NEW DRUG APPROVAL

Brand Name	Cabenuva®
Generic Name	cabotegravir and rilpivirine
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 and Type 4 - New Combination

Dispensing Restriction: None

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.

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Efficacy

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)
Key Endpoints	• Primary endpoint: Percentage of patients with HIV RNA ≥50 copies/mL at Week 48 • Secondary endpoints: o Percentage of patients with HIV RNA <50 copies/mL at Week 48 o Patient satisfaction with ARV regimen via HIVTSQs or HIVTSQc	
Efficacy Results* (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.

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Safety

ADVERSE EVENTS

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.

WARNINGS & 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.
- Serious post-injection reactions with rilpivirine were reported. Monitor and treat as clinically indicated.
- Hepatotoxicity has been reported in patients receiving cabotegravir or rilpivirine. Monitoring of liver chemistries is recommended. Discontinue Cabenuva® if hepatotoxicity is suspected.
- Depressive disorders have been reported with Cabenuva®. Immediate medical evaluation is recommended for depressive symptoms.
- 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.

CONTRAINDICATIONS

- Previous hypersensitivity reaction to cabotegravir or rilpivirine.
- Coadministration with drugs where significant decreases in cabotegravir and/or rilpivirine plasma concentrations may occur, which may result in loss of virologic response.

Clinical Pharmacology

MECHANISMS OF ACTION

Cabotegravir: HIV-1 integrase strand transfer inhibitor (INSTI); cabotegravir, an analog of dolutegravir, prevents viral DNA integration into the host genome and inhibits HIV replication.

Rilpivirine: Non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1; inhibits HIV-1 replication by noncompetitive inhibition of HIV-1 reverse transcriptase.

Dose & Administration

ADULTS

- 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.
- For intramuscular (IM) gluteal injection only.
- 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.

PEDIATRICS

Safety and efficacy have not been established.

GERIATRICS

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.

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)

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