113 (5%)	2/98 (2%)

Age (years)		
<35	4/137 (3%)	1/145 (1%)
35 to <50	3/242 (1%)	2/239 (1%)
≥50	2/143 (1%)	2/139 (1%)
Prior exposure to cabotegravir plus rilpivirine		
None	5/327 (2%)	5/327 (2%)
1 to 24 Weeks	3/69 (4%)	0/68
>24 Weeks	1/126 (1%)	0/128
Baseline third-agent class		
Protease inhibitor-containing regimen	1/40 (3%)	1/30 (3%)
Integrase inhibitor-containing regimen	3/136 (2%)	2/141 (1%)
NNRTI-containing regimen	1/151 (1%)	2/156 (1%)
Cabotegravir plus rilpivirine	4/195 (2%)	0/196

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

CABENUVA is supplied in 2 dosing kits. Each kit contains 1 vial of cabotegravir extended-release injectable suspension and 1 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 and Handling

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.

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; do not put back into the refrigerator. If not used within 6 hours, they must be discarded.

Once the suspensions have been drawn into the respective syringes, the injections should be administered as soon as possible, but may remain in the syringes for up to 2 hours. The filled syringes should not be placed in the refrigerator. If the medicines remain in the syringes for more than 2 hours, the filled syringes and needles must be discarded [*see Dosage and Administration (2.9)*].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Advise patients to immediately contact their healthcare provider if they develop a rash. Instruct patients to immediately stop taking CABENUVA and seek medical attention if they develop a rash associated with any of the following symptoms, as it may be a sign of a more serious reaction such as DRESS or severe hypersensitivity: fever; generally ill feeling; extreme tiredness; muscle or joint aches; blisters; oral blisters or lesions; eye inflammation; facial swelling; swelling of the eyes, lips, tongue, or mouth; difficulty breathing; and/or signs and symptoms of liver problems (e.g., yellowing of the skin or whites of the eyes; dark or tea-colored urine; pale-colored stools or bowel movements; nausea; vomiting; loss of appetite; or pain, aching, or sensitivity on the right side below the ribs). Advise patients that if hypersensitivity occurs, they will be closely monitored, laboratory tests will be ordered, and appropriate therapy will be initiated [*see Warnings and Precautions (5.1)*].

Adverse Reactions Following Injections

Advise patients that injection site reactions have been reported in the majority of patients receiving CABENUVA. These local reactions typically consist of one or more of the following: pain, erythema, tenderness, pruritus, and local swelling. Systemic reactions have also been reported, such as fever, musculoskeletal pain, and sciatica pain [*see Adverse Reactions (6.1)*]. Serious post-injection reactions were reported within minutes after the injection of rilpivirine, including dyspnea, bronchospasm, agitation, abdominal cramping, rash/urticaria, dizziness, flushing, sweating, oral numbness, changes in blood pressure, and back pain (e.g., back and chest). These events began to resolve within minutes after the injection. Advise patients that they will be observed briefly (approximately 10 minutes) after the injection. If they experience a post-injection reaction, they will be monitored and appropriate treatment administered [*see Warnings and Precautions (5.2)*].

Hepatotoxicity

Inform patients that hepatotoxicity has been reported with cabotegravir and rilpivirine, components of CABENUVA [see *Warnings and Precautions (5.3), Adverse Reactions (6.1)*]. Inform patients that monitoring for liver transaminases is recommended.

Depressive Disorders

Inform patients that depressive disorders (including depressed mood, depression, major depression, mood altered, mood swings, unusual mood, negative thoughts, suicidal ideation, suicide attempt) have been reported with at least one of the components of CABENUVA. Advise patients to seek prompt medical evaluation if they experience depressive symptoms [see *Warnings and Precautions (5.4), Adverse Reactions (6.1)*].

Drug Interactions

Inform patients that CABENUVA may interact with other drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort. CABENUVA is an extended-release injectable that may be systemically present for 12 months or longer. These residual concentrations are not expected to affect the exposures of antiretroviral drugs that are initiated after discontinuation of CABENUVA [see *Contraindications (4), Drug Interactions (7)*].

Adherence to CABENUVA

Counsel patients about the importance of continued medication adherence and scheduled visits to help maintain viral suppression and to reduce risk of loss of virologic response and development of resistance [see *Dosage and Administration (2.1), Warnings and Precautions (5.6)*].

Two Options for Dosing Frequency

Advise the patient that CABENUVA can be injected monthly or every 2 months after oral lead-in with cabotegravir and rilpivirine to assess tolerability. Discuss the two injection dosing frequency options with the patient prior to starting CABENUVA and decide which injection dosing frequency would be the most appropriate option for the patient [see *Dosage and Administration (2.1)*].

Missed Dose

Inform patients that CABENUVA can remain in the body for up to 12 months or longer after receiving their last injection. Advise patients that they should contact their healthcare provider if they miss or plan to miss a scheduled injection visit and that oral therapy with VOCABRIA and EDURANT may be used up to 2 months to replace missed injection visits, or any other fully suppressive oral antiretroviral regimen may be used until injections are resumed. Advise patients that if they stop treatment with CABENUVA, they will need to take other medicines to treat their HIV-1 infection [see *Dosage and Administration (2.2, 2.8), Warnings and Precautions (5.6)*].

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to CABENUVA during pregnancy. Patients who are of reproductive potential should be informed of the long duration of exposure of CABENUVA and that there is very limited clinical experience in human pregnancy [see *Warnings and Precautions (5.6)*, *Use in Specific Populations (8.1)*].

Lactation

Inform individuals with HIV-1 infection that the potential risks of breastfeeding include: (1) HIV 1 transmission (in HIV-1–negative infants), (2) developing viral resistance (in HIV-1–positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults [see *Use in Specific Populations (8.2)*].

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CBN:xPI

PHARMACIST—DETACH HERE AND GIVE LEAFLET TO PATIENT

PATIENT INFORMATION

CABENUVA [KAB-en-ew-vah]

(cabotegravir extended-release injectable suspension;
rilpivirine extended-release injectable suspension)
co-packaged for intramuscular use

What is CABENUVA?

CABENUVA is a prescription medicine that is used without other human immunodeficiency virus-1 (HIV-1) medicines to treat HIV-1 infection in people 12 years of age and older who weigh at least 77 pounds (35 kg) to replace their current HIV-1 medicines when their healthcare provider determines that they meet certain requirements.

HIV-1 is the virus that causes acquired immune deficiency syndrome (AIDS).

CABENUVA contains 2 different medicines:

- cabotegravir
- rilpivirine

It is not known if CABENUVA is safe and effective in children younger than 12 years of age or weighing less than 77 pounds (35 kg).

Do not receive CABENUVA if you:

- have ever had an allergic reaction to cabotegravir or rilpivirine.
- are taking any of the following medicines:
 - carbamazepine
 - oxcabazepine
 - phenobarbital
 - phenytoin
 - rifabutin
 - rifampin
 - rifapentine
 - dexamethasone (more than a single-dose treatment)
 - St John's wort (*Hypericum perforatum*)

Before you receive CABENUVA, tell your healthcare provider about all your medical conditions, including if you:

- have ever had a skin rash or an allergic reaction to medicines that contain cabotegravir or rilpivirine.
- have or have had liver problems, including hepatitis B or C infection.
- have or ever had kidney problems.
- have ever had mental health problems.
- are pregnant or plan to become pregnant. It is not known if CABENUVA will harm your unborn baby. CABENUVA can remain in your body for up to 12 months or longer after the last injection. Tell your healthcare provider if you become pregnant during or after treatment with CABENUVA.

Pregnancy Registry. There is a pregnancy registry for those who take CABENUVA during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. CABENUVA may pass into your breast milk. Talk to your healthcare provider about the following risks to your baby from breastfeeding during or after treatment with CABENUVA:

- the HIV-1 virus may pass to your baby if your baby does not have HIV-1 infection.
- the HIV-1 virus may become harder to treat if your baby has HIV-1 infection.
- your baby may get side effects from CABENUVA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with CABENUVA. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

You can ask your healthcare provider or pharmacist for a list of medicines that interact with CABENUVA.

Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take CABENUVA with other medicines.

How will I receive CABENUVA?

- Your healthcare provider will inject CABENUVA into the muscle of each side of your buttocks or on the same side of your buttocks at least 2 cm apart.
- You will receive CABENUVA as 2 injections (cabotegravir and rilpivirine), either one time every month or one time every 2 months.
- Before receiving your first injection doses of CABENUVA, your healthcare provider may have you take 1 VOCABRIA (cabotegravir) tablet and 1 EDURANT (rilpivirine) tablet 1 time a day for 1 month (at least 28 days). This will allow your healthcare provider to assess how well you tolerate these medicines.
- CABENUVA is a long-acting medicine and may stay in your system for 12 months or longer after your last injection.
- Stay under the care of a healthcare provider during treatment with CABENUVA. It is important that you attend your planned appointments to receive your injection doses of CABENUVA.
- If you miss or plan to miss a scheduled monthly or every-2-month injection of CABENUVA by more than 7 days, call your healthcare provider right away to discuss your treatment options.
- If you stop treatment with CABENUVA you will need to take other medicines to treat your HIV-1 infection and reduce the risk of developing viral resistance. Call your healthcare provider right away to discuss your treatment options.

What are the possible side effects of CABENUVA?

CABENUVA may cause serious side effects including:

- **Allergic reactions.** Call your healthcare provider right away if you develop a rash with CABENUVA. **Stop receiving CABENUVA and get medical help right away if you develop a rash with any of the following signs or symptoms:**
 - fever
 - generally ill feeling
 - tiredness
 - muscle or joint aches
 - trouble breathing
 - blisters or sores in mouth
 - blisters
 - redness or swelling of the eyes
 - swelling of the mouth, face, lips, or tongue
- **Post-injection reactions.** Post-injection reaction symptoms have happened within minutes in some people after receiving their rilpivirine injection. Most symptoms resolved within minutes after the injection. Symptoms of post-injection reactions may include:

- trouble breathing
- narrowing of airways
- stomach cramps
- sweating
- numbness of your mouth
- pain (e.g., back and chest)
- feeling anxious
- feeling warm
- rash
- feeling lightheaded or feeling like you are going to pass out (faint)
- blood pressure changes

- **Liver problems.** Liver problems have happened in people with or without history of liver problems or other risk factors. Your healthcare provider may do blood tests to check your liver function. People with a history of liver problems or people who have certain liver function test changes may have an increased risk of developing new or worsening changes in certain liver tests during treatment with CABENUVA.

Call your healthcare provider right away if you develop any of the following signs or symptoms of liver problems:

- your skin or the white part of your eyes turns yellow (jaundice)
- dark or “tea-colored” urine
- light-colored stools (bowel movements)
- nausea or vomiting
- loss of appetite
- pain, aching, or tenderness on the right side-of your stomach area
- itching

- **Depression or mood changes. Call your healthcare provider or get emergency medical help right away if you develop any of the following symptoms:**

- feeling sad or hopeless
- feeling anxious or restless
- have thoughts of hurting yourself (suicide) or have tried to hurt yourself

The most common side effects of CABENUVA include:

- pain, tenderness, hardened mass or lump, swelling, redness, itching, bruising, and warmth at the injection site
- fever
- tiredness
- headache
- muscle or bone pain
- nausea
- sleep problems
- dizziness
- rash

These are not all the possible side effects of CABENUVA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of CABENUVA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about CABENUVA that is written for health professionals.

What are the ingredients in CABENUVA?

Cabotegravir extended-release injectable suspension:

Active ingredient: cabotegravir

Inactive ingredients: mannitol, polyethylene glycol (PEG) 3350, polysorbate 20, and Water for Injection.

Rilpivirine extended-release injectable suspension:

Active ingredient: rilpivirine

Inactive ingredients: citric acid monohydrate, poloxamer 338, Water for Injection, glucose monohydrate to ensure isotonicity, sodium dihydrogen phosphate monohydrate, and sodium hydroxide to adjust pH.

Manufactured for:



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For more information, go to www.cabenuva.com or call 1-877-844-8872.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 12/2023

INSTRUCTIONS FOR USE

CABENUVA
(KAB-en-ew-vah)

Cabotegravir extended-release
injectable suspension
400 mg/2 mL (200 mg/mL)

co-packaged with
Rilpivirine extended-release
injectable suspension
600 mg/2 mL (300 mg/mL)

For gluteal intramuscular use only.

Healthcare Professional
administration only.



Overview:

A complete dose of CABENUVA requires two injections: 400 mg (2 mL) of cabotegravir and 600 mg (2 mL) of rilpivirine.

Cabotegravir and rilpivirine are suspensions that do not need further dilution or reconstitution.

The preparation steps for both medicines are the same. Carefully follow these instructions when preparing the suspension for injection to avoid leakage.

Cabotegravir and rilpivirine are for gluteal intramuscular use only. Each injection must be administered to separate gluteal intramuscular sites (on opposite sides or at least 2 cm apart).

Note: The ventrogluteal site is recommended. **The administration order is not important.**





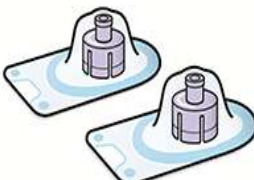
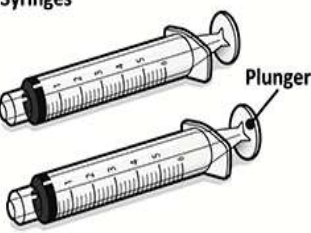
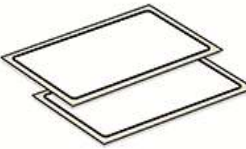
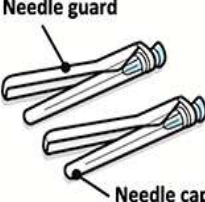
Storage information

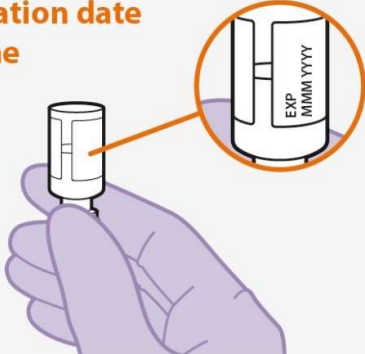


Store in refrigerator at 2°C to 8°C (36°F to 46°F).

Do not freeze.

Prior to administration:

- Before preparing the injections, the vials may sit in the carton at room temperature (maximum temperature of 25°C [77°F]) for up to 6 hours; do not put back into the refrigerator. If not used within 6 hours, the medicines must be discarded.
- Once the medicines have been drawn into the syringes, they can remain in the syringes for up to 2 hours before injection. The filled syringes should not be placed in the refrigerator. If the medicines remain in the syringes for more than 2 hours, the filled syringes and needles must be discarded.
- It is recommended to label each syringe with the time that the medicine has been drawn into the syringe if the medicine is not administered immediately.

<p>Cabotegravir vial</p>  <p>Vial cap (Rubber stopper under cap)</p>	<p>Rilpivirine vial</p>  <p>Vial cap (Rubber stopper under cap)</p>	<p>Vial adapters</p> 
<p>Syringes</p>  <p>Plunger</p>	<p>Syringes labels</p> 	<p>Injection needles</p>  <p>Needle guard Needle cap</p>
<p>Your pack contains:</p>		
<ul style="list-style-type: none"> • 1 vial of Cabotegravir • 1 vial of Rilpivirine • 2 vial adapters • 2 syringes • 2 syringe labels • 2 injection needles (23 gauge, 1½ inch) <p>Consider the patient's build and use medical judgment to select an appropriate injection needle length.</p>		
<p>You will also need:</p>		
<ul style="list-style-type: none"> • Non-sterile gloves • 4 alcohol wipes • 4 gauze pads • A suitable sharps container 		

Preparation:	
1. Inspect both vials.	
<p>Check expiration date and medicine</p>  <p>Figure A</p>	<ul style="list-style-type: none"> Check that the expiration date has not passed. See Figure A. Inspect the vials immediately. If you can see foreign matter, do not use the product. <p>Note: The Cabotegravir vial has a brown tint to the glass.</p> <p>Do not use if the expiration date has passed.</p>
2. Wait 15 minutes.	
 <p>Figure B</p>	<ul style="list-style-type: none"> Wait at least 15 minutes before you are ready to give the injection to allow the medicine to come to room temperature. See Figure B.
3. Shake the vial vigorously.	
 <p>Figure C</p>	<ul style="list-style-type: none"> Hold the vial firmly, and vigorously shake for a full 10 seconds. See Figure C. <p>Note: Vial preparation order is not important.</p>

4. Inspect suspension.

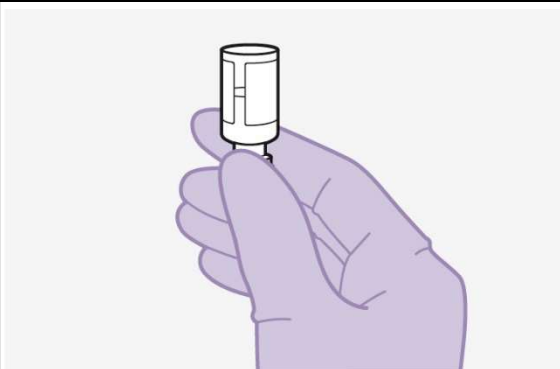


Figure D

- Invert the vial and confirm the suspension is uniform. It should look uniform. **See Figure D.**
- If the suspension is not uniform, shake the vial again.
- It is also normal to see small air bubbles.

5. Remove the vial cap.

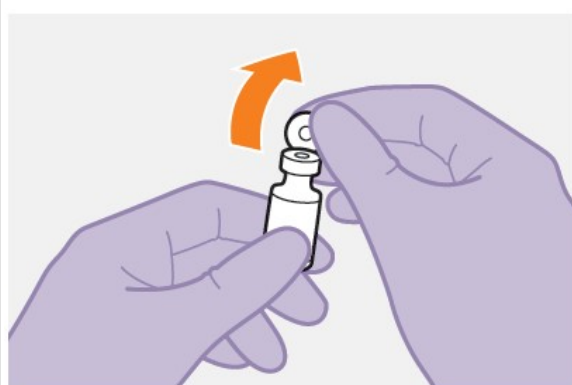


Figure E

- Remove the cap from the vial. **See Figure E.**
 - Wipe the rubber stopper with an alcohol wipe.
- Do not** allow anything to touch the rubber stopper after wiping it.

6. Peel open the vial adapter.

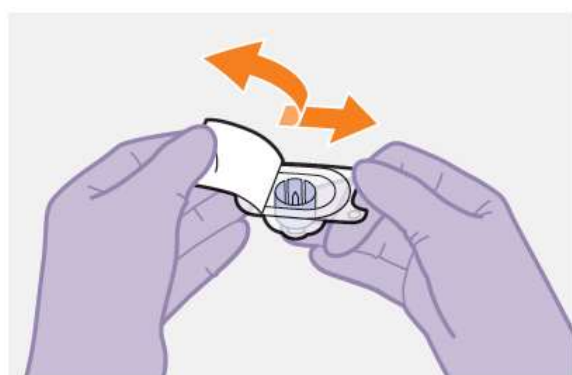


Figure F

- Peel off the paper backing from the vial adapter packaging. **See Figure F.**
- Note: Do not** remove the adapter from its packaging for the next step. The adapter **will not** fall out when its packaging is turned upside down.

7. Place vial on flat surface and attach the vial adapter.



Figure G

- Ensure the vial is upright and on a flat surface.
- Press the vial adapter straight down onto the vial, as shown.
- The vial adapter should click securely into place.

8. Lift off the packaging.



Figure H

- Lift off the vial adapter packaging, as shown. **See Figure H.**

9. Prepare the syringe.

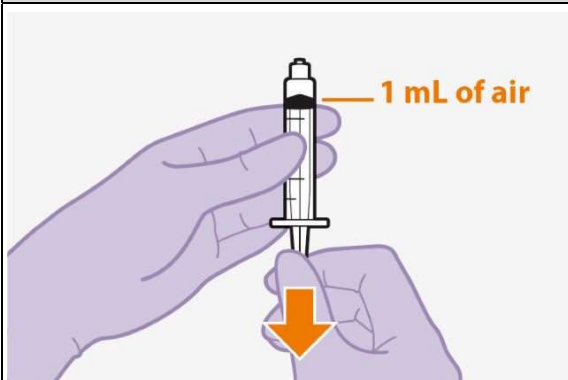


Figure I

- Remove the syringe from its packaging.
- Draw 1 mL of air into the syringe. This will make it easier to draw up the medicine later. **See Figure I.**

10. Attach the syringe.

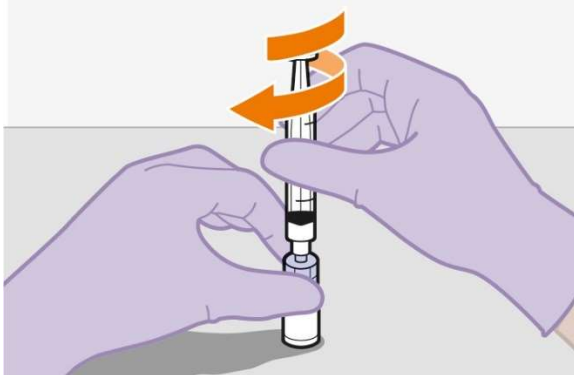


Figure J

- Hold the vial adapter and vial firmly, as shown.
- Screw the syringe firmly onto the vial adapter. **See Figure J.**

11. Press the plunger.

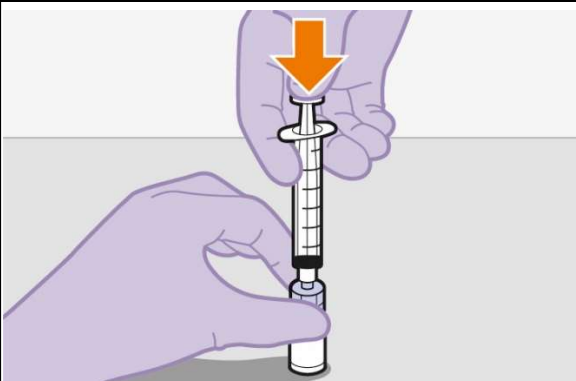


Figure K

- Press the plunger all the way down to push the air into the vial. **See Figure K.**

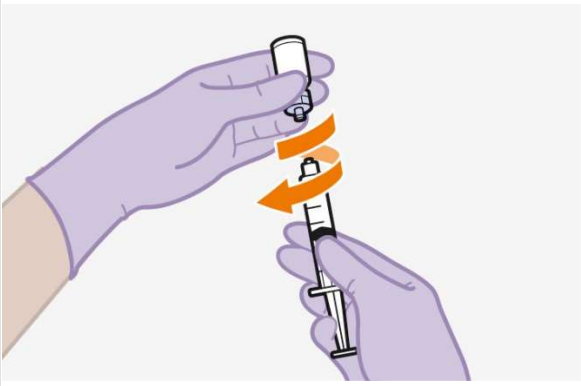
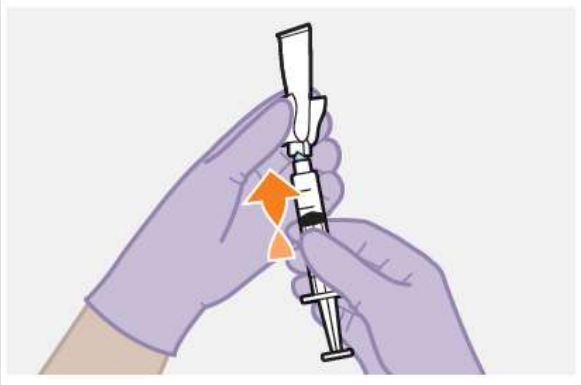

12. Slowly draw up the dose.



Figure L

- Invert the syringe and vial and slowly withdraw as much of the medicine as possible into the syringe. There may be more medicine than the dose amount. **See Figure L.**

Note: Keep the syringe upright to avoid leakage.

13. Unscrew the syringe.	
 <p>Figure M</p>	<ul style="list-style-type: none"> • Hold the syringe plunger firmly in place as shown to prevent leakage. It is normal to feel some back pressure. • Unscrew the syringe from the vial adapter, holding the vial adapter as shown. See Figure M. <p>Note: Check that the suspension looks uniform and milky white.</p>
14. Attach the needle and affix syringe label.	
 <p>Figure N</p>	<ul style="list-style-type: none"> • Peel open the needle packaging part way to expose the needle base. • Keeping the syringe upright, firmly twist the syringe onto the needle. • Remove the needle packaging from the needle. See Figure N. • Write the name of the medicine on the syringe label. Affix the label to the syringe making sure the gradations remain visible.
Injection:	
15. Prepare the injection site.	
 <p>Figure O</p>	<p>Injections must be administered to a gluteal site. See Figure O.</p> <p>Select from the following areas for the injection:</p> <ul style="list-style-type: none"> • Ventrogluteal, as shown (recommended) • Dorsogluteal, not shown (upper outer quadrant) <p>Note: For gluteal intramuscular use only. Do not inject intravenously.</p>

16. Remove the cap.

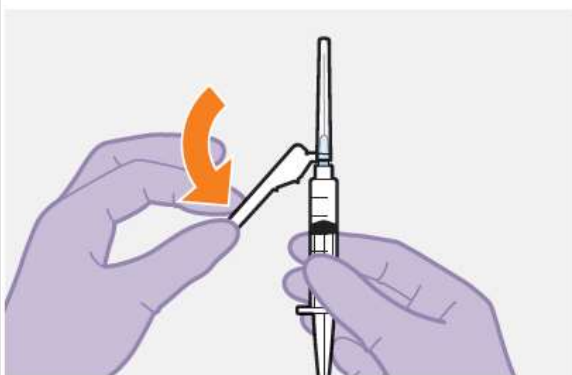


Figure P

- Fold the needle guard away from the needle. **See Figure P.**
- Pull off the injection needle cap.

17. Remove extra liquid from the syringe.

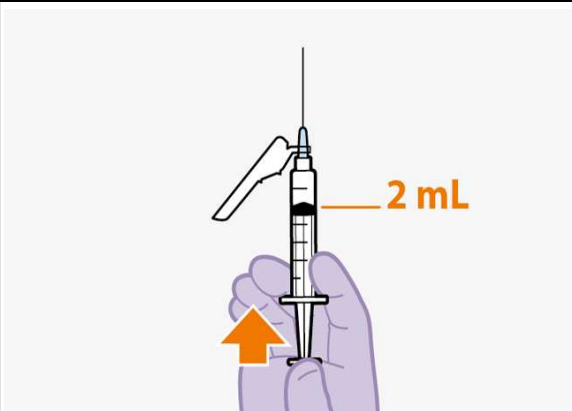


Figure Q

- Hold the syringe with the needle pointing up. Press the plunger to the 2-mL dosing mark to remove extra liquid and any air bubbles. **See Figure Q.**

Note: Clean the injection site with an alcohol wipe. Allow the skin to air dry before continuing.

18. Stretch the skin.



Figure R

Use the z-track injection technique to minimize medicine leakage from the injection site.

- Firmly drag the skin covering the injection site, displacing it by about an inch (2.5 cm). **See Figure R.**
- Keep it held in this position for the injection.

19. Insert the needle.

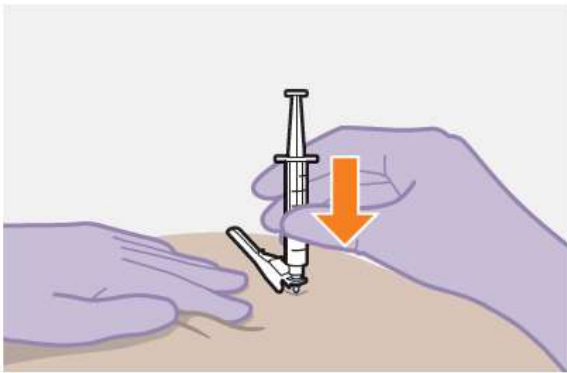


Figure S

- Insert the needle to its full depth, or deep enough to reach the muscle. **See Figure S.**

20. Inject the dose of medicine.

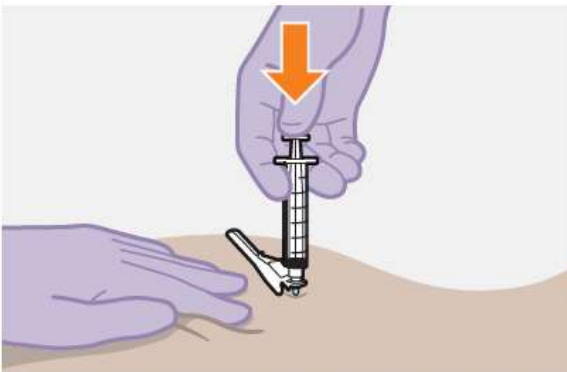


Figure T

- Still holding the skin stretched – slowly press the plunger all the way down. **See Figure T.**
- Ensure the syringe is empty.
- Withdraw the needle and release the stretched skin immediately.

21. Assess the injection site.

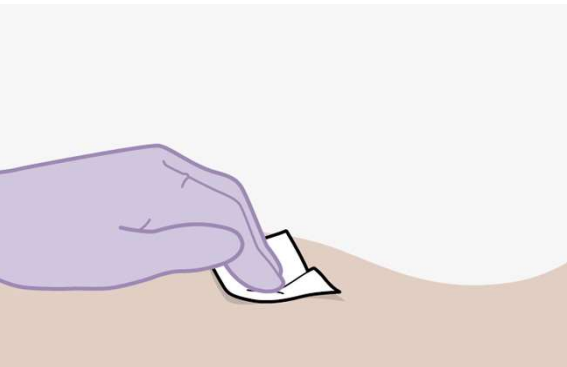


Figure U

- Apply pressure to the injection site using a gauze pad. **See Figure U.**
 - A small bandage may be used if bleeding occurs.
- Do not** massage the area.

22. Make the needle safe.

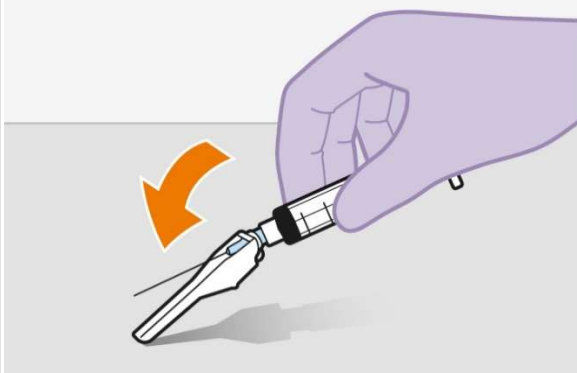


Figure V

- Fold the needle guard over the needle. **See Figure V.**

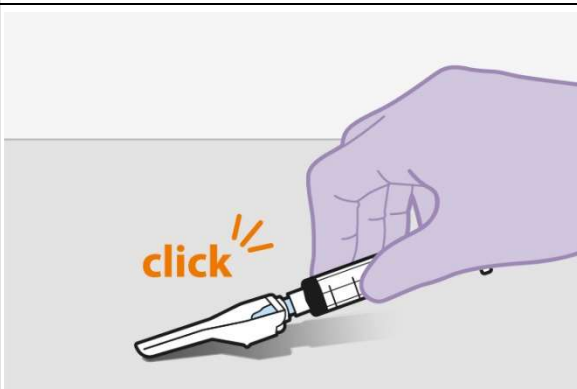


Figure W

- Gently apply pressure using a hard surface to lock the needle guard in place.
- The needle guard will make a click when it locks. **See Figure W.**


After injection:

23. Dispose safely.



Figure X

- Dispose of used needles, syringes, vials, and vial adapters according to local health and safety laws. **See Figure X.**

Repeat for 2nd medicine.	
 Repeat all steps for 2nd medicine	<ul style="list-style-type: none">• If you have not yet injected both medicines, use the same steps for preparation and injection of the other medicine.• The second medicine must be injected into a separate gluteal intramuscular site (on opposite sides or at least 2 cm apart).

Questions and Answers

1. How long can the medicines be left out of the refrigerator?

It is best to inject the medicines as soon as they reach room temperature. However, the vials may sit in the carton at room temperature (maximum temperature of 25°C [77°F]) for up to 6 hours; do not put back into the refrigerator. If not used within 6 hours, the medicines must be discarded.

2. How long can the medicines be left in the syringes?

It is best to inject the (room temperature) medicines as soon as possible after drawing them up. However, the medicines can remain in the syringes for up to 2 hours before injection. The filled syringes should not be placed in the refrigerator.

If the medicines remain in the syringes for more than 2 hours, the filled syringes and needles must be discarded.

3. Why do I need to inject air into the vials?

Injecting 1 mL of air into the vials makes it easier to draw up the medicines into the syringes. Without the air, some liquid may flow back into the vials unintentionally, leaving less medicine than intended in the syringes.

4. Does the order in which I give the medicines matter?

No, the order is unimportant.

5. Is it safe to warm the vials up to room temperature more quickly?

It is best to let the vials come to room temperature naturally. However, you can use the warmth of your hands to speed up the warm-up time, but make sure the vials do not get above 25°C (77°F).

Do not use any other heating methods.

Manufactured for:



ViiV Healthcare

Durham, NC 27701

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CBN:xIFU2

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised:12/2023

INSTRUCTIONS FOR USE

CABENUVA
(KAB-en-ew-vah)

Cabotegravir extended-release
injectable suspension
600 mg/3 mL (200 mg/mL)

co-packaged with

Rilpivirine extended-release
injectable suspension
900 mg/3 mL (300 mg/mL)

For gluteal intramuscular use only.

Healthcare Professional
administration only.



Overview:

A complete dose of CABENUVA requires two injections: 600 mg (3 mL) of cabotegravir and 900 mg (3 mL) of rilpivirine.

Cabotegravir and rilpivirine are suspensions that do not need further dilution or reconstitution.

The preparation steps for both medicines are the same. Carefully follow these instructions when preparing the suspension for injection to avoid leakage.

Cabotegravir and rilpivirine are for gluteal intramuscular use only. Each injection must be administered to separate gluteal intramuscular sites (on opposite sides or at least 2 cm apart).

Note: The ventrogluteal site is recommended. **The administration order is not important.**








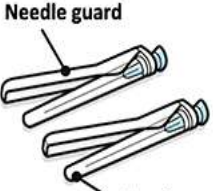
Storage information

Store in refrigerator at 2°C to 8°C (36°F to 46°F).

Do not freeze.

Prior to administration:

- Before preparing the injections, the vials may sit in the carton at room temperature (maximum temperature of 25°C [77°F]) for up to 6 hours; do not put back into the refrigerator. If not used within 6 hours, the medicines must be discarded.
- Once the medicines have been drawn into the syringes, they can remain in the syringes for up to 2 hours before injection. The filled syringes should not be placed in the refrigerator. If the medicines remain in the syringes for more than 2 hours, the filled syringes and needles must be discarded.
- It is recommended to label the syringe with each time that the medicine has been drawn into the syringe if the medicine is not administered immediately.

<p>Cabotegravir vial</p>  <p>Vial cap (Rubber stopper under cap)</p>	<p>Rilpivirine vial</p>  <p>Vial cap (Rubber stopper under cap)</p>	<p>Vial adapters</p> 
<p>Syringes</p>  <p>Plunger</p>	<p>Syringes labels</p> 	<p>Injection needles</p>  <p>Needle guard</p> <p>Needle cap</p>
<p>Your pack contains:</p> <ul style="list-style-type: none"> • 1 vial of Cabotegravir • 1 vial of Rilpivirine • 2 vial adapters • 2 syringes • 2 syringe labels • 2 injection needles (23 gauge, 1½ inch) <p>Consider the patient's build and use medical judgment to select an appropriate injection needle length.</p>		
<p>You will also need:</p> <ul style="list-style-type: none"> • Non-sterile gloves • 4 alcohol wipes • 4 gauze pads • A suitable sharps container 		

Preparation:

1. Inspect both vials.

Check expiration date and medicine

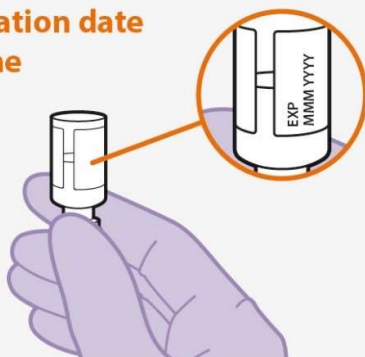


Figure A

- Check that the expiration date has not passed. **See Figure A.**
- Inspect the vials immediately. If you can see foreign matter, do not use the product.

Note: The Cabotegravir vial has a brown tint to the glass.

Do not use if the expiration date has passed.

2. Wait 15 minutes.



Figure B

- Wait at least 15 minutes before you are ready to give the injection to allow the medicine to come to room temperature. **See Figure B.**

3. Shake the vial vigorously.

10
secs



Figure C

- Hold the vial firmly, and vigorously shake for a full 10 seconds. **See Figure C.**

Note: Vial preparation order is not important.

4. Inspect suspension.

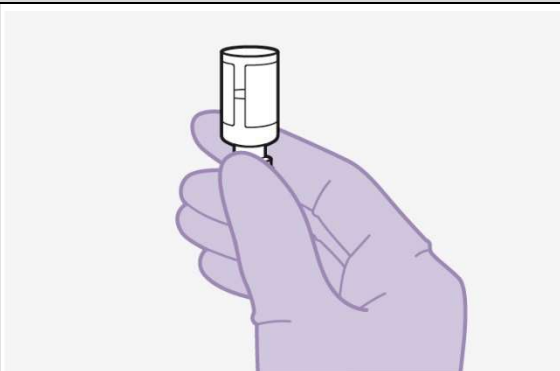


Figure D

- Invert the vial and confirm the suspension is uniform. It should look uniform. **See Figure D.**
- If the suspension is not uniform, shake the vial again.
- It is also normal to see small air bubbles.

5. Remove the vial cap.

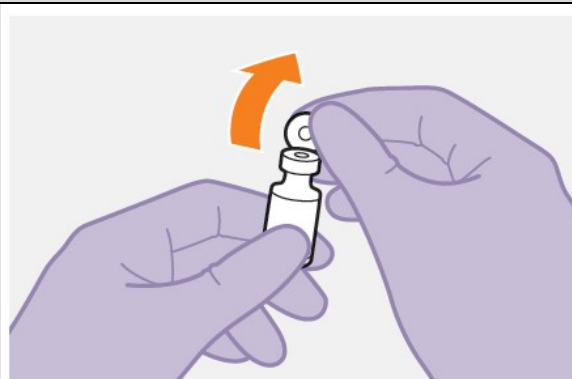


Figure E

- Remove the cap from the vial. **See Figure E.**
 - Wipe the rubber stopper with an alcohol wipe.
- Do not** allow anything to touch the rubber stopper after wiping it.

6. Peel open the vial adapter.

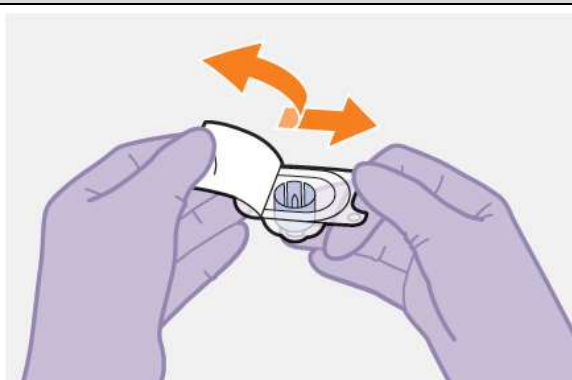


Figure F

- Peel off the paper backing from the vial adapter packaging. **See Figure F.**
- Note:** **Do not** remove the adapter from its packaging for the next step. The adapter **will not** fall out when its packaging is turned upside down.

7. Place vial on flat surface and attach the vial adapter.



Figure G

- Ensure the vial is upright and on a flat surface.
- Press the vial adapter straight down onto the vial, as shown.
- The vial adapter should click securely into place.

8. Lift off the packaging.



Figure H

- Lift off the vial adapter packaging, as shown. **See Figure H.**

9. Prepare the syringe.

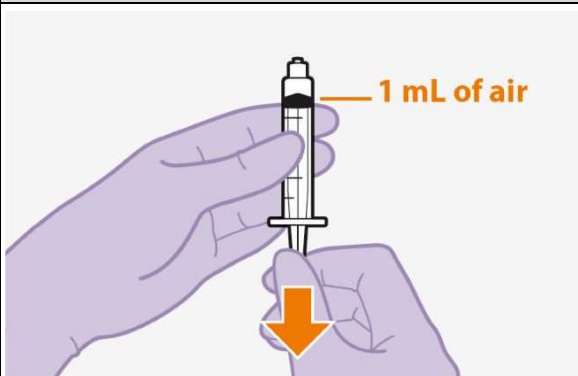


Figure I

- Remove the syringe from its packaging.
- Draw 1 mL of air into the syringe. This will make it easier to draw up the medicine later. **See Figure I.**

10. Attach the syringe.

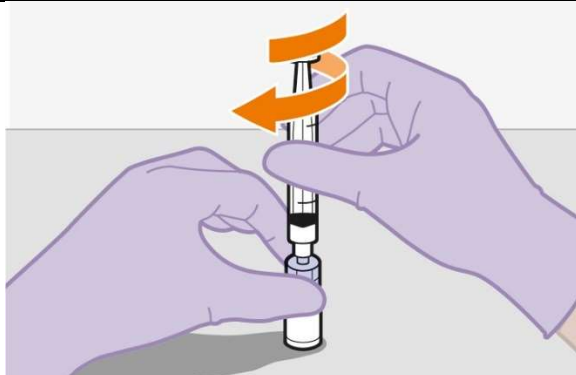


Figure J

- Hold the vial adapter and vial firmly, as shown.
- Screw the syringe firmly onto the vial adapter. **See Figure J.**

11. Press the plunger.

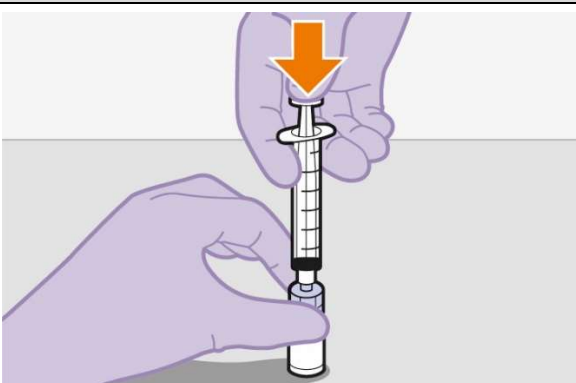


Figure K

- Press the plunger all the way down to push the air into the vial. **See Figure K.**

12. Slowly draw up the dose.

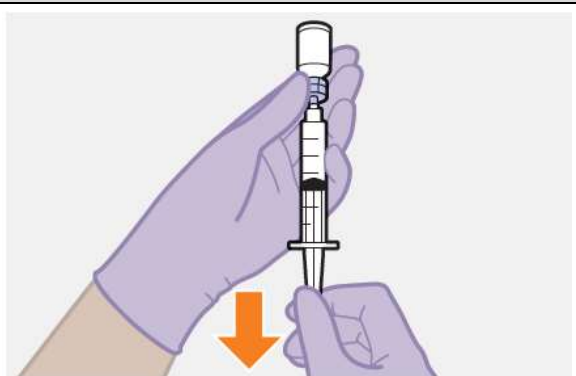
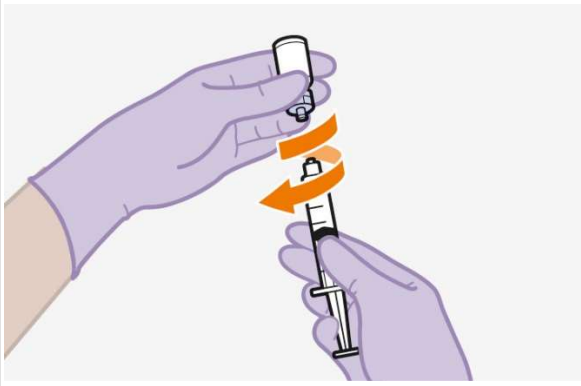
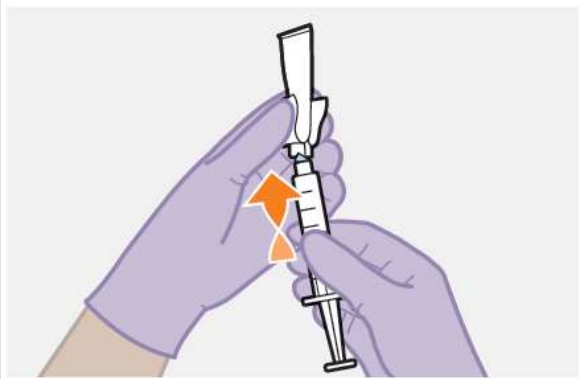
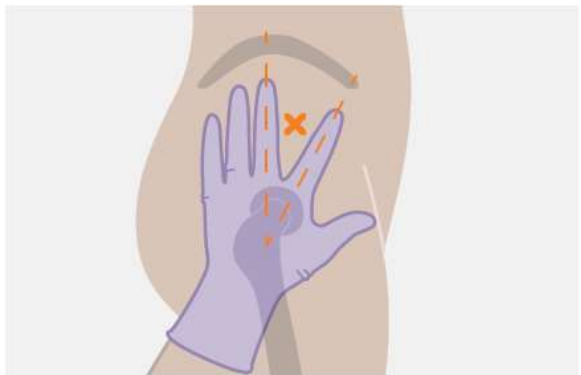


Figure L

- Invert the syringe and vial and slowly withdraw as much of the medicine as possible into the syringe. There may be more medicine than the dose amount. **See Figure L.**

Note: Keep the syringe upright to avoid leakage.

13. Unscrew the syringe.	
 <p>Figure M</p>	<ul style="list-style-type: none"> • Hold the syringe plunger firmly in place as shown to prevent leakage. It is normal to feel some back pressure. • Unscrew the syringe from the vial adapter, holding the vial adapter as shown. See Figure M. <p>Note: Check that the suspension looks uniform and milky white.</p>
14. Attach the needle and affix syringe label.	
 <p>Figure N</p>	<ul style="list-style-type: none"> • Peel open the needle packaging part way to expose the needle base. • Keeping the syringe upright, firmly twist the syringe onto the needle. • Remove the needle packaging from the needle. See Figure N. • Write the name of the medicine on the syringe label. Affix the label to the syringe making sure the gradations remain visible.
Injection:	
15. Prepare the injection site.	
 <p>Figure O</p>	<p>Injections must be administered to a gluteal site. See Figure O.</p> <p>Select from the following areas for the injection:</p> <ul style="list-style-type: none"> • Ventrogluteal, as shown (recommended) • Dorsogluteal, not shown (upper outer quadrant) <p>Note: For gluteal intramuscular use only. Do not inject intravenously.</p>

16. Remove the cap.

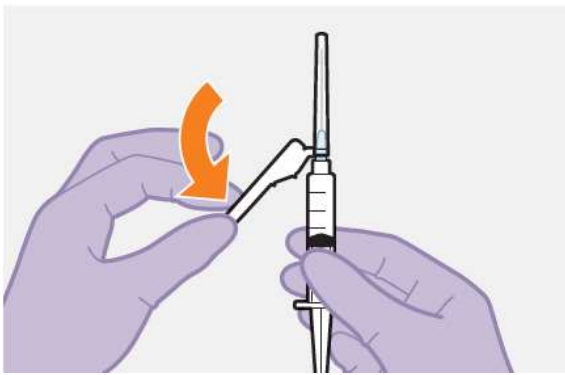


Figure P

- Fold the needle guard away from the needle. **See Figure P.**
- Pull off the injection needle cap.

17. Remove extra liquid from the syringe.

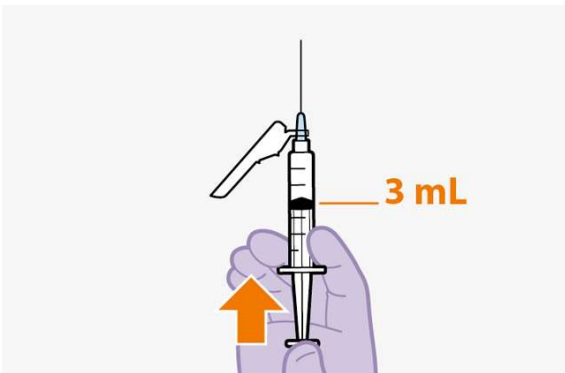


Figure Q

- Hold the syringe with the needle pointing up. Press the plunger to the 3-mL dosing mark to remove extra liquid and any air bubbles. **See Figure Q.**

Note: Clean the injection site with an alcohol wipe. Allow the skin to air dry before continuing.

18. Stretch the skin.

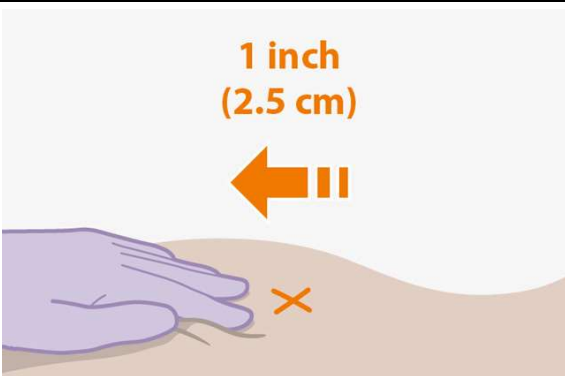


Figure R

Use the z-track injection technique to minimize medicine leakage from the injection site.

- Firmly drag the skin covering the injection site, displacing it by about an inch (2.5 cm). **See Figure R.**
- Keep it held in this position for the injection.

19. Insert the needle.

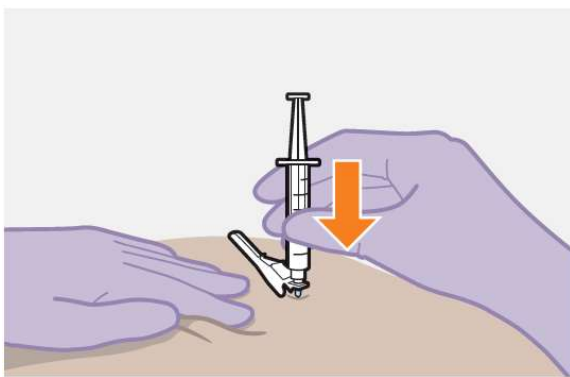


Figure S

- Insert the needle to its full depth, or deep enough to reach the muscle. **See Figure S.**

20. Inject the dose of medicine.

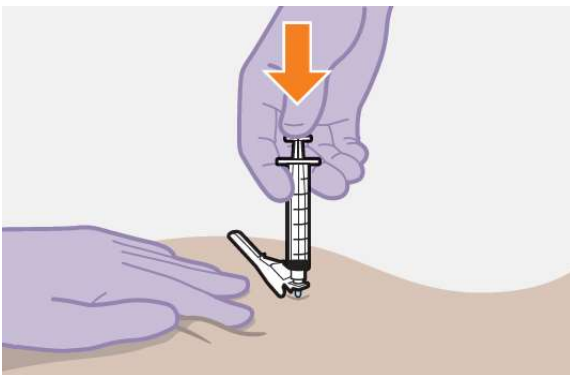


Figure T

- Still holding the skin stretched – slowly press the plunger all the way down. **See Figure T.**
- Ensure the syringe is empty.
- Withdraw the needle and release the stretched skin immediately.

21. Assess the injection site.

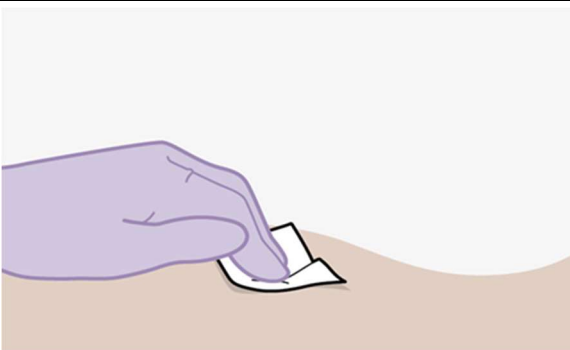


Figure U

- Apply pressure to the injection site using a gauze pad. **See Figure U.**
 - A small bandage may be used if bleeding occurs.
- Do not** massage the area.

22. Make the needle safe.

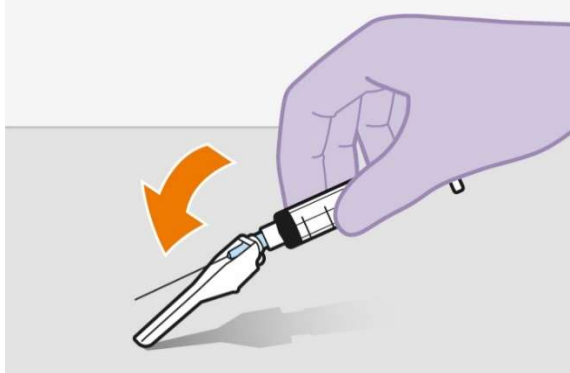


Figure V

- Fold the needle guard over the needle. **See Figure V.**

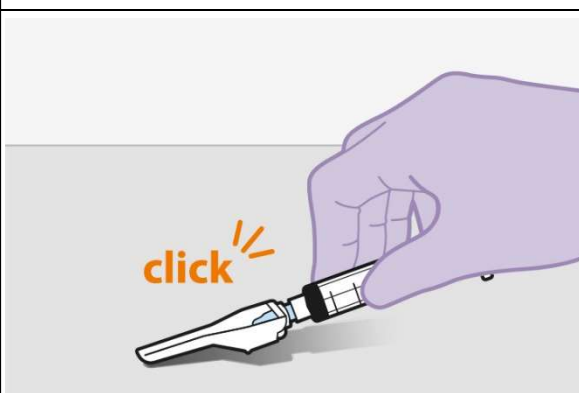


Figure W

- Gently apply pressure using a hard surface to lock the needle guard in place.
- The needle guard will make a click when it locks. **See Figure W.**

After injection:

23. Dispose safely.

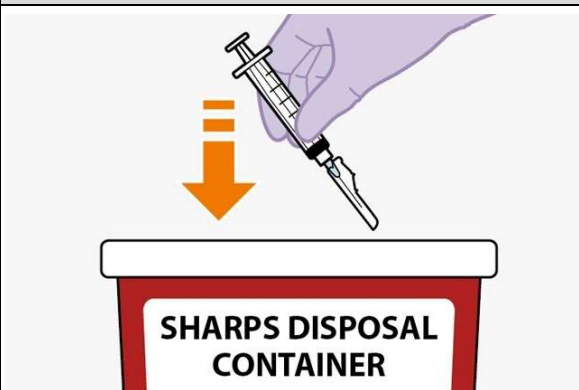



Figure X

- Dispose of used needles, syringes, vials, and vial adapters according to local health and safety laws. **See Figure X.**

Repeat for 2nd medicine.	
 <p>Repeat all steps for 2nd medicine</p>	<ul style="list-style-type: none"> • If you have not yet injected both medicines, use the same steps for preparation and injection of the other medicine. • The second medicine must be injected into a separate gluteal intramuscular site (on opposite sides or at least 2 cm apart).

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4. Does the order in which I give the medicines matter?

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