Lenacapavir

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Lenacapavir (LEN, Sunlenca, Yeztugo)

Formulations

Tablets

- [Sunlenca] Lenacapavir: 300 mg for treatment
- [Yeztugo] Lenacapavir: 300 mg for HIV pre-exposure prophylaxis (PrEP)

Single-Use Vial for Subcutaneous Injections

- [Sunlenca] Lenacapavir: 463.5 mg/1.5 mL suspension for treatment
- [Yeztugo] Lenacapavir: 463.5 mg/1.5 mL suspension for HIV PrEP

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Child and Adolescent Dose

- The safety and efficacy of using lenacapavir (LEN) in children and adolescents has not been established.

Adult Dose

- Approved for use in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection who are experiencing virologic failure on their current antiretroviral (ARV) regimen due to resistance, intolerance, or safety considerations. LEN is used in combination with an optimized background regimen.
- Approved for use as HIV pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults and adolescents weighing ≥35 kg who are at risk for HIV-1 acquisition. Individuals must have a negative HIV-1 test prior to initiating.

Initiation Option 1 (For Sunlenca or Yeztugo)

- Day 1: 927 mg by SQ injection (two 1.5-mL SQ injections in the abdomen) and 600 mg orally (two 300-mg tablets)
- Day 2: 600 mg orally (two 300-mg tablets)

Initiation Option 2 (For Sunlenca Only)

- Day 1: 600 mg orally (two 300-mg tablets)
- Day 2: 600 mg orally (two 300-mg tablets)
- Day 8: 300 mg orally (one 300-mg tablet)
- Day 15: 927 mg by SQ injection (two 1.5-mL SQ injections in the abdomen)

Selected Adverse Events

- Injection site reaction
- Nausea
- Headache

Special Instructions

- If LEN is discontinued, initiate an alternative, fully suppressive ARV regimen ≤28 weeks after the final injection of LEN to avoid virologic resistance.
- Planned missed injections: If scheduled injection is to be missed by more than 2 weeks, Sunlenca tablets may be used for oral bridging for up to 6 months until injections resume. Recommended dosage is 300 mg orally once every 7 days.
- Unplanned missed injections: If more than 28 weeks since last injection and tablets have not been taken for oral bridging, restart initiation from Day 1 (using Option 1 or Option 2) if clinically appropriate.

Metabolism/Elimination

- Minor metabolism by cytochrome P450 3A4 and uridine diphosphate glucuronosyltransferase 1A1.
- Major route of elimination is unchanged drug in feces.

Maintenance • 927 mg by SQ injection (two 1.5-mL SQ injections in the abdomen) every 26 weeks +/- 2 weeks from date of last injection	**Dosing in Patients With Hepatic Impairment** • No dosage adjustments were recommended for adults with mild (Child-Pugh-Turcotte Class A: score 5–6) or moderate (Child-Pugh-Turcotte Class B: score 7–9) hepatic impairment. **Dosing in Patients With Renal Impairment** • Creatinine clearance (CrCl) ≥15 mL/minute: No dosage adjustment is required. • CrCl <15 mL/minute: No dosage adjustments are provided in the manufacturer's prescribing information (i.e., not studied).[1] • Dialysis: No dosage adjustments are required. Not expected to be significantly removed by dialysis due to high protein binding. There is one published case report of a patient with estimated glomerular filtration rate 4 mL/min on hemodialysis who received LEN, fostemsavir, and lamivudine, with resultant viral suppression sustained over 1 year.[2]

Drug Interactions

Additional information about drug interactions is available in the Liverpool HIV Drug Interaction Checker.

- *Metabolism:*
  - *Treatment (Sunlenca):* Concomitant administration of lenacapavir (LEN) (a moderate cytochrome P450 [CYP] 3A inhibitor) with moderate or strong CYP3A inducers may significantly decrease LEN plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to LEN. Concomitant administration with strong inducers is contraindicated and with moderate inducers **is not recommended.**
  - *Pre-exposure prophylaxis (PrEP) (Yeztugo):* Concomitant administration of Yeztugo with moderate or strong inducers can be considered, with dosing adjustments. Supplemental dosing instructions are provided in Section 2.5 of the FDA label and specifies additional doses of Yeztugo to give when a moderate or strong CYP3A inducer is initiated.
- Combined P-glycoprotein, uridine diphosphate glucuronosyltransferase 1A1, and strong CYP3A inhibitors may significantly increase plasma concentrations of LEN. Concomitant administration of LEN with these inhibitors **is not recommended.**
- LEN is a moderate inhibitor of CYP3A. Due to the long half-life of LEN following subcutaneous (SQ) administration, LEN may increase the exposure of drugs primarily metabolized by CYP3A.
- Drug interactions may occur up to 9 months after the last SQ dose of LEN.

Major Toxicities

- *More common (incidence >10%):* Injection site reactions (62% to 83%)—including pain (19% to 31%), swelling (23% to 36%), erythema (25% to 31%), induration (15%), or the development of a nodule (14% to 25%)—were reported. Most injection site reactions resolve within days; however, nodules may persist for long periods of time consistent with their depot formulation.[3-5] Nausea (12% to 14%), headache (8% to 13%),[4,5] constipation (11% to 13%),[3,4] and diarrhea (8% to

14%)[3-5] have been reported. No Grade 3 or 4 laboratory abnormalities were deemed clinically significant; the most frequent was abnormal creatinine clearance (CrCl) (13%). Low levels of CrCl or estimated glomerular filtration rate or high creatinine levels were transient or unconfirmed abnormalities.[4]

- *Less common (more severe):* Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy (ART).

Resistance

In a randomized, placebo-controlled, double-blind, multicenter trial (CAPELLA), treatment-emergent LEN resistance developed in 14 of 72 participants (19%) at 2 years, with capsid substitutions including M66I, Q67H/K/N, K70H/N/R/S, and N74D/H/K, all linked to functional LEN monotherapy. Resistance largely occurred early in the trial (i.e., 8 participants by Week 26), and half of the patients with resistance development had evidence of low adherence to their optimized background therapy as indicated by plasma drug concentrations. Of these 14 participants, 5 developed LEN resistance before Week 26 and 9 at 52 weeks or later.[3] Notably, 7 of the 14 were able to achieve viral suppression on continued LEN, with a change in or resumption of an optimized background regimen.[4,6]

The reported prevalence of LEN-resistance mutations is low (0.14%) among individuals who were ART naive.[7,8] A recent study analyzed 10,057 HIV genotypic sequences from clinical trials and publicly available datasets (of which approximately 5% were A1 and 4% were D subtypes), and found a 0% prevalence of polymorphisms associated with LEN resistance, except for T107A. T107A was present at 1.8% and 0% among the subtype A1 and subtype D genomes, respectively. [8]

The International Antiviral Society–USA maintains a list of updated HIV Drug Resistance Mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

LEN is not approved by the U.S. Food and Drug Administration (FDA) for use in pediatric patients for *treatment* of HIV; LEN is approved for use as *HIV PrEP* among adolescents weighing ≥35 kg who are at risk for HIV-1 acquisition. LEN was approved by the FDA in 2022 in combination with other antiretrovirals (ARVs) and is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection who are experiencing virologic failure on their current ARV regimen due to resistance, intolerance, or safety considerations. LEN is given alongside two other fully active agents in the treatment of HIV if at least one agent has a high barrier to resistance; otherwise, three fully active agents are recommended in addition to LEN.[9]

There are limited data on the efficacy and safety of LEN in people with HIV who are initiating ART.

LEN is in Phase 3 development for HIV PrEP in adults and adolescents and received FDA approval as PrEP on June 18, 2025. The Phase 3 PURPOSE-1 study of LEN as PrEP in female adolescents aged ≥16 years and women showed 100% efficacy of LEN, with no cases of HIV among 2,134 women and adolescent girls receiving LEN, as compared to 16 incident cases of HIV in 1,068 women receiving tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) PrEP (incidence 0 and 1.69 per 100 person-years, respectively; $P < 0.001$).[10] On the basis of this data, the Data Monitoring Committee recommended that the blinded phase of the trial be stopped at the interim analysis and LEN be offered to all participants. Published results of the Phase 3 PURPOSE-2 study of LEN as PrEP in men and individuals with other self-expressions who have sex with men are now available.

PURPOSE-2 found two cases of incident HIV (0.10 per 100 person-years; n = 2,180) in the group that received LEN and nine cases of incident HIV in the group that received TDF/FTC (0.93 per 100 person-years; n = 1,087), with 96% relative risk reduction (95% confidence interval (CI), 82%–99%) as compared to the estimated baseline HIV incidence of 2.37 per 100 person-years (incidence rate ratio 0.04; *P* < 0.001). When compared to the group who received TDF/FTC, the HIV incidence rate ratio in the LEN group was 0.11; 95% CI, 0.02 to 0.51; *P* = 0.002).[11]

Efficacy and Pharmacokinetics in Clinical Trials

Clinical Trials in Adults

The CAPELLA trial evaluated LEN in combination with an optimized background ART regimen in 72 patients with multidrug-resistant HIV-1.[4] Because CAPELLA was a clinical trial, the optimized background ART regimen did not include experimental agents. CAPELLA enrolled participants 23 to 78 years of age (enrollment criteria included those ≥12 years of age) who were experiencing virologic failure on their current regimen and with documented resistance to at least two ARV medications from at least three of the four main classes (nucleoside reverse transcriptase inhibitors, non–nucleoside reverse transcriptase inhibitors, protease inhibitors, and integrase strand transfer inhibitors) and to no more than two fully active ARV drugs from the four main classes that could be effectively combined. Patients were enrolled in two cohorts according to change in plasma HIV-1 RNA level between the screening and cohort-selection visits. In cohort 1, patients were first randomly assigned in a 2:1 ratio to receive oral LEN or placebo in addition to their failing therapy for 14 days. During the maintenance period, starting on Day 15, patients in the LEN group received SQ LEN once every 6 months, and those in the placebo group received oral LEN, followed by SQ LEN. Both groups also received optimized background therapy. In cohort 2, all the patients received open-label oral LEN with optimized background therapy on Days 1 through 14, and then SQ LEN was administered once every 6 months starting on Day 15. The primary endpoint was defined by the percentage of patients in the first cohort who had a decrease of at least 0.5 $\log_{10}$ copies/mL viral load from baseline to Day 15. The secondary endpoint was a viral load of <50 copies/mL at Week 26. The results showed that 21 of 24 (88%) patients in the LEN group met the primary endpoint, as compared to 2 of 12 (17%) patients in the placebo group (*P* < 0.001); 81% of patients met the secondary endpoint.[12] None of the patients developed serious adverse events that were considered related to LEN. At 2-year follow-up in CAPELLA, 14 participants had developed emergent LEN resistance, 7 of whom resuppressed to <50 copies/mL with maintenance of LEN and concomitant changes to or reinitiation of a background regimen. A high rate of viral suppression was achieved in this treatment-experienced cohort, with (when missing results were excluded) 44 of 54 (82%) (95% CI, 67% to 94%) achieving suppression to <50 copies/mL.[13] LEN added to an optimized background regimen led to high efficacy in highly treatment-experienced participants with multidrug resistance but could select for resistance when used unintentionally as functional monotherapy (e.g., when patients have poor adherence to a self-administered optimized background regimen).[12]

CALIBRATE was a Phase 2, randomized, open-label trial that enrolled 183 treatment-naive patients with HIV ≥18 years of age to evaluate the efficacy of LEN in various combinations versus bictegravir (BIC)/tenofovir alafenamide/3TC combination pill. At Week 54, virologic suppression was greater for the BIC-containing combination pill group (92%) compared to various combinations with LEN (75% to 87%).[5] Final results showed that at Week 132, viral suppression was 98% to 100% among 130 participants without missing data who received at least one dose of LEN.[14] No serious treatment-related adverse events occurred. Across all LEN-containing treatment groups, five participants discontinued LEN due to adverse events. Injection site reactions were mostly mild to moderate. Resistance-associated mutations emerged among four participants undergoing LEN treatment.

Observational or Effectiveness Data

One case series[15] reported on the salvage strategy of the use of LEN as part of a hybrid long-acting ART regimen in adults with viremia and resistance to one or more components of long-acting ART. This series included one patient with perinatally acquired HIV and a large viral reservoir who achieved viral suppression on the combination of LEN and cabotegravir/rilpivirine (CAB/RPV). A cohort from Ward 86 in San Francisco reported on the use of LEN concurrently with CAB/RPV in an adult with sluggish viral load decline on CAB/RPV.[16] Accumulating data suggest that real-world use of LEN and CAB, LEN and CAB/RPV, or LEN and 3TC is associated with favorable clinical outcomes among adults who do not achieve or maintain suppression on oral ART.[17,18]

Pharmacokinetic Considerations

The elimination half-life of LEN is about 10 to 12 days (oral formulation) and 8 to 12 weeks (SQ formulation). Residual concentrations of LEN long-acting injection may remain in the systemic circulation of patients for ≥12 months. To minimize the potential risk of resistance development under conditions of functional monotherapy at subtherapeutic levels, an alternative, fully suppressive ARV regimen should be initiated no later than 28 weeks after the final LEN injection when possible.

Hepatic and Renal Impairment

Two Phase 1 single-dose studies have assessed LEN pharmacokinetics (PK) in the setting of hepatic impairment (Child-Pugh-Turcotte Class B) or renal impairment (with CrCl <15 mL/min).
Ten participants with impaired hepatic or renal function and 10 participants with normal hepatic and renal function were given a single oral dose of LEN 300 mg and PK measured thereafter. Compared to participants with normal hepatic function, people with hepatic impairment had LEN areas under the concentration-time curve extrapolated to infinity (AUC_{inf}) and maximum plasma concentrations (C_{max}) 1.47-fold and 2.61-fold higher, respectively. For participants with renal impairment, LEN AUC_{inf} and C_{max} were 1.84-fold and 2.62-fold[1] higher, respectively, compared to those with normal renal function. These exposure changes were not considered clinically significant, and no LEN dosing adjustments were recommended for people with mild (Child-Pugh-Turcotte Class A: score 5–6) or moderate (Child-Pugh-Turcotte Class B: score 7–9) hepatic impairment or for people with mild (60 ≤ CrCl ≤ 89 mL/min), moderate (30 ≤ CrCl ≤ 59 mL/min), and severe (≤15 CrCl <30 mL/min) renal impairment.

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