Lenacapavir (LEN, Sunlenca)

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Formulations

Tablet: 300 mg

Single-Use Vial for Subcutaneous Injection: 463.5 mg/1.5 mL suspension

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.

Initiation Option 1

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

Initiation Option 2

- 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 subcutaneous injection (two 1.5 mL subcutaneous injections in the abdomen)

Maintenance

- 927 mg by subcutaneous injection (two 1.5 mL subcutaneous injections in the abdomen) every 26 weeks +/- 2 weeks from date of last injection

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.

Metabolism/Elimination

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

Dosing in Patients with Hepatic Impairment

- No dosage adjustment reported. Data on use in patients with severe hepatic impairment are insufficient.

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).
- Dialysis: No dosage adjustments are required. Not expected to be significantly removed by dialysis due to high protein binding.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* 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.**
- 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 65%)—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.[1-3] Nausea (12% to 14%), headache (8% to 13%),[2,3] constipation (11% to 13%),[1,2] and diarrhea (8% to 14%)[1-3] 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.[2]
- *Less common (more severe):* Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy (ART).

Resistance

Resistance to LEN was noted in 8 of 72 patients in the CAPELLA trial (mainly in those with M66I mutations). Resistance largely occurred early in the trial, and half of these patients had low adherence to their optimized background therapy as indicated by plasma drug concentrations.[2] After 26 weeks, only one patient developed LEN resistance.[1]

The reported prevalence of LEN-resistance mutations is low (0.14%) among drug-naive individuals.[4]

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. LEN was approved by the FDA in 2022 in combination with other antiretroviral(s) (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.[5]

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 prevention in adults and adolescents.[6]

LEN has not been studied in pregnancy, and it is unknown if LEN is excreted in breast milk.[7]

Efficacy and Pharmacokinetics in Clinical Trials

Clinical Trials in Adults

A randomized, placebo-controlled, double-blind, multicenter trial (CAPELLA) evaluated LEN in combination with an optimized background ART regimen in 72 patients with multidrug resistant HIV-1.[2] 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.[8] None of the patients developed serious adverse events that were considered related to LEN. At 52-week follow-up in CAPELLA, nine participants had emergent LEN resistance, four of whom resuppressed to <50 copies/mL. A high rate of virological suppression was achieved in this treatment-experienced cohort, with 83% (95% confidence interval [CI], 67% to 94%) achieving suppression to <50 copies/mL and 86% (95% CI, 71% to 95%) achieving suppression to <200 copies/mL.[1] 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).[8]

CALIBRATE is a Phase 2, ongoing, 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/emtricitabine combination pill. At Week 54, virologic

suppression was greater for the BIC-containing combination pill group (92%) compared to various combinations with LEN (85% to 90%). This ongoing study will follow participants through 80 weeks of therapy.[3]

Pharmacokinetics

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, an alternative, fully suppressive ARV regimen should be initiated no later than 28 weeks after the final LEN injection when possible.

References

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