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

---------- INDICATIONS AND USAGE----------
CABENUVA, a 2-drug co-packaged product of cabotegravir, a human immunodeficiency virus type-1 (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 to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. (1)

----------DOSAGE AND ADMINISTRATION----------
- Prior to initiating treatment with CABENUVA, oral lead-in dosing should be used for approximately 1 month to assess the tolerability of cabotegravir and rilpivirine. (2.2)
- For intramuscular (IM) gluteal injection only. (2.3, 2.5)
- Recommended Dosing Schedule: Initiate injections of CABENUVA (600 mg of cabotegravir and 900 mg of rilpivirine) on the last day of oral lead-in and continue with injections of CABENUVA (400 mg of cabotegravir and 600 mg of rilpivirine) every month thereafter. (2.3)

---------- DOSAGE FORMS AND STRENGTHS----------
Cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension, co-packaged as follows: (3)
CABENUVA 400-mg/600-mg Kit:
- single-dose vial of 400 mg/2 mL (200 mg/mL) cabotegravir
- single-dose vial of 600 mg/2 mL (300 mg/mL) rilpivirine

CABENUVA 600-mg/900-mg Kit:
- single-dose vial of 600 mg/3 mL (200 mg/mL) cabotegravir
- single-dose vial of 900 mg/3 mL (300 mg/mL) rilpivirine

---------- 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 other 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. Immediate medical 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 injection doses of CABENUVA. 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)

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: After oral use of rilpivirine, exposures were generally lower during pregnancy compared with the postpartum period. (8.1)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)

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

Revised: 1/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CABENUVA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine *[see Clinical Studies (14.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Adherence to CABENUVA

CABENUVA must be administered by a healthcare professional. Prior to starting CABENUVA, healthcare professionals should carefully select patients who agree to the required monthly 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 Warnings and Precautions (5.6)]*.

2.2 Oral Lead-in Dosing to Assess Tolerability of CABENUVA

Oral lead-in should be used for approximately 1 month (at least 28 days) prior to the initiation of CABENUVA to assess the tolerability of cabotegravir and rilpivirine. The recommended oral lead-in daily dose is one 30-mg tablet of VOCABRIA (cabotegravir) and one 25-mg tablet of EDURANT (rilpivirine). See Table 1 for recommended oral lead-in and intramuscular injection dosing schedule for CABENUVA *[Dosage and Administration (2.3)]*.

2.3 Intramuscular Injection Dosing with CABENUVA

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

Initiate injections on the last day of oral lead-in. CABENUVA contains cabotegravir and rilpivirine extended-release injectable suspensions. The recommended initial injection doses of CABENUVA in adults are a single 600-mg (3-mL) gluteal intramuscular injection of cabotegravir and a single 900-mg (3-mL) gluteal intramuscular injection of rilpivirine. Administer cabotegravir and rilpivirine at separate gluteal injection sites (on opposite sides or 2 cm apart) during the same visit *[see Dosage and Administration (2.5)]*. Continuation injections should be initiated a month after the initiation injections.

Continuation Injections (CABENUVA 400-mg/600-mg Kit)

After the initiation injections, the recommended monthly continuation injection doses of CABENUVA in adults are a single 400-mg (2-mL) gluteal intramuscular injection of cabotegravir and a single 600-mg (2-mL) gluteal intramuscular injection of rilpivirine at each visit. Administer cabotegravir and rilpivirine at separate gluteal injection sites (on opposite sides or 2 cm apart) during the same visit *[see Dosage and*

Administration (2.5)]. Patients may be given CABENUVA up to 7 days before or after the date the patient is scheduled to receive monthly injections.

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

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

2.4 Missed Injections

Adherence to the monthly injection dosing schedule is strongly recommended. Patients who miss a scheduled injection visit should be clinically reassessed to ensure resumption of therapy remains appropriate. Refer to Table 2 for dosing recommendations after missed injections.

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

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

Unplanned Missed Injections

If monthly injections are missed or delayed by more than 7 days and oral therapy has not been taken in the interim, clinically reassess the patient to determine if resumption of injection dosing remains appropriate *[see Warnings and Precautions (5.6)]*. If injection dosing will be continued, see Table 2 for dosing recommendations.

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

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

	(2-mL) cabotegravir and 600-mg (2-mL) rilpivirine intramuscular monthly injection dosing schedule.

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

2.5 Administration Instructions

Refer to the Instructions for Use for complete administration instructions with illustrations.

A complete dose requires 2 injections: one injection of cabotegravir and one injection of rilpivirine *[see Dosage and Administration (2.3)]*.

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 2 cm apart) during the same visit. The ventrogluteal site is recommended. 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: greater than 30 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. 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 which 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. If 2 hours are exceeded, the medication, syringes, and needles must be discarded *[see How Supplied/Storage and Handling (16)]*.

3 DOSAGE FORMS AND STRENGTHS

CABENUVA contains a single-dose vial of cabotegravir as a white to light pink, free-flowing extended-release injectable suspension and a single-dose vial of rilpivirine as a white to off-white extended-release injectable suspension, co-packaged as follows:

<u>CABENUVA 400-mg/600-mg Kit</u>

- Injection: 400 mg/2 mL (200 mg/mL) of cabotegravir suspension in single-dose vial

- Injection: 600 mg/2 mL (300 mg/mL) of rilpivirine suspension in single-dose vial

CABENUVA 600-mg/900-mg Kit
- Injection: 600 mg/3 mL (200 mg/mL) of cabotegravir suspension in single-dose vial
- Injection: 900 mg/3 mL (300 mg/mL) of rilpivirine suspension in single-dose vial

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 (UDP)-glucuronosyl transferase (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

Hypersensitivity reactions have been reported during postmarketing experience with rilpivirine-containing regimens *[see Adverse Reactions (6.2)]*. Reactions include cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). 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. Remain vigilant and discontinue CABENUVA if a hypersensitivity reaction is suspected *[see Adverse Reactions (6.1)]*.

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 (2.2), Contraindications (4)]*.

5.2 Post-Injection Reactions

In clinical trials, serious post-injection reactions were reported within minutes after the injection of rilpivirine, including dyspnea, agitation, abdominal cramping, flushing, sweating, oral numbness, and changes in blood pressure. These events were reported in less than 1% of subjects and began to resolve within a few minutes after the injection. These events may have been associated with inadvertent (partial) intravenous administration *[see Adverse Reactions (6.1)]*.

Carefully follow the Instructions for Use when preparing and administering CABENUVA to avoid accidental intravenous administration *[see Dosage and Administration (2.5)]*. 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 or 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 the recommended oral dosage) in healthy adults resulted in mean steady-state C_{max} values 4.4-fold and 11.6-fold higher than C_{max} values associated with the recommended 600-mg dose of rilpivirine extended-release injectable suspension and prolonged 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 Drug Interactions (7.3, 7.4)]*.

See Table 5 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 (7.2)]*.

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 injection dosing schedule because non-adherence to monthly injections or missed doses could lead to loss of virologic response and development of resistance *[see Dosage and Administration (2.1), Adverse Reactions (6.1), Drug Interactions (7.2)]*.

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 injection doses of CABENUVA. 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.

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 *[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: 54 weeks) and data from VOCABRIA (cabotegravir) tablets and EDURANT (rilpivirine) tablets administered in combination as oral lead-in therapy (median time exposure: 5.3 weeks). 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 for other adverse reactions associated with oral rilpivirine.

The most common adverse reactions regardless of severity reported in greater than or equal to 2% of adult subjects in the pooled analyses from FLAIR and ATLAS are presented in Table 3. Selected laboratory abnormalities are included in Table 4.

Overall, 4% of subjects in the group receiving CABENUVA and 2% of subjects in the control group 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 less than 1%).

Table 3. 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)

	Cabotegravir plus Rilpivirine (n = 591)		Current Antiretroviral Regimen (n = 591)	
Adverse Reactions	**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.

Injection-Associated Adverse Reactions

Local Injection Site Reactions (ISRs): The most frequent adverse reactions associated with the intramuscular administration of CABENUVA were ISRs. After 14,682 injections, 3,663 ISRs were reported. One percent (1%) of subjects discontinued treatment with CABENUVA because of ISRs. Most ISRs were mild (Grade 1, 75%) or moderate (Grade 2, 36%). Four percent (4%) of subjects experienced

severe (Grade 3) ISRs, and no subjects experienced Grade 4 ISRs. The most commonly reported ISR was localized pain/discomfort (79%) regardless of severity or relatedness. Other manifestations of ISRs reported in more than 1% of subjects over the duration of the analysis period included nodules (14%), induration (12%), swelling (8%), erythema (4%), pruritus (4%), bruising (3%), warmth (2%), and hematoma (2%). Abscess and cellulitis at the injection site were each reported in less than 1% of subjects. The median duration of ISR events was 3 days.

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. No cases were serious or led to withdrawal and the occurrences of pyrexia may represent a response to administration of CABENUVA via intramuscular injection.

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-syncopal reactions were reported in less than 1% of subjects after injection with rilpivirine or cabotegravir.

Less Common Adverse Reactions

The following select adverse reactions (regardless of severity) occurred in less than 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.

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 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.

Laboratory Abnormalities

Selected laboratory abnormalities with a worsening grade from baseline and representing the worst-grade toxicity are presented in Table 4.

Table 4. Selected Laboratory Abnormalities (Grades 3 to 4; Week 48 Pooled Analyses) in FLAIR and ATLAS Trials

Laboratory Parameter	Cabotegravir plus Rilpivirine (n = 591)	Current Antiretroviral Regimen (n = 591)
ALT (≥5.0 x ULN)	2%	<1%
AST (≥5.0 x ULN)	2%	<1%
Total bilirubin (≥2.6 x ULN)	<1%	<1%
Creatine phosphokinase (≥10.0 x ULN)	8%	4%
Lipase (≥3.0 x ULN)	5%	3%

ULN = Upper limit of normal.

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) micrograms/dL in the group receiving EDURANT compared with -0.02 (-0.48, 0.44) micrograms/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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving an oral rilpivirine-containing regimen. 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.

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 and EDURANT 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 1A9 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-fold 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 and EDURANT 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 5. 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 5 includes potentially significant interactions but is not all inclusive.

Table 5. 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 Contraindications (4)]*.
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 (*Hypericum perforatum*)	↓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 *[Warnings and Precautions (5.5)]*. 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 women 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 women 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 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 Metropolitan Atlanta Congenital Defects Program (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 women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 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 greater than 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 (greater than 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 an observational 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 390 exposures to oral rilpivirine-containing regimens during the first trimester of pregnancy and over 170 during second/third trimester of pregnancy, the prevalence of birth defects in live births was 1.3% (95% CI: 0.4% to 3.0%) and 1.1% (95% CI: 0.1% to 4.0%) 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 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 (greater than 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 (greater than 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

The Centers for Disease Control and Prevention recommends that HIV-1−infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

It is not known if the components of CABENUVA are present in human breast milk, affect human milk production, or have effects on the breastfed infant. When administered to lactating rats, cabotegravir and rilpivirine were present in milk *(see Data)*. If cabotegravir and/or rilpivirine are present in human milk, residual exposures may remain for 12 months or longer after the last injections have been administered *[see Warnings and Precautions (5.6)]*.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), (3) adverse reactions in a breastfed infant similar to those seen in adults, and (4) detectable cabotegravir and rilpivirine concentrations in systemic circulation for up to 12

months or longer after discontinuing injections of CABENUVA, instruct mothers not to breastfeed if they are receiving CABENUVA.

Data

Animal 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.

Rilpivirine: Animal lactation studies with rilpivirine have not been conducted. However, rilpivirine was detected in the plasma of nursing pups on Lactation Day 7 in the rat pre- and postnatal development study.

8.4 Pediatric Use

The safety and efficacy of CABENUVA have not been evaluated in pediatric patients.

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 greater than or equal to 60 to less than 90 mL/min) or moderate renal impairment (creatinine clearance greater than or equal to 30 to less than 60 mL/min). In patients with severe renal impairment (creatinine clearance 15 to less than 30 mL/min) or end-stage renal disease (creatinine clearance less than 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 greater than 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

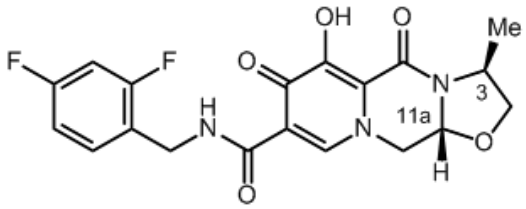
There is no known specific treatment for overdose with cabotegravir or rilpivirine. If overdose occurs, monitor the patient and apply standard supportive treatment as required, including monitoring of vital

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

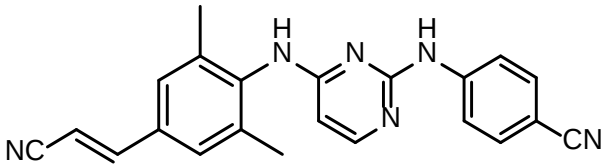
CABENUVA contains cabotegravir extended-release injectable suspension, an HIV INSTI, co-packaged with rilpivirine extended-release injectable suspension, an HIV NNRTI.

Cabotegravir: The chemical name for cabotegravir is (*3S,11aR*)-N-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide.The empirical formula is $C_{19}H_{17}F_2N_3O_5$ 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. Each sterile single-dose vial contains 2 mL or 3 mL of the following: cabotegravir 200 mg/mL and the following inactive ingredients: mannitol (35 mg/mL), polyethylene glycol (PEG) 3350 (20 mg/mL), polysorbate 20 (20 mg/mL), and Water for Injection.

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 $C_{22}H_{18}N_6$ 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 for 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-fold and 5.4-fold above the geometric mean steady-state C_{max} associated with the recommended 30-mg dose of oral cabotegravir and the recommended 400-mg monthly dose 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 monthly dose of rilpivirine extended-release injectable suspension.

When rilpivirine 75-mg and 300-mg once-daily oral doses (3 and 12 times 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-fold and 11.6-fold, respectively, higher than the mean steady-state C_{max} observed with the recommended 600-mg monthly dose of rilpivirine extended-release injectable suspension. 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, Metabolism, and Excretion

The pharmacokinetic properties of the components of CABENUVA are provided in Table 6. The multiple-dose pharmacokinetic parameters are provided in Table 7. For the pharmacokinetic properties of oral cabotegravir and oral rilpivirine, refer to the full prescribing information for VOCABRIA and EDURANT, respectively.

Table 6. 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
Metabolism		
Metabolic pathways	UGT1A1 UGT1A9 (minor)	CYP3A
Excretion		
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)

[a] When taken orally with a high-fat meal versus fasted, the $AUC_{(0\text{-inf})}$ (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 one week after 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 injection site.

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

BLQ = Below limit of quantification.

Table 7. Pharmacokinetic Parameters following Once-Daily Oral Cabotegravir and Rilpivirine and following Initiation and Monthly Continuation Intramuscular Injections of the Components of CABENUVA

Drug	Dosing Phase	Dosage Regimen	Geometric Mean (5^{th}, 95^{th} Percentile)[a]		
			$AUC_{(0\text{-tau})}$[b] (mcg•h/mL)	**C_{max} (mcg/mL)**	**C_{tau} (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[d]	600 mg IM initial dose	1,591 (714, 3,245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
	Monthly Injection[e]	400 mg IM monthly	2,415 (1,494, 3,645)	4.2 (2.5, 6.5)	2.8 (1.7, 4.6)

Drug	Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
			$AUC_{(0\text{-}tau)}$[b] (ng•h/mL)	C_{max} (ng/mL)	C_{tau} (ng/mL)
Rilpivirine	Oral Lead-In[b,f]	25 mg once daily	2,083 (1,125, 3,748)	116 (48.6, 244)	78.9 (32.2, 180)
	Initial Injection[d]	900 mg IM initial dose	41,069 (20,062, 76,855)	139 (87.6, 219)	37.2 (19.4, 69.2)
	Monthly Injection[e]	600 mg IM monthly	65,603 (37,239, 113,092)	116 (66.8, 199)	82.2 (47.5, 140)

[a] Pharmacokinetic parameter values based on individual post-hoc estimates from separate cabotegravir and rilpivirine population pharmacokinetic models (pooled FLAIR and ATLAS, n = 581), except for oral rilpivirine *(see footnote e)*.

[b] tau is dosing interval: 24 hours for oral cabotegravir and rilpivirine; 1 month for cabotegravir and rilpivirine extended-release injectable suspensions.

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

[d] Initial injection $AUC_{(0\text{-}tau)}$ and C_{max} values primarily reflect values following oral dosing because the initial injection was administered on the same day as the last oral dose; however, the C_{tau} value at Week 4 reflects the initial injection.

[e] Monthly injection pharmacokinetic parameter values represent Week 48 data.

[f] Oral rilpivirine: $AUC_{(0\text{-}tau)}$ based on population pharmacokinetic estimates of rilpivirine 25 mg once daily from pooled Phase 3 trials with EDURANT (rilpivirine); C_{tau} based on observed data from FLAIR and ATLAS; C_{max} based on observed data for rilpivirine 25 mg once daily from a pharmacokinetic substudy in pooled Phase 3 trials with EDURANT.

IM = Intramuscular.

Specific Populations

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

The effect of hepatitis B and C 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.

The pharmacokinetics of cabotegravir (oral or injectable) and of injectable rilpivirine have not been studied in pediatric patients and data are limited in subjects aged 65 years or older *[see Use in Specific Populations (8.4, 8.5)]*.

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 greater than 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 greater than 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)]*.

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; multidrug resistance protein (MRP)2 or MRP4.

In vitro, cabotegravir inhibited renal OAT1 (IC_{50} = 0.81 microM) and OAT3 (IC_{50} = 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, 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 8, 9, 10, and 11.

Table 8. 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_{τ} 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)

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

Table 9. 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)
Ethinylestradiol/ 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	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	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)

CI = Confidence Interval; n = Maximum number of subjects with data; NA = Not available; ↔ = 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 10. 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_{τ} 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)

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

Table 11. 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	150 mg once daily[a]	16	1.35 (1.08 to 1.68)	1.04 (0.97 to 1.12)	0.85 (0.69 to 1.03)
2-hydroxy-atorvastatin			1.58 (1.33 to 1.87)	1.39 (1.29 to 1.50)	1.32 (1.10 to 1.58)
4-hydroxy-atorvastatin			1.28 (1.15 to 1.43)	1.23 (1.13 to 1.33)	NA
Chlorzoxazone 500-mg single dose taken 2 hours after rilpivirine	150 mg once daily[a]	16	0.98 (0.85 to 1.13)	1.03 (0.95 to 1.13)	NA
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
Ethinylestradiol 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-desacetylrifampin	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 50-mg single dose *N*-desmethyl-sildenafil	75 mg once daily[a]	16	0.93 (0.80 to 1.08) 0.90 (0.80 to 1.02)	0.97 (0.87 to 1.08) 0.92 (0.85 to 0.99)[c]	NA 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)

CI = Confidence Interval; n = Maximum number of subjects with data; 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 $AUC_{(0-\infty)}$ = 15.
[c] $AUC_{(0\text{-last})}$.

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 which is essential for the HIV replication cycle. The mean 50% inhibitory concentration (IC_{50}) 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 (EC_{50}) values of 0.22 nM 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 EC_{50} value of 0.19 nM (range: 0.02 nM to 1.06 nM, n = 24). The median EC_{50} 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 EC_{50} value was 0.12 nM (range: 0.10 nM to 0.14 nM, n = 4).

Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for $HIV\text{-}1_{IIIB}$ 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 EC_{50} 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 EC_{50} values ranging from 2.88 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 which 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-fold to 410-fold change. The combinations of E138K+Q148K and V72I+E138K+Q148K conferred the greatest reductions of 53-fold 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 and ATLAS trials, there were 7 confirmed virologic failures (2 consecutive HIV-1 RNA greater than or equal to 200 copies/mL) on cabotegravir plus rilpivirine (7/591, 1.2%) and 7 confirmed virologic failures on current antiretroviral regimen (7/591, 1.2%). Of the 7 virologic failures in the cabotegravir plus rilpivirine arm, 6 had post-baseline resistance data. All 6 had treatment-emergent NNRTI resistance-associated substitutions K101E, V108I, E138A, E138K, or H221H/L in reverse transcriptase, and 5 of them showed reduced phenotypic susceptibility to rilpivirine (range: 2.4-fold to 7.1-fold).

Additionally, 4 of the 6 (67%) cabotegravir plus rilpivirine virologic failures with post-baseline resistance data had treatment-emergent INSTI resistance-associated substitutions and reduced phenotypic susceptibility to cabotegravir (Q148R [n = 2; 5-fold and 9-fold decreased susceptibility to cabotegravir], G140R [n = 1; 7-fold decreased susceptibility to cabotegravir], or N155H [n = 1; 3-fold decreased susceptibility to cabotegravir]).

In comparison, 2 of the 7 (29%) virologic failures in the current antiretroviral regimen arm 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, conferring resistance to efavirenz in their regimen.

In other Phase 2 and 3 clinical trials (207966, LATTE and LATTE-2), virologic failures on cabotegravir plus rilpivirine also showed emergent genotypic and phenotypic cabotegravir and rilpivirine resistance (with emergent INSTI resistance-associated substitutions Q148R, N155H, E138K+Q148R,

E138K+G140A+Q148R, G140S+Q148R, Q148R+N155H, and NNRTI resistance-associated substitutions K101E, K101E+E138A or K, K101E+M230L, K103N+K238T, K103N+E138G+K238T, E138K or Q, and Y188L).

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

Five of the 7 cabotegravir plus rilpivirine virologic failures in FLAIR and ATLAS had HIV-1 subtype A1 and the integrase substitution L74I detected at baseline and failure timepoints. Subjects with subtype A1 infection whose virus did not have L74I at baseline did not experience virologic failure (Table 12). In addition, there was no detectable phenotypic resistance to cabotegravir conferred by the presence of L74I at baseline.

The other 2 virologic failures had subtype AG and did not have the integrase substitution L74I at baseline or at failure. Six of the virologic failures with subtype A1 and AG were from Russia where the prevalence of subtypes A, A1, and AG are high. Subtypes A, A1, and AG are uncommon in the United States.

The presence of the integrase substitution L74I in other subtypes, such as subtype B commonly seen in the United States, was not associated with virologic failure (Table 12). In contrast to the Phase 3 trials where all virologic failures were subtype A1 or AG, subtypes of the cabotegravir plus rilpivirine virologic failures in Phase 2 clinical trials included A1, A, B, and C.

Table 12. Rate of Virologic Failure in FLAIR Trial: Baseline Analysis (Subtypes A1 and B, and Presence of Integrase Substitution L74I)

Patient Characteristics	Cabotegravir plus Rilpivirine[a]	Current Antiretroviral Regimen[b]
Subtype A1	3/8 (38%)	1/4 (25%)
+L74I	3/5 (60%)	1/3 (33%)
-L74I	0/3	0/1
Subtype B	0/174	2/174 (1%)
+L74I	0/12	0/11
-L74I	0/153	2/150 (1%)
Missing data	0/9	0/13
Russia	4/54 (7%)	1/39 (3%)
+L74I	3/35 (9%)	1/29 (3%)
-L74I	1/12 (8%)	0/7
Missing data	0/7	0/3

[a] There were 4 virologic failures in the cabotegravir arm. One virologic failure in the cabotegravir arm had subtype AG.

[b] There were 3 virologic failures in the current antiretroviral regimen arm. Two virologic failures in the current antiretroviral regimen arm had subtype B.

Cross-Resistance

Cabotegravir: Cross-resistance has been observed among INSTIs. Cabotegravir had reduced susceptibility (greater than 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-fold to 81-fold). The substitutions E138K+Q148K and Q148R+N155H conferred the greatest reductions in susceptibility of 81-fold 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-fold 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) greater than 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) greater than 36 times (male) and 40 times (female) the exposure in humans at the RHD.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adults

The efficacy of CABENUVA has been evaluated in two 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)-naive 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 less than 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.
- 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 less than 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.

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

At baseline, in FLAIR and ATLAS, respectively, the median age was 34 years and 40 years, 22% and 32% were female, 24% and 31% were nonwhite. In both studies, 7% had CD4+ cell count less than 350 cells/mm^3; 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 greater than or equal to 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 13 and 14.

Table 13. Virologic Outcomes of Randomized Treatment in FLAIR and ATLAS Trials at Week 48

	FLAIR		ATLAS	
Virologic Outcomes	**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

[a] Includes subjects who discontinued for lack of efficacy and discontinued while not suppressed.
n = Number of subjects in each treatment group, CI = Confidence interval, CAB = Cabotegravir, RPV = Rilpivirine, CAR = Current antiretroviral regimen.

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

Table 14. Proportion of Subjects in FLAIR and ATLAS Trials with Plasma HIV-1 RNA Greater than or Equal to 50 copies/mL at Week 48 for Key Baseline Factors

	FLAIR		ATLAS	
Baseline Factors	**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

BMI				
<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.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

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

- One single-dose vial of cabotegravir extended-release injectable suspension containing 400 mg/2 mL (200 mg/mL) of cabotegravir.
- One single-dose vial of rilpivirine extended-release injectable suspension containing 600 mg/2 mL (300 mg/mL) of rilpivirine

CABENUVA 600-mg/900-mg Kit (NDC 49702-240-15) containing:

- One single-dose vial of cabotegravir extended-release injectable suspension containing 600 mg/3 mL (200 mg/mL) of cabotegravir.
- One single-dose vial of rilpivirine extended-release injectable suspension containing 900 mg/3 mL (300 mg/mL) of rilpivirine.

Each dosing kit also contains 2 syringes, 2 syringe labels, 2 vial adapters, and 2 needles for intramuscular injection (23-gauge, 1½ inch). The vial stoppers are not made with natural rubber latex.

Storage 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. 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 syringe for up to 2 hours. If 2 hours are exceeded, the medication, syringes, and needles must be discarded *[see Dosage and Administration (2.5)]*.

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, agitation, abdominal cramping, flushing, sweating, oral numbness, and changes in blood pressure. These events began to resolve within a few 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, feeling tense, negative thoughts, suicidal ideation or attempt) have been reported with at least one of the components of CABENUVA. Advise patients to seek immediate medical evaluation if they experience depressive symptoms *[see Warnings and Precautions (5.4), Adverse Reactions (6.1)]*.

Drug Interactions

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 which 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)]*.

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 monthly injection visit and that oral therapy may be used to replace up to 2 consecutive monthly injections. 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 (2.1, 2.5), 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

Instruct mothers with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

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Manufactured for:

ViiV Healthcare
Research Triangle Park, NC 27709

by:

GlaxoSmithKline
Research Triangle Park, NC 27709

CBN:1PI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

CABENUVA (kab' en ue vah)
(cabotegravir extended-release injectable suspension;
rilpivirine extended-release injectable suspension)
co-packaged for intramuscular use

What is CABENUVA?

CABENUVA is a prescription medicine used without other Human Immunodeficiency Virus-1 (HIV-1) medicines to treat HIV-1 infection in adults 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.

Do not receive CABENUVA if you:

- have ever had an allergic reaction to cabotegravir or rilpivirine.
- are taking any of the following medicines:
  - carbamazepine
  - oxcarbazepine
  - 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 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.

  Pregnancy Registry. There is a pregnancy registry for women 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. **Do not breastfeed if you take CABENUVA.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - It is not known if CABENUVA can pass to your baby in your breast milk. Talk with your healthcare provider about the best way to feed your baby during treatment with 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.
- You will receive CABENUVA as 2 injections (cabotegravir and rilpivirine), one time every month.
- Before receiving your first injection doses of CABENUVA, your healthcare provider will have you take 1 VOCABRIA (cabotegravir) tablet and 1 EDURANT (rilpivirine) tablet one time a day for one 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 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 a few minutes after the injection. Symptoms of post-injection reactions may include:
  - trouble breathing
  - stomach cramps
  - sweating
  - numbness of your mouth
  - feeling anxious
  - feeling warm
  - feeling lightheaded or feeling like you are going to pass out (faint)
  - blood pressure changes
- **Liver problems**. People with a history of hepatitis B or C virus 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. Liver problems have also happened in people without history of liver problems or other risk factors. Your healthcare provider may do blood tests to check your liver function.

  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 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 have 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 healthcare provider or pharmacist 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:

ViiV Healthcare

Research Triangle Park, NC 27709

by:

GlaxoSmithKline

Research Triangle Park, NC 27709

CBN:1PIL

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. Issued: 01/2021

INSTRUCTIONS FOR USE

CABENUVA
(kab' en ue vah)

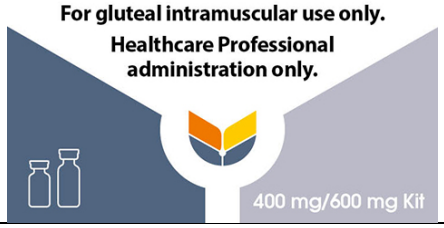
Cabotegravir extended-release injectable suspension
400 mg/2 mL (200 mg/mL)

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.

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). The administration order is not important.

Note: The ventrogluteal site is recommended.

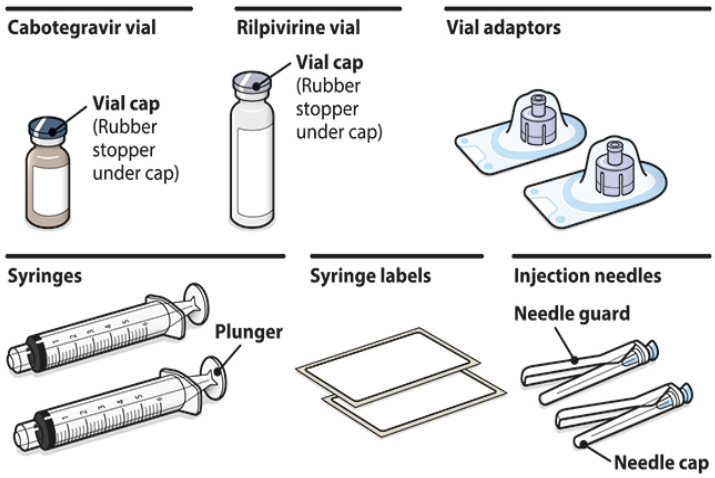
Storage information

- 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. If not used within 6 hours, the medication must be discarded.
- Once the medicines have been drawn into the syringe, the medication can remain in the syringes for up to 2 hours before injecting. If 2 hours are exceeded, the medication, syringes, and needles must be discarded.
- It is recommended to label the syringe with the time that the medication has been drawn into the syringe if the medication is not administered immediately.



Your pack contains:

- 1 vial of Cabotegravir
- 1 vial of Rilpivirine
- 2 vial adaptors
- 2 syringes
- 2 syringe labels
- 2 injection needles (23 gauge, 1½ inch)

Consider the patient's build and use medical judgment to select an appropriate injection needle length.

You will also need:

- Non-sterile gloves
- 4 alcohol wipes
- 4 gauze pads
- A suitable sharps container

Preparation:

1. Inspect both vials.

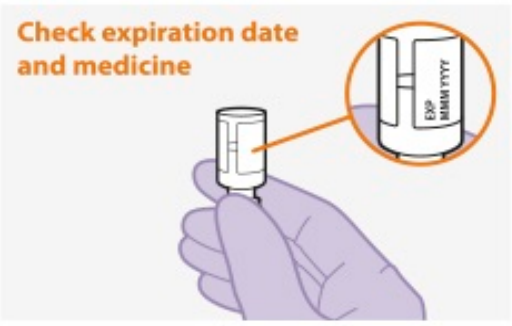


Figure A

- 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 medication to come to room temperature. **See Figure B.**

3. Shake the vial vigorously.

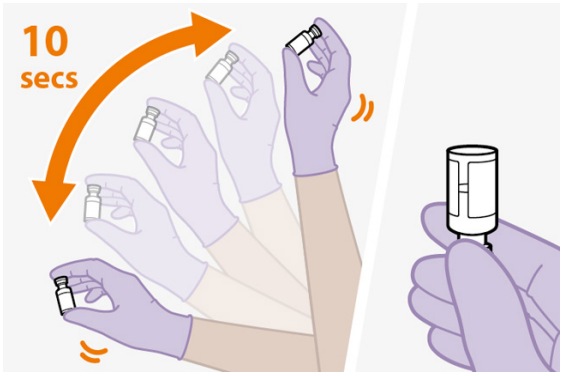


Figure C

- Hold the vial firmly, and vigorously shake for a full 10 seconds. **See Figure C.**
- Invert the vial and confirm the suspension is uniform.
- If the suspension is not uniform, shake the vial again.
- It is also normal to see small air bubbles.

4. Remove the vial cap.

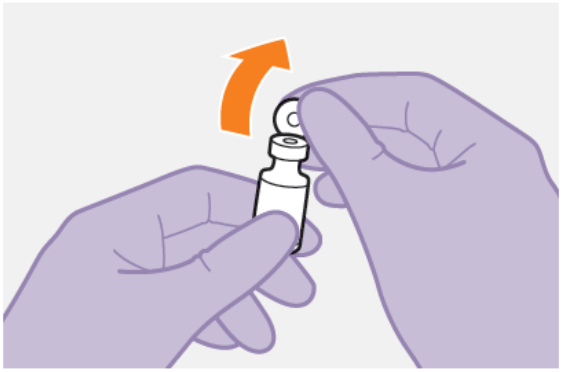


Figure D

- Remove the cap from the vial. **See Figure D.**
- Wipe the rubber stopper with an alcohol wipe.

Do not allow anything to touch the rubber stopper after wiping it.

5. Peel open the vial adaptor.

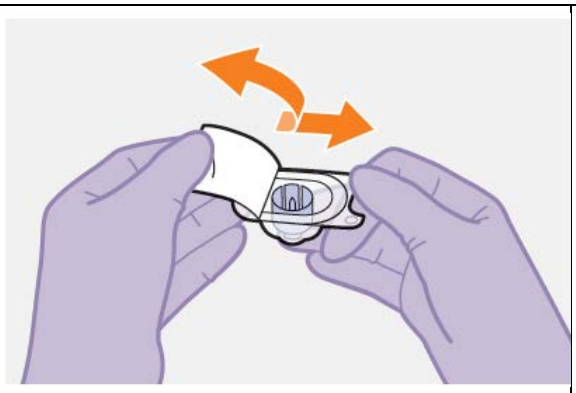


Figure E

- Peel off the paper backing from the vial adaptor packaging. **See Figure E.**

Note: Keep the adaptor in place in its packaging for the next step.

6. Attach the vial adaptor.

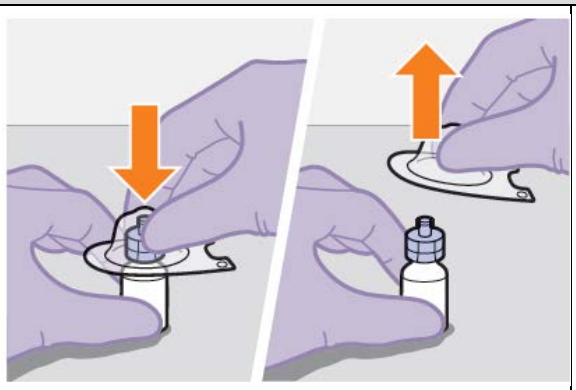


Figure F

- Press the vial adaptor straight down onto the vial using the packaging, as shown.
  The vial adaptor should snap securely into place.
- When you are ready, lift off the vial adaptor packaging as shown.

See Figure F.

7. Prepare the syringe.

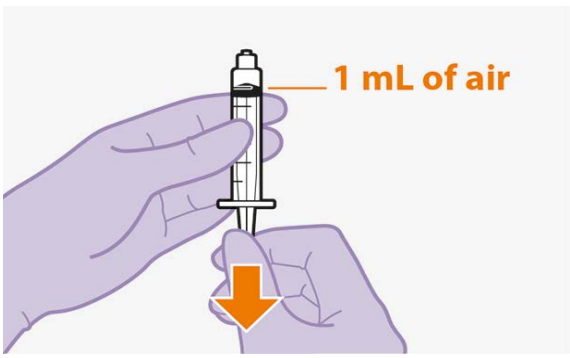


Figure G

- 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 G.**

8. Attach the syringe.

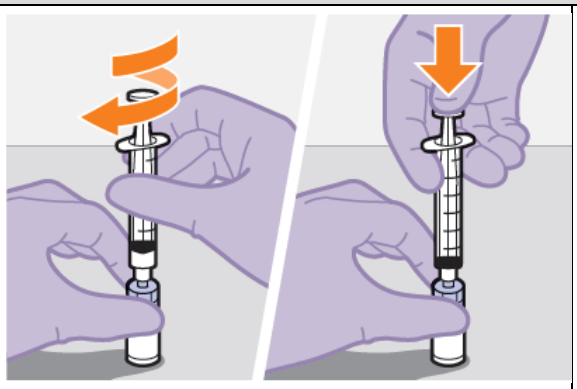


Figure H

- Hold the vial adaptor and vial firmly, as shown.
- Screw the syringe firmly onto the vial adaptor.
- Press the plunger all the way down to push the air into the vial.

See Figure H.

9. Slowly draw up the dose.

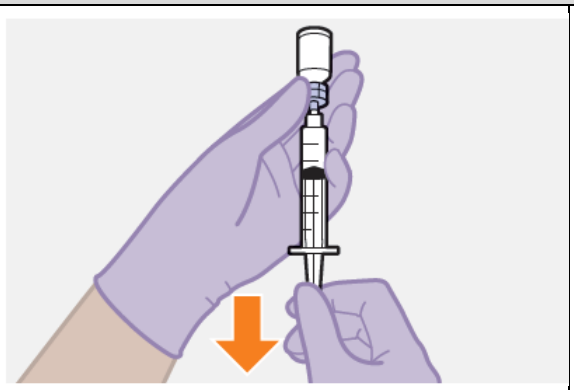


Figure I

- 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 I.**

10. Unscrew the syringe.

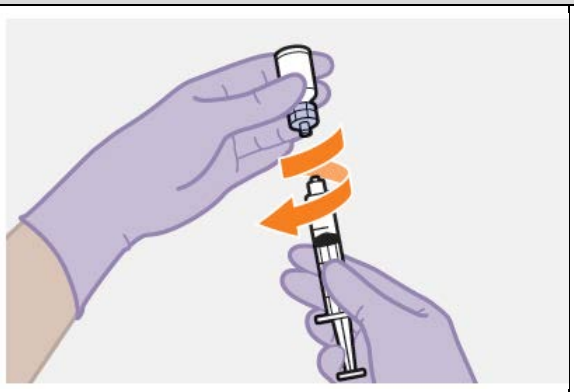


Figure J

- Unscrew the syringe from the vial adaptor, holding the vial adaptor as shown.

See Figure J.

Note: Keep the syringe upright to avoid leakage. Check that the suspension looks uniform and milky white.

11. Attach the needle and affix syringe label.

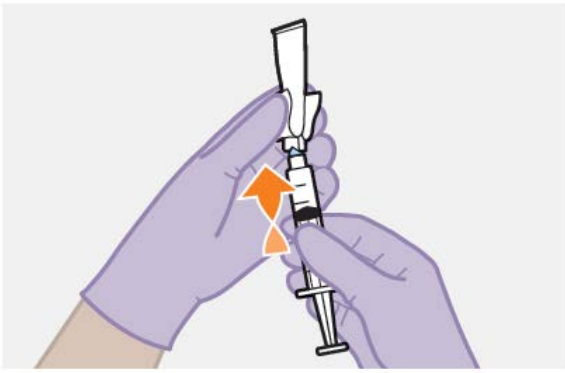


Figure K

- 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.
- Write the name of the medicine on the syringe label. Affix the label to the syringe making sure the gradations remain visible.

See Figure K.

Injection:

12. Prepare the injection site.

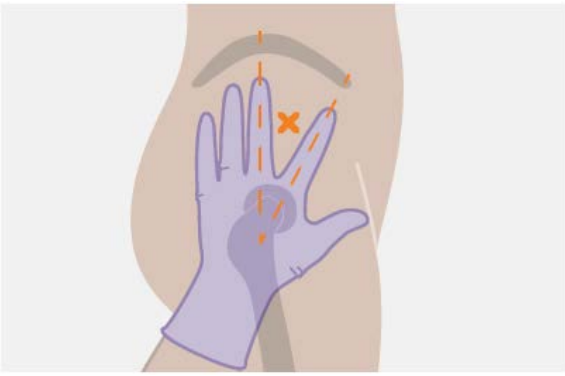


Figure L

Injections must be administered to the gluteal sites. **See Figure L**.

Select from the following areas for the injection:

• Ventrogluteal, as shown (recommended)

• Dorsogluteal (upper outer quadrant)

Note: For gluteal intramuscular use only. **Do not** inject intravenously.

13. Remove the cap.

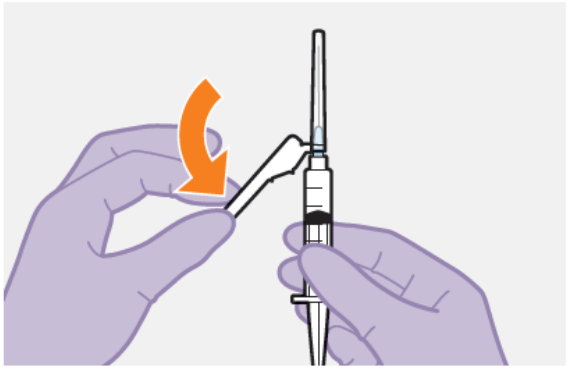


Figure M

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

14. Remove extra liquid from the syringe.

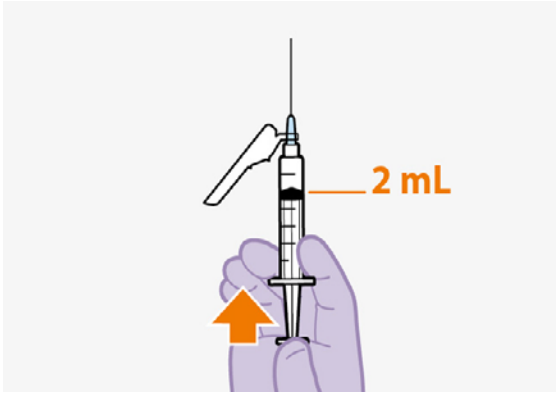


Figure N

- 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 N.**

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

15. Stretch the skin.

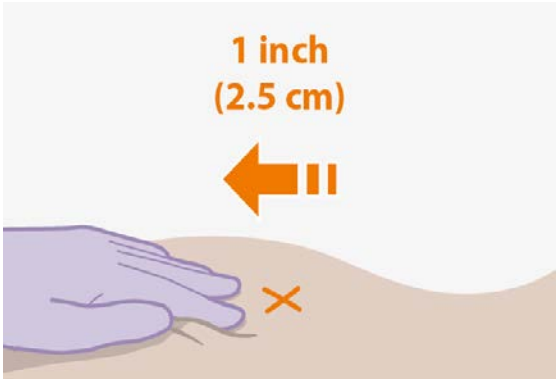


Figure O

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 O.**
- Keep it held in this position for the injection.

16. Insert the needle.

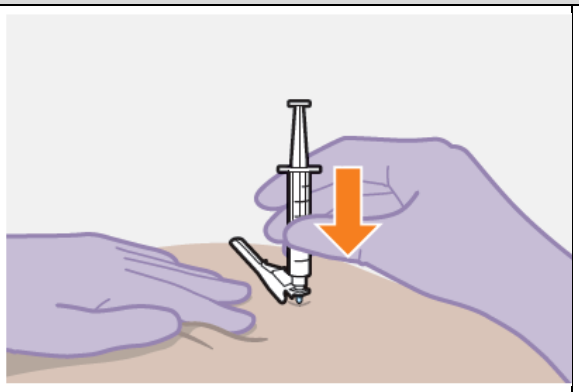


Figure P

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

17. Inject the dose of medicine.

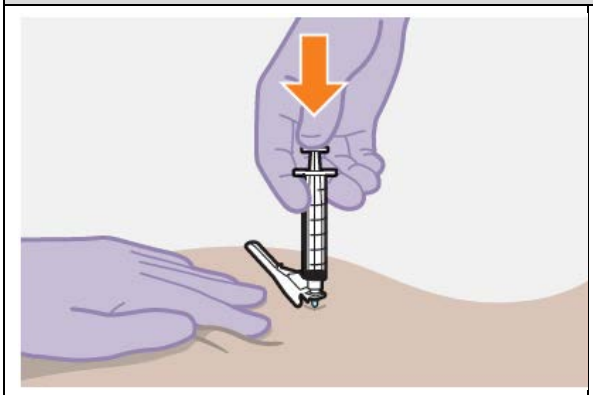


Figure Q

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

18. Assess the injection site.

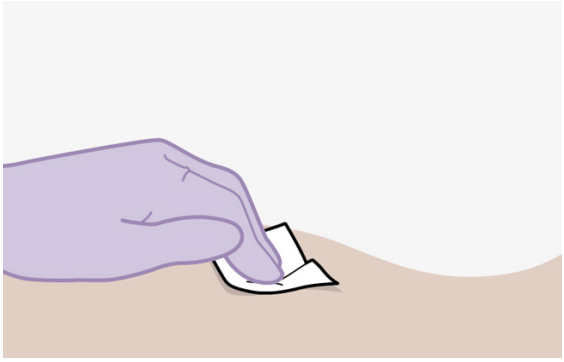


Figure R

- Apply pressure to the injection site using a gauze pad. **See Figure R.**
- A small bandage may be used if bleeding occurs.

Do not massage the area.

19. Make the needle safe.

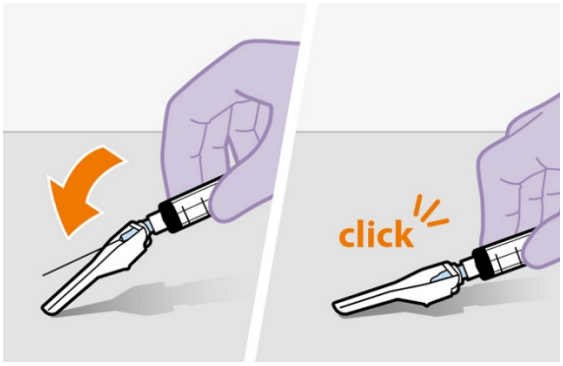


Figure S

- Fold the needle guard over the needle.
- 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 S.

After injection:

20. Dispose safely.

Figure T

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

Repeat for 2nd medicine.

- 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 medicine be left out of the refrigerator?

It is best to inject the medicine as soon as it reaches 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. If not used within 6 hours, the medication must be discarded.

2. How long can the medicine be left in the syringe?

It is best to inject the (room temperature) medicine as soon as possible after drawing it up. However, the medication can remain in the syringe for up to 2 hours before injecting.

If 2 hours are exceeded, the medication, syringes, and needles must be discarded.

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

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

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

Research Triangle Park, NC 27709

by:

GlaxoSmithKline

Research Triangle Park, NC 27709

CBN:1IFU2

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Issued: 01/2021

INSTRUCTIONS FOR USE

CABENUVA
(kab' en ue 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.

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). The administration order is not important.

Note: The ventrogluteal site is recommended.

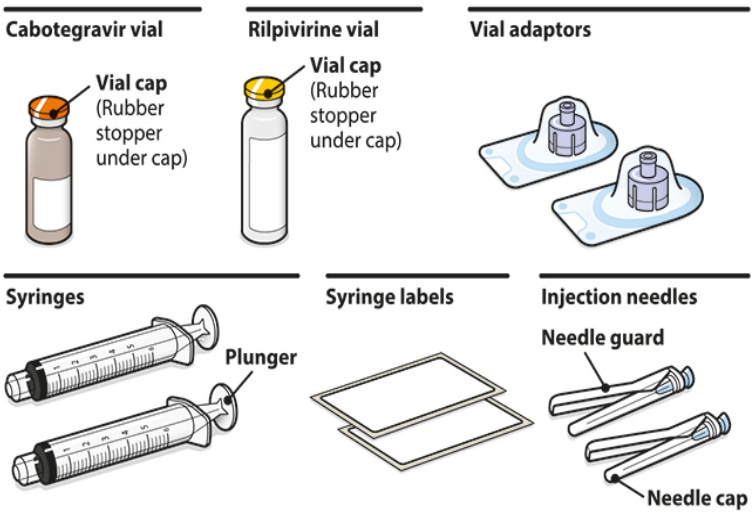
Storage information

• 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. If not used within 6 hours, the medication must be discarded.
- Once the medicines have been drawn into the syringe, the medication can remain in the syringes for up to 2 hours before injecting. If 2 hours are exceeded, the medication, syringes, and needles must be discarded.
- It is recommended to label the syringe with the time that the medication has been drawn into the syringe if the medication is not administered immediately.



Your pack contains:

- 1 vial of Cabotegravir
- 1 vial of Rilpivirine
- 2 vial adaptors
- 2 syringes
- 2 syringe labels
- 2 injection needles (23 gauge, 1½ inch)

Consider the patient's build and use medical judgment to select an appropriate injection needle length.

You will also need:

- Non-sterile gloves
- 4 alcohol wipes
- 4 gauze pads
- A suitable sharps container

Preparation:

1. Inspect both vials.

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 medication to come to room temperature. **See Figure B.**

3. Shake the vial vigorously.

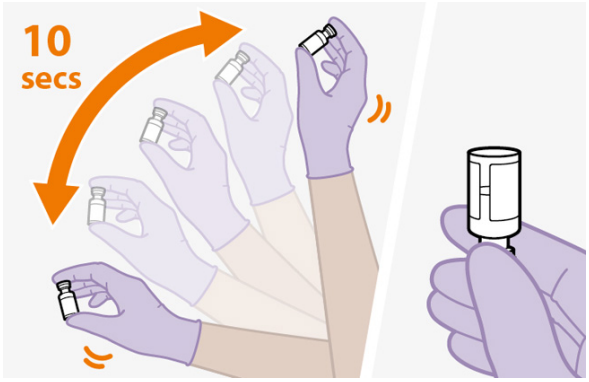


Figure C

- Hold the vial firmly, and vigorously shake for a full 10 seconds. **See Figure C.**
- Invert the vial and confirm the suspension is uniform.
- If the suspension is not uniform, shake the vial again.
- It is also normal to see small air bubbles.

4. Remove the vial cap.

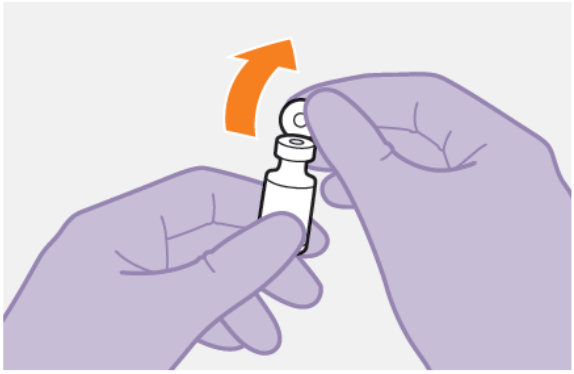


Figure D

- Remove the cap from the vial. **See Figure D.**
- Wipe the rubber stopper with an alcohol wipe.

Do not allow anything to touch the rubber stopper after wiping it.

5. Peel open the vial adaptor.

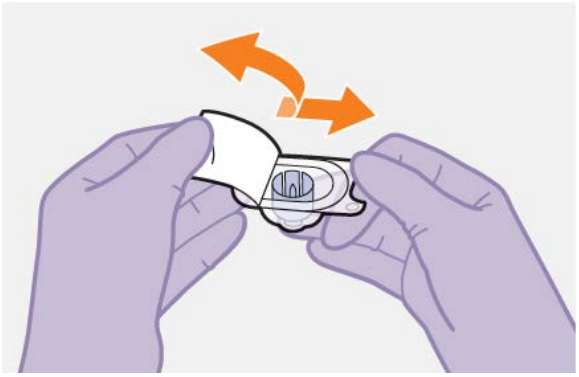


Figure E

- Peel off the paper backing from the vial adaptor packaging. **See Figure E.**

Note: Keep the adaptor in place in its packaging for the next step.

6. Attach the vial adaptor.

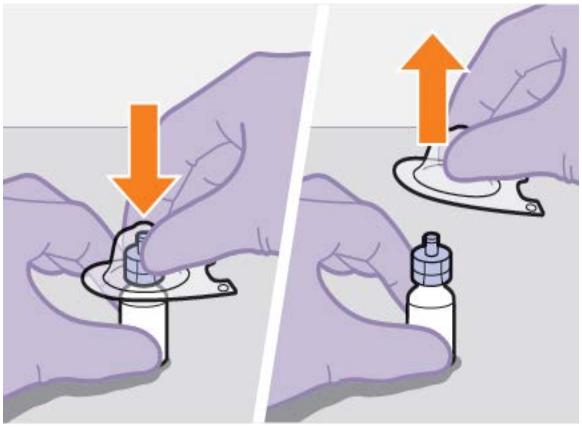


Figure F

- Press the vial adaptor straight down onto the vial using the packaging, as shown.
  The vial adaptor should snap securely into place.
- When you are ready, lift off the vial adaptor packaging as shown.

See Figure F.

7. Prepare the syringe.

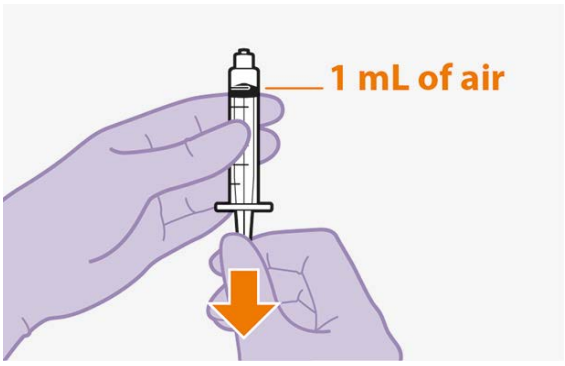


Figure G

- 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 G.**

8. Attach the syringe.

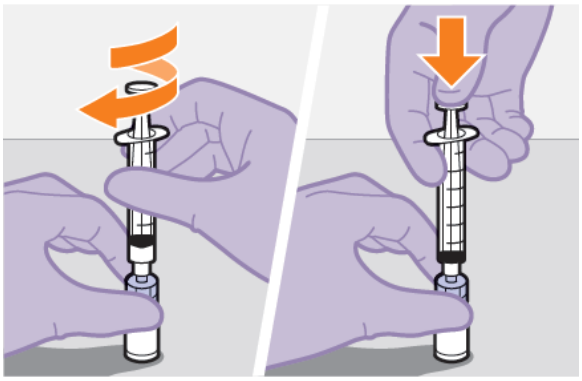


Figure H

- Hold the vial adaptor and vial firmly, as shown.
- Screw the syringe firmly onto the vial adaptor.
- Press the plunger all the way down to push the air into the vial.

See Figure H.

9. Slowly draw up the dose.

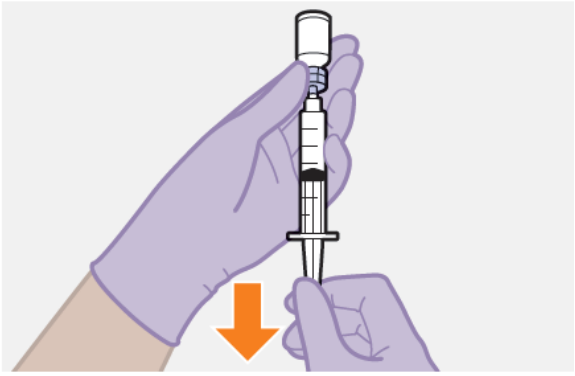


Figure I

- 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 I.**

10. Unscrew the syringe.

Figure J

- Unscrew the syringe from the vial adaptor, holding the vial adaptor as shown. **See Figure J.**

Note: Keep the syringe upright to avoid leakage. Check that the suspension looks uniform and milky white.

11. Attach the needle and affix syringe label.

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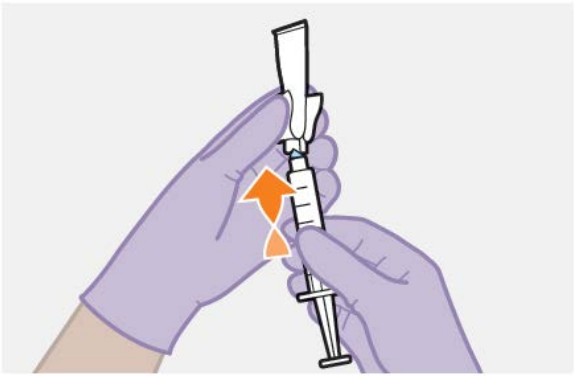
<tr><td> 
Figure K</td><td>

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.
Write the name of the medicine on the syringe label. Affix the label to the syringe making sure the gradations remain visible.

See Figure K.
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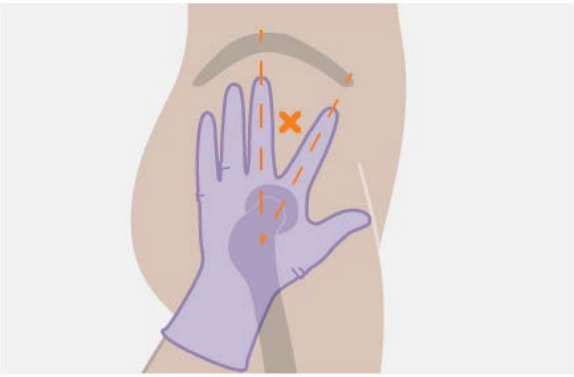
<tr><td colspan="2">Injection:</td></tr>
<tr><td colspan="2">12. Prepare the injection site.</td></tr>
<tr><td> 
Figure L</td><td>
Injections must be administered to the gluteal sites. See Figure L.
Select from the following areas for the injection:
• Ventrogluteal, as shown (recommended)
• Dorsogluteal (upper outer quadrant)

Note: For gluteal intramuscular use only. Do not inject intravenously.
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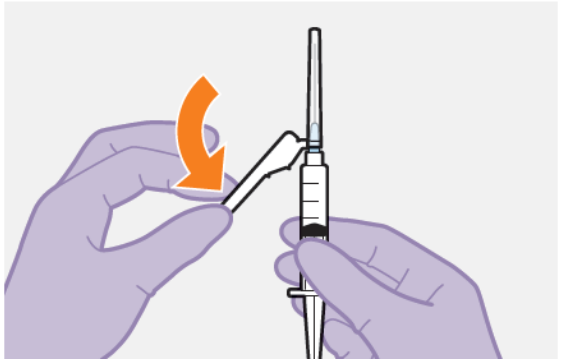
<tr><td colspan="2">13. Remove the cap.</td></tr>
<tr><td> 
Figure M</td><td>

Fold the needle guard away from the needle. See Figure M.
Pull off the injection needle cap.

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<tr><td colspan="2">14. Remove extra liquid from the syringe.</td></tr>
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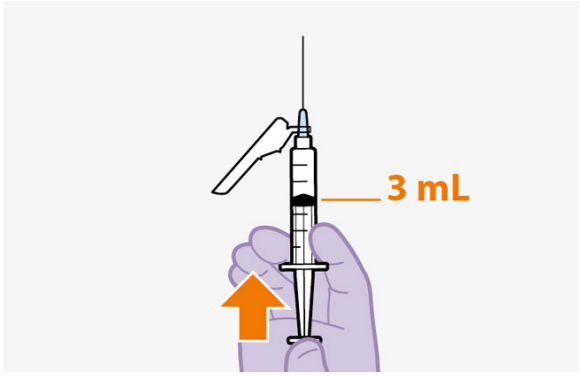

Figure N

- 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 N.**

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

15. Stretch the skin.

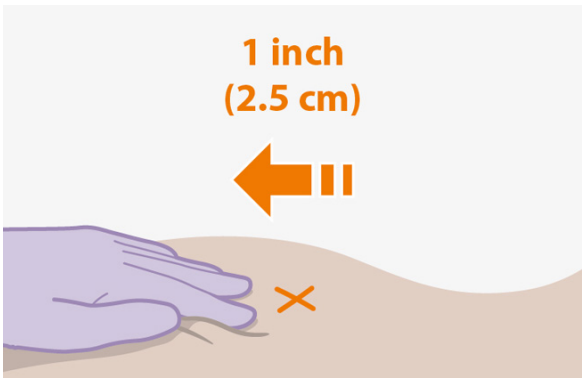

Figure O

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 O.**
- Keep it held in this position for the injection.

16. Insert the needle.

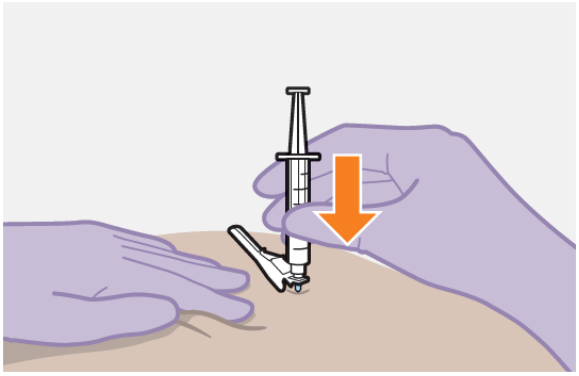

Figure P

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

17. Inject the dose of medicine.

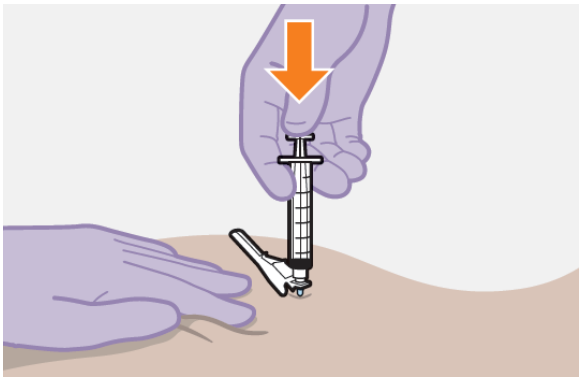

Figure Q

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

18. Assess the injection site.

Figure R

- Apply pressure to the injection site using a gauze pad. **See Figure R.**
- A small bandage may be used if bleeding occurs.

Do not massage the area.

19. Make the needle safe.

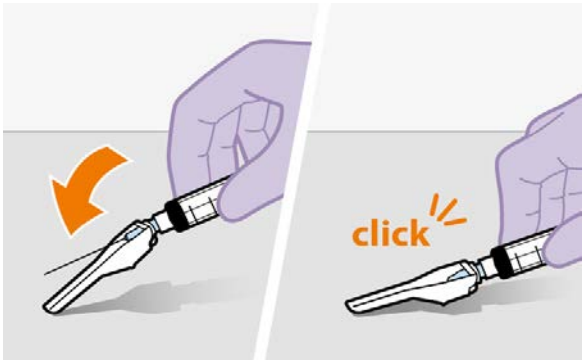

Figure S

- Fold the needle guard over the needle.
- 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 S.

After injection:

20. Dispose safely.

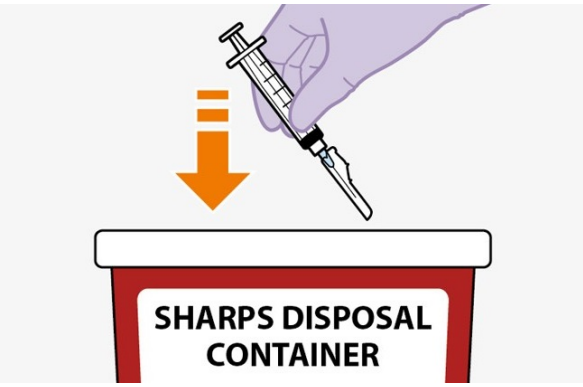

Figure T

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

Repeat for 2nd medicine.

- 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 medicine be left out of the refrigerator?

It is best to inject the medicine as soon as it reaches 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. If not used within 6 hours, the medication must be discarded.

2. How long can the medicine be left in the syringe?

It is best to inject the (room temperature) medicine as soon as possible after drawing it up. However, the medication can remain in the syringe for up to 2 hours before injecting.

If 2 hours are exceeded, the medication, syringes, and needles must be discarded.

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

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

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

Research Triangle Park, NC 27709

by:

GlaxoSmithKline

Research Triangle Park, NC 27709

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This Instructions for Use has been approved by the U.S. Food and Drug Administration. Issued: 01/2021