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

VOCABRIA (cabotegravir) tablets, for oral use
Initial U.S. Approval: 2021

---------- INDICATIONS AND USAGE----------
VOCABRIA is a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with EDURANT (rilpivirine) for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as:

- oral lead-in to assess the tolerability of cabotegravir prior to administration of CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions. (1)
- oral therapy for patients who will miss planned injection dosing with CABENUVA. (1)

----------DOSAGE AND ADMINISTRATION----------

- One tablet of VOCABRIA 30 mg taken orally once daily for approximately 1 month in combination with one tablet of EDURANT (rilpivirine) 25 mg taken orally once daily with a meal. (2.1)

---------- DOSAGE FORMS AND STRENGTHS----------

- Tablets: 30 mg (3)

---------- CONTRAINDICATIONS ----------

- Previous hypersensitivity reaction to cabotegravir. (4)
- Coadministration with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, and rifapentine. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Hypersensitivity reactions have been reported in association with other integrase inhibitors. Discontinue VOCABRIA immediately if signs or symptoms of hypersensitivity reactions develop. (5.1)
- Hepatotoxicity has been reported in patients receiving cabotegravir. Monitoring of liver chemistries is recommended. Discontinue VOCABRIA if hepatotoxicity is suspected. (5.2)
- Depressive disorders have been reported with VOCABRIA. Prompt evaluation is recommended for depressive symptoms. (5.3)
- Risks Associated with Combination Treatment: Review the prescribing information for EDURANT for information on rilpivirine prior to initiation of VOCABRIA in combination with EDURANT. (5.5)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (Grades 1 to 4) observed in at least 3 subjects receiving VOCABRIA were headache, nausea, abnormal dreams, anxiety, and insomnia. (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 VOCABRIA. (4, 5.4, 7)
- Because VOCABRIA in combination with EDURANT (rilpivirine) 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 may decrease the plasma concentrations of cabotegravir. (4, 7.2, 7.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- 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

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VOCABRIA is indicated in combination with EDURANT (rilpivirine) for short-term treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as *[see Dosage and Administration (2.1)]*:

- oral lead-in to assess the tolerability of cabotegravir prior to administration of cabotegravir extended-release injectable suspension, a component of CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions.
- oral therapy for patients who will miss planned injection dosing with CABENUVA.

2 DOSAGE AND ADMINISTRATION

2.1 Oral Lead-in Dosing to Assess Tolerability of Cabotegravir

Consult the prescribing information for CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspension before initiating VOCABRIA to ensure therapy with CABENUVA is appropriate. See full prescribing information for CABENUVA.

Oral lead-in should be used for approximately 1 month (at least 28 days) to assess the tolerability of cabotegravir prior to the initiation of CABENUVA. The recommended oral daily dose is one 30-mg tablet of VOCABRIA in combination with one 25-mg tablet of EDURANT (rilpivirine). The last oral dose should be taken on the same day injections with CABENUVA are started.

Take VOCABRIA once daily with EDURANT at approximately the same time each day with a meal *[see Clinical Pharmacology (12.3)]*.

Because VOCABRIA is indicated in combination with rilpivirine tablets, the prescribing information for EDURANT should also be consulted.

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

If a patient plans to miss a scheduled injection of CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions by more than 7 days, take daily oral therapy to replace up to 2 consecutive monthly injection visits. The recommended oral daily dose is one 30-mg tablet of VOCABRIA (cabotegravir) and one 25-mg tablet of EDURANT (rilpivirine). Take VOCABRIA with EDURANT at approximately the same time each day with a meal. The first dose of oral therapy should be taken approximately 1 month after the last injection dose of CABENUVA and continued until the day injection dosing is restarted. See full prescribing information for CABENUVA to resume monthly injection dosing.

3 DOSAGE FORMS AND STRENGTHS

VOCABRIA tablets are white, film-coated, oval tablets debossed with “SV CTV” on one side. Each film-coated tablet contains 30 mg of cabotegravir (equivalent to 31.62 mg cabotegravir sodium).

4 CONTRAINDICATIONS

VOCABRIA is contraindicated in patients:

- with previous hypersensitivity reaction to cabotegravir *[see Warnings and Precautions (5.1)]*.
- receiving the following coadministered drugs for which significant decreases in cabotegravir plasma concentrations may occur due to uridine diphosphate (UDP)-glucuronosyl transferase (UGT)1A1 enzyme induction, which may result in loss of virologic response *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)]:*
    - Anticonvulsants: Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
    - Antimycobacterials: Rifampin, rifapentine

Prior to initiation of VOCABRIA, note that use of CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions with rifabutin is contraindicated.

Since VOCABRIA is taken in combination with rilpivirine tablets, the prescribing information for EDURANT should be consulted for additional contraindications.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious or severe hypersensitivity reactions have been reported in association with other integrase inhibitors and could occur with VOCABRIA *[see Adverse Reaction (6.1)]*. Remain vigilant and discontinue VOCABRIA if a hypersensitivity reaction is suspected.

Discontinue VOCABRIA 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 *[see Dosage and Administration (2.1), Contraindications (4), Adverse Reactions (6.1)]*.

5.2 Hepatotoxicity

Hepatotoxicity has been reported in patients receiving cabotegravir 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 VOCABRIA should be discontinued if hepatotoxicity is suspected.

5.3 Depressive Disorders

Depressive disorders (including depressed mood, depression, mood altered, mood swings) have been reported with VOCABRIA *[see Adverse Reactions (6.1)]*. Promptly evaluate patients with depressive symptoms to assess whether the symptoms are related to VOCABRIA and to determine whether the risks of continued therapy outweigh the benefits.

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

The concomitant use of VOCABRIA 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 VOCABRIA, and possible development of viral resistance *[see Contraindications (4), Drug Interactions (7.3)]*.

See Table 1 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 VOCABRIA; review concomitant medications during therapy with VOCABRIA.

5.5 Risks Associated with Rilpivirine Treatment

VOCABRIA is indicated for use in combination with EDURANT (rilpivirine) *[see Dosage and Administration (2.1)]*. Review the prescribing information for EDURANT for information on rilpivirine prior to initiation of VOCABRIA in combination with rilpivirine.

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)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)*
- Depressive disorders *[see Warnings and Precautions (5.3)]*

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. See full prescribing information for CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions for additional safety information. Since VOCABRIA is taken in combination with rilpivirine tablets, the prescribing information for EDURANT (rilpivirine) should be consulted for relevant information on rilpivirine.

The safety assessment of VOCABRIA for oral lead-in therapy prior to therapy with 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.

Adverse reactions were reported following exposure to VOCABRIA tablets and EDURANT tablets administered in combination as oral lead-in therapy (median time exposure: 5.3 weeks). Adverse reactions included those attributable to the oral formulation 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 during the oral lead-in period were headache, nausea, abnormal dreams, anxiety, and insomnia all of which occurred in at least 3 subjects, with an incidence less than or equal to 1%.

During the oral lead-in period, 6 (1%) subjects discontinued due to adverse events, including asthenia, myalgia, depression suicidal, and headache.

7 DRUG INTERACTIONS

7.1 Concomitant Use with Other Antiretroviral Medicines

Because VOCABRIA in combination with EDURANT (rilpivirine) is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended *[see Indications and Usage (1), Drug Interactions (7.4), Clinical Pharmacology (12.3)]*. Refer to the prescribing information for EDURANT for relevant information on rilpivirine.

Prior to initiating oral therapy, the prescribing information for CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions should be consulted to ensure therapy with CABENUVA will be appropriate.

7.2 Potential for Other Drugs to Affect VOCABRIA

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 VOCABRIA with these drugs is contraindicated *[see Contraindications (4)]*.

Coadministration of oral cabotegravir with polyvalent cation-containing products may lead to decreased absorption of cabotegravir *[see Drug Interactions (7.3)]*.

7.3 Established and Other Potentially Significant Drug Interactions

Information regarding potential drug interactions with cabotegravir are provided in Table 1. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of the interaction and potential for loss of virologic response *[see Contraindications (4), Warnings and Precautions (5.4), Clinical Pharmacology (12.3)]*. Table 1 includes potentially significant interactions but is not all inclusive.

VOCABRIA in combination with EDURANT (rilpivirine) is intended as a complete antiretroviral regimen for treatment of HIV-1 in patients who are virologically suppressed. Refer to the prescribing

information for EDURANT for established or potentially significant interactions that should be considered during concomitant administration of VOCABRIA and EDURANT.

Table 1. Drug Interactions with VOCABRIA

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Antacids containing polyvalent cations (e.g., Aluminum or magnesium hydroxide, calcium carbonate)	↓Cabotegravir	Administer antacid products at least 2 hours before or 4 hours after taking VOCABRIA.
Anticonvulsants: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	↓Cabotegravir	Coadministration is contraindicated with VOCABRIA due to potential for loss of virologic response and development of resistance *[see Contraindications (4)]*.
Antimycobacterials[a]: Rifampin[b] Rifapentine	↓Cabotegravir	

↓ = Decrease.

[a] Rifabutin can be coadministered with cabotegravir; however, it is contraindicated with CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions.

[b] *See Clinical Pharmacology (12.3) for magnitude of interaction.*

7.4 Drugs without Clinically Significant Interactions with Cabotegravir

Based on drug interaction study results, the following drugs can be coadministered with cabotegravir without a dose adjustment: etravirine, midazolam, oral contraceptives containing levonorgestrel and ethinyl estradiol, rifabutin, and rilpivirine *[see Clinical Pharmacology (12.3)]*. Prior to initiating oral therapy, note that use of CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions with rifabutin is contraindicated.

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 VOCABRIA 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 VOCABRIA 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 VOCABRIA during pregnancy, NTDs were associated with dolutegravir, another integrase inhibitor. Discuss the benefit-risk of using VOCABRIA with individuals of childbearing potential or during pregnancy.

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)*.

Data

Human Data: 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.

Animal Data: 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.

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 cabotegravir is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, cabotegravir was present in milk *(see Data)*.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving VOCABRIA.

Data

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

8.4 Pediatric Use

The safety and efficacy of VOCABRIA have not been established in pediatric patients.

8.5 Geriatric Use

Clinical trials of VOCABRIA 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 VOCABRIA 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

No dosage adjustment of VOCABRIA is necessary for patients with mild to moderate (creatinine clearance equal to 30 mL/min to less than 90 mL/min) or severe renal impairment (creatinine clearance less than 30 mL/min) *[see Clinical Pharmacology (12.3)]*. The effect of end-stage renal disease (creatinine clearance less than15 mL/min) on the pharmacokinetics of cabotegravir is unknown. As cabotegravir is greater than 99% protein bound, dialysis is not expected to alter exposures of cabotegravir.

Since VOCABRIA is taken in combination with oral rilpivirine, the prescribing information for EDURANT (rilpivirine) should be consulted for additional recommendations in patients with severe impairment or end-stage renal disease.

8.7 Hepatic Impairment

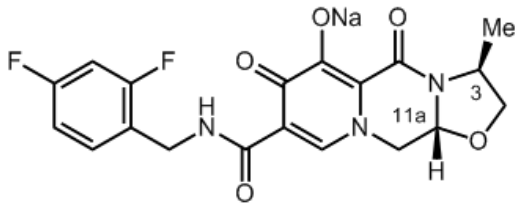
No dosage adjustment of VOCABRIA is necessary for patients with mild or moderate hepatic impairment (Child-Pugh A or B). The effect of severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of cabotegravir is unknown *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no known specific treatment for overdose with VOCABRIA. If overdose occurs, monitor the patient and apply standard supportive treatment as required. As cabotegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

11 DESCRIPTION

VOCABRIA contains cabotegravir, as cabotegravir sodium, an HIV integrase strand transfer inhibitor (INSTI). The chemical name of cabotegravir sodium is sodium (*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 $C_{19}H_{16}F_2N_3NaO_5$ and the molecular weight is 427.34 g/mol. It has the following structural formula:



Cabotegravir sodium is a white to almost white crystalline solid that is slightly soluble in water.

Each immediate-release film-coated tablet of VOCABRIA for oral administration contains 30 mg of cabotegravir (equivalent to 31.62 mg cabotegravir sodium) and the inactive ingredients: hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablet film-coating contains hypromellose, polyethylene glycol, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cabotegravir is an HIV-1 antiretroviral drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose of cabotegravir 150 mg orally every 12 hours (10 times the recommended total daily oral lead-in dosage of VOCABRIA) 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 above the geometric mean steady-state C_{max} associated with the recommended 30-mg dose of oral cabotegravir. For additional QT information related to the injectable formulations of cabotegravir and rilpivirine (CABENUVA) and the oral formulation of rilpivirine (EDURANT), refer to the prescribing information for CABENUVA and EDURANT.

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetic properties of cabotegravir are provided in Table 2. The multiple-dose pharmacokinetic parameters are provided in Table 3.

Table 2. Pharmacokinetic Properties of Cabotegravir

Absorption	
T_{max} (h), median	3
Effect of high-fat meal (relative to fasting): $AUC_{(0\text{-inf})}$ ratio[a]	1.14 (1.02, 1.28)
Distribution	
% Bound to human plasma proteins	>99.8
Blood-to-plasma ratio	0.52
CSF-to-plasma concentration ratio (median [range])[b]	0.003 (0.002 to 0.004)
$t_{1/2}$ (h), mean	41
Metabolism	
Metabolic pathways	UGT1A1 UGT1A9 (minor)
Excretion	
Major route of elimination	Metabolism
% of dose excreted as total ^{14}C (unchanged drug) in urine[c]	27 (0)
% of dose excreted as total ^{14}C (unchanged drug) in feces[c]	59 (47)

[a] Geometric mean ratio (fed/fasted) in pharmacokinetic parameters and 90% confidence interval. High-calorie/high-fat meal = 870 kcal, 53% fat.

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

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

Table 3. Multiple-Dose Pharmacokinetic Parameters of Oral Cabotegravir

Parameter	Geometric Mean (5^{th}, 95^{th} Percentile)[a]
C_{max} (mcg/mL)	8.0 (5.3, 11.9)
$AUC_{(0\text{-}tau)}$ (mcg.h/mL)	145 (93.5, 224)
C_{tau} (mcg/mL)	4.6 (2.8, 7.5)

[a] Pharmacokinetic parameter values were based on individual post-hoc estimates from the final population pharmacokinetic model for subjects receiving 30 mg of oral cabotegravir once daily in FLAIR and ATLAS trials.

Specific Populations

No clinically significant differences in the pharmacokinetics of cabotegravir 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. The pharmacokinetics of cabotegravir has 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: No clinically significant differences in the pharmacokinetics of cabotegravir are expected 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)]*.

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)]*.

Drug Interaction Studies

Cabotegravir is not a clinically relevant inhibitor of the following enzymes and transporters: cytochrome P450 (CYP)1A2, 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.

The effects of coadministered drugs on the exposure of cabotegravir are summarized in Table 4 and the effects of cabotegravir on the exposure of coadministered drugs are summarized in Table 5.

Table 4. 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 5. 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.

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.

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).

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

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.

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 6). 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 6). 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 6. 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 (0)
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

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.

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.

Mutagenesis

Cabotegravir was 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.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adults

The use of VOCABRIA in combination with EDURANT (rilpivirine) as an oral lead-in and in patients who miss planned injections with CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions was evaluated in two Phase 3 randomized, multicenter, active-controlled, parallel-arm, open-label, non-inferiority trials (Trial 201584: FLAIR [NCT02938520] and Trial 201585: ATLAS [NCT02951052]) in subjects who were virologically suppressed (HIV-1 RNA less than 50 copies/mL). Please refer to the CABENUVA prescribing information for additional information.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each VOCABRIA tablet contains 30 mg of cabotegravir and is a white, oval, film-coated, biconvex tablet debossed with “SV CTV” on one side.

Bottle of 30 tablets with child-resistant closure NDC 49702-248-13.

Store below 30°C (86°F)

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 VOCABRIA and seek medical attention if they develop a rash associated with any of the following symptoms: 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)]*.

Hepatotoxicity

Inform patients that hepatotoxicity has been reported with cabotegravir *[see Warnings and Precautions (5.2), Adverse Reactions (6.1)]*. Inform patients that monitoring for liver transaminases is recommended.

Depressive Disorders

Inform patients that depressive disorders (including depressed mood, depression, mood altered, mood swings) have been reported with VOCABRIA. Promptly evaluate patients with severe depressive symptoms to assess whether the symptoms are related to VOCABRIA and to determine whether the risks of continued therapy outweigh the benefits *[see Warnings and Precautions (5.3), Adverse Reactions (6.1)]*.

Drug Interactions

VOCABRIA 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 *[see Contraindications (4), Drug Interactions (7)]*.

Dosage and Administration

Inform patients that it is important to take VOCABRIA once daily on a regular dosing schedule with a meal at the same time as EDURANT (rilpivirine) and to avoid missing doses, as this can result in development of resistance. Instruct patients that if they miss a dose of VOCABRIA, to take it as soon as they remember *[see Dosage and Administration (2), Clinical Pharmacology (12.3)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to VOCABRIA during pregnancy *[see 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

VCB:1PI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

VOCABRIA (voe Kab' ree ah)
(cabotegravir)
tablets, for oral use

What is VOCABRIA?

VOCABRIA is a prescription medicine that is used in combination with another Human Immunodeficiency Virus-1 (HIV-1) medicine called EDURANT (rilpivirine) for short-term treatment of HIV-1 infection in adults to replace their current HIV-1 medicines when their healthcare provider determines that they meet certain requirements. VOCABRIA is for use:

- to assess the tolerability of cabotegravir before receiving the long-acting medicine called CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions.
- oral therapy for people who will miss planned injection dosing with CABENUVA.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

You should also read the Patient Information for EDURANT.

It is not known if VOCABRIA is safe and effective in children.

Do not take VOCABRIA if you:

- have ever had an allergic reaction to cabotegravir.
- are taking any of the following medicines:
  - o carbamazepine
  - o oxcarbazepine
  - o phenobarbital
  - o phenytoin
  - o rifampin
  - o rifapentine

Before you take VOCABRIA, 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.
- have ever had liver problems.
- have ever had mental health problems.
- are pregnant or plan to become pregnant. It is not known if VOCABRIA will harm your unborn baby.

  Pregnancy Registry. There is a pregnancy registry for women who take VOCABRIA 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 VOCABRIA.**
  - o You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - o It is not known if VOCABRIA 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 VOCABRIA.

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

Some medicines interact with VOCABRIA. 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 VOCABRIA.

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

How should I take VOCABRIA?

- Take 1 VOCABRIA tablet and 1 EDURANT (rilpivirine) tablet one time a day for one month (at least 28 days) exactly as your healthcare provider tells you.
- You will receive treatment with VOCABRIA tablets in combination with EDURANT tablets for one month (at least 28 days) before you receive CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions for the first time. This will allow your healthcare provider to assess how well you tolerate these medicines.
- Your final dose of VOCABRIA and EDURANT tablets should be taken on the same day you receive your first injections 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.
- VOCABRIA may be taken with or without food.
- If you take VOCABRIA at the same time as EDURANT, you should take it with a meal.
- If you take antacid products that contain aluminum or magnesium hydroxide or calcium carbonate, they should be taken at least 2 hours before or 4 hours after you take VOCABRIA. Do not miss a dose of VOCABRIA. If you miss a dose of VOCABRIA, take it as soon as you remember.
- Stay under the care of a healthcare provider during treatment with VOCABRIA.
- Do not change your dose or stop taking VOCABRIA without talking to your healthcare provider.
- Do not miss a dose of VOCABRIA. If you miss a dose of VOCABRIA, take it as soon as you remember.
- Do not run out of VOCABRIA. The virus in your blood may increase and the virus may become harder to treat.
- If you take too much VOCABRIA, go to the nearest hospital emergency room right away.

What are the possible side effects of VOCABRIA?

VOCABRIA may cause serious side effects including:

- **Allergic reactions.** Call your healthcare provider right away if you develop a rash with VOCABRIA**. Stop taking VOCABRIA 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
- **Liver problems**. Liver problems have happened in people with or without history of liver problems or other risk factors. Your healthcare provider may do blood tests to check your liver function. **Call your healthcare provider right away if you develop any of the following signs or symptoms of liver problems:**
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or “tea-colored” urine
  - light-colored stools (bowel movements)
  - nausea or vomiting
  - loss of appetite
  - pain, aching, or tenderness on the right side of your stomach area
  - itching
- **Depression or mood changes. Call your healthcare provider or get emergency medical help right away if you 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 VOCABRIA include:

- headache
- nausea
- abnormal dreams
- anxiety
- sleep disorders

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

How should I store VOCABRIA?

- Store VOCABRIA below 86°F (30°C).

Keep VOCABRIA and all medicines out of the reach of children.

General information about the safe and effective use of VOCABRIA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VOCABRIA for a condition for which it was not prescribed. Do not give VOCABRIA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about VOCABRIA that is written for health professionals.

What are the ingredients in VOCABRIA?

Active ingredient: cabotegravir

Inactive ingredients: hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

The tablet film-coating contains: hypromellose, polyethylene glycol and titanium dioxide.

Manufactured for:

ViiV Healthcare

Research Triangle Park, NC 27709

by:

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Research Triangle Park, NC 27709

VCB:1PIL

For more information call 1-877-844-8872.

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