NEW DRUG APPROVAL

Brand Name	Vocabria®
Generic Name	cabotegravir
Drug Manufacturer	ViiV Healthcare Company

New Drug Approval

FDA Approval Date: January 21, 2021

Review Designation: Priority

Type of Review: Type 1 - New Molecular Entity

Dispensing Restrictions: Limited Distribution, Specialty Only

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

HIV infection is a chronic disease caused by a retrovirus in which cellular immune function is progressively damaged, resulting in life-threatening opportunistic infections and direct end-organ injury from persistent inflammation.

AIDS is the most advanced stage of HIV disease, characterized by seropositivity for HIV infection in combination with evidence of advanced immunosuppression, demonstrated either by the occurrence of specific opportunistic infections and neoplasms or by a CD4+ lymphocyte count less than 200 cells/microL.

Approximately 1.2 million people are living with HIV in the United States. In 2018, 36,400 new infections occurred. The rate of new infections has remained flat since 2014. HIV impacts the black, Hispanic, and LGBTQ communities disproportionately. According to another CDC report, of the people with HIV (diagnosed and undiagnosed) in 2018, about 76% have received some HIV care, 58% were retained in care, and 65% were virally suppressed or undetectable. Having a suppressed or undetectable viral load protects the health of a person living with HIV, preventing disease progression.

The annual number of HIV infections in 2018, compared with 2014, decreased among persons aged 13–24, but remained stable among all other age groups. In 2018, the rate was highest for persons aged 25-34 (31.5), followed by the rate for persons aged 35-44.

Efficacy

The safety and efficacy of Cabenuva® and Vocabria® were evaluated in two Phase 3, randomized, open-label, multinational, noninferiority trials, summarized in the table below.

Table 2. Summary of ATLAS and FLAIR Trials		
	ATLAS (NCT02951052)	**FLAIR (NCT02938520)**
Study Population	• Adult patients with HIV RNA <50 copies/mL for at least 6 months while on standard oral ART • Oral ART regimens consisted of 2 NRTIs plus an NNRTI, INSTI, boosted protease inhibitor (PI), or unboosted atazanavir • Exclusion criteria included patients taking Triumeq (abacavir, dolutegravir, lamivudine), active HBV infection, and INSTI or NNRTI resistance mutations • Median age: 42 years • 33% female; 32% non-white • ARV regimen included NRTI + NNRTI (50%), INSTI (33%), and PI (17%)	• HIV treatment-naïve adults with HIV RNA ≥1000 copies/mL at screening • Exclusion criteria included active hepatitis B virus (HBV) infection and presence of NNRTI resistance mutations • Median age: 34 years • 22% female; 26% non-white • 20% had HIV RNA of 100,000 copies/mL at baseline
Interventions	616 patients were randomized (1:1) to one of the following: • Continue current oral ART (n = 308) • Receive Cabenuva* (n = 308)	Oral induction therapy with Triumeq (abacavir, dolutegravir, lamivudine) was initiated in 629 patients. At 16 weeks, patients with HIV RNA <50 copies/mL (N = 566) were randomized (1:1) to one of the following: • Continue Triumeq (n = 283) • Receive Cabenuva* (n = 283)

Table 2. Summary of ATLAS and FLAIR Trials

	ATLAS (NCT02951052)	FLAIR (NCT02938520)

Key Endpoints	• Primary endpoint: Percentage of patients with HIV RNA ≥50 copies/mL at Week 48
	• Secondary endpoints:
	  ○ Percentage of patients with HIV RNA <50 copies/mL at Week 48
	  ○ Patient satisfaction with ARV regimen via HIVTSQs or HIVTSQc	

Efficacy Results[a] (Cabenuva vs. oral ART)	Primary endpoint: 1.6% vs. 1.0% (95% CI, −1.2 to 2.5) Secondary endpoint: 92.5% vs. 95.5 (95% CI, −6.7 to 0.7)	Primary endpoint: 2.1% vs. 2.5% (95% CI, −2.8 to 2.1) Secondary endpoint: 93.6% vs. 93.3.% (95% CI, −3.7 to 4.5)
Virologic Failure	• Occurred in 3 participants in the Cabenuva group (2 with HIV subtype A/A1) and 4 participants in the oral ART group	• Occurred in 4 participants in the Cabenuva group (3 with HIV subtype A/A1) and 3 participants in the oral ART group
Study Withdrawal	• 26 (8%) participants in the Cabenuva group and 18 (6%) in the oral ART. Adverse events were the most common reason.	• 25 (9%) participants in the Cabenuva group and 22 (8%) in the oral ART group. Adverse events were the most common reason.
Adverse Events	• Injection site reactions occurred in 83% of patients (99% were mild to moderate). • Overall adverse events (excluding injection site reactions) were more common in the Cabenuva group. • Nasopharyngitis, headache, and upper respiratory tract infection were the most common adverse events in the Cabenuva group, occurring in >10% of patients.	• Injection site reactions occurred in 86% of patients (99% were mild to moderate) • Overall adverse events (excluding injection site reactions) were more common in the Cabenuva group, including serious adverse events. • Nasopharyngitis, headache, upper respiratory tract infection, and diarrhea were the most common adverse events in the Cabenuva group, occurring in >10% of patients.
Patient Satisfaction	• At Week 44, the adjusted mean increase in score from baseline on the HIVTSQs was 5.68 points higher in the Cabenuva group than in the oral ART group; 97% of participants selected the injectable regimen over oral ART.	• At Week 48, the HIVTSQc total score for satisfaction with current treatment as compared with induction treatment was higher in the Cabenuva group than in the oral ART group; 99% of survey responders preferred Cabenuva over the previous oral therapy.

Sources: Swindells S, et al. *N Engl J Med.* 2020;382(12):1112-1123; Orkin C, et al. *N Engl J Med.* 2020;382(12):1124-1135.
Abbreviations: HIVTSQc = HIV Treatment Satisfaction Questionnaire, change version; HIVTSQs = HIV Treatment Satisfaction Questionnaire, status version
*The Cabenuva group received oral cabotegravir 30 mg + oral rilpivirine 25 mg once daily for 4 weeks as a "lead-in" to assess tolerability, followed by an initiation dose of 600 mg cabotegravir/900 mg rilpivirine IM, then 400 mg cabotegravir/600 mg rilpivirine IM every 4 weeks for 52 weeks.

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Safety

ADVERSE EVENTS

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.

WARNINGS & PRECAUTIONS

- **Hypersensitivity reactions:** It has been reported in association with other integrase inhibitors. Discontinue immediately if signs or symptoms of hypersensitivity reactions develop.
- **Hepatotoxicity**: Hepatotoxicity has been reported in patients receiving cabotegravir. Monitoring of liver chemistries is recommended and treatment with Vocabria®. Should be discontinued if hepatotoxicity is suspected.
- **Depressive disorders**: Depressive disorders (including depressed mood, depression, mood altered, mood swings) have been reported with Vocabria®. Promptly evaluate patients with depressive symptoms to assess whether the symptoms are related to Vocabria® to determine whether the risks of continued therapy outweigh the benefits.
- **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. Consider the potential for drug interactions prior to and during therapy; review concomitant medications during therapy.
- **Risks Associated with Rilpivirine Treatment:** Vocabria® is indicated for use in combination with Edurant® (rilpivirine). Review the prescribing information for Edurant® for information on rilpivirine prior to initiation of Vocabria® in combination with rilpivirine.

CONTRAINDICATIONS

- Hypersensitivity to cabotegravir or rilpivirine.
- Coadministration with the following uridine diphosphateglucuronosyltransferase (UGT)1A1 and/or cytochrome P450 (CYP) 3A enzyme inducers, which may reduce plasma levels of cabotegravir or rilpivirine and increase the risk of virologic failure:
  - Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin;
  - Antimycobacterials: rifabutin, rifampin, rifapentine;
  - Systemic glucocorticoid: dexamethasone (more than single-dose treatment);
  - Herbal product: St. John's Wort.

Clinical Pharmacology

MECHANISMS OF ACTION

Inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration.

Dose & Administration

ADULTS

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.

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PEDIATRICS

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

GERIATRICS

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.

RENAL IMPAIRMENT

There are no dosage adjustments provided in the manufacturer's labeling.

HEPATIC IMPAIRMENT

There are no dosage adjustments provided in the manufacturer's labeling.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 30 mg