Lenacapavir (Sunlenca®) New Drug Update

January 2023

Nonproprietary Name	lenacapavir
Brand Name	Sunlenca
Manufacturer	Gilead
Form	Oral tablets and injection for subcutaneous (SC) use
Strength	300 mg tablets 463.5 mg/1.5 mL (309 mg/mL) solution in single-dose vials (SDV)
FDA Approval	December 22, 2022
Market Availability	Available
FDA Approval Classification	Breakthrough Therapy, Fast Track, Priority Review
FDB Classification- Specific Therapeutic Class (HIC3)	Antiretroviral - Capsid Inhibitors (W0N)

INDICATION[1]

Lenacapavir (Sunlenca), a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

PHARMACOKINETICS

Drug exposure to lenacapavir is similar between the 2 recommended initiation options described in the dosing section. SC administration results in a 100% absolute bioavailability, whereas oral administration has an absolute bioavailability of 6% to 10%. The time to maximum drug levels (T_{max}) following oral administration is 4 hours; in contrast, SC dosing achieves T_{max} in 77 to 84 days. Administration with a high-fat meal increases the exposure and maximum concentration of orally administered lenacapavir. Lenacapavir is highly (> 98.5%) bound to human plasma proteins with a half-life of 10 to 12 days for oral administration and 8 to 12 weeks for SC administration. The major metabolic pathway for lenacapavir is cytochrome P450 (CYP) 3A, and the minor pathway is UDP glucuronosyltransferase family 1 member A1 (UGT1A1). Lenacapavir is primarily (76%) excreted in the feces with 33% excreted as unchanged drug and < 1% excreted in urine. Its estimated exposure was 43% to 100% greater in patients with HIV-1 infection compared to subjects without HIV-1.

CONTRAINDICATIONS/WARNINGS

Lenacapavir is **contraindicated** with concurrent use of strong CYP3A inducers due to reduced lenacapavir plasma levels which can lead to loss of efficacy and development of resistance.

Lenacapavir carries a warning for immune reconstitution syndrome which has occurred in patients treated with combination antiretroviral (ARV) therapy. An inflammatory response to indolent or residual opportunistic infections may occurring during the initial phase of treatment or autoimmune disorders may occur months following initiation.

As lenacapavir can remain in systemic circulation for 12 months or longer following SC administration, patients must receive maintenance doses every 6 months to avoid loss of response and development of resistance. Due to the long-acting properties of lenacapavir, which is a moderate CYP3A inhibitor, the exposure and adverse effects from CYP3A substrates started within 9 months of the last SC dose can be increased; product labeling for sensitive CYP3A substrates should be consulted for dosing recommendations when used concurrently with lenacapavir, a moderate CYP3A inhibitor. When lenacapavir therapy is discontinued, an alternative suppressive ARV regimen should be initiated within 28 weeks following the final injection to reduce the likelihood for the development of viral resistance. If the patient experiences virological failure during therapy, the patient should be switched to an alternative regimen.

Local injection site reactions (ISRs), including swelling, pain, erythema, nodule, induration, pruritus, extravasation, or masses, can occur following SC administration. Nodules and indurations can require a longer time than other ISRs to resolve; these ISRs may be palpable (1 to 4 cm in size) and may be caused by a SC drug depot with inflammation or granulomatous response.

DRUG INTERACTIONS

As lenacapavir is a CYP3A substrate, strong or moderate CYP3A inducers can significantly reduce plasma levels of lenacapavir leading to loss of efficacy and development of resistance; concurrent use with strong CYP3A inducers is contraindicated and concurrent use with moderate CYP3A inducers is not recommended.

Lenacapavir is also a substrate for P-glycoprotein (P-gp) and UGT1A1. As a result, agents which are combined P-gp, UGT1A1, and strong CYP3A inhibitors can significantly raise plasma levels of lenacapavir; concurrent use with these agents should be avoided.

The prescribing information for lenacapavir details clinically significant drug interactions and prevention/management strategies for a number of other agents, including digoxin (use with caution and monitor digoxin levels), direct oral anticoagulants (DOAC) (consult the DOAC product labeling for management), anticonvulsants (contraindicated or not recommended, depending on the agent), ARV agents (certain agents described as being not recommended), antimycobacterials (contraindicated or not recommended, depending on the agent), systemic corticosteroids (use lower steroids doses, titrate carefully and monitor), ergot derivatives (generally not recommended), St. John's wort (contraindicated), lovastatin or simvastatin (initiate with lowest dose and increase carefully with monitoring), narcotics metabolized by CYP3A (e.g., fentanyl, oxycodone) (careful monitoring), tramadol (reduced tramadol dose may be required), methadone or buprenorphine (use lowest dose with careful titration), naloxegol (generally avoid use, if possible), phosphodiesterase-5 inhibitors (tadalafil for pulmonary arterial hypertension: not recommended; consult product labeling for dosing when these agents are used for erectile dysfunction), and midazolam or triazolam (caution advised). This list is not all inclusive. No clinically significant interactions have been identified with the following agents: darunavir/cobicistat (Prezcobix®), cobicistat (Tybost®), famotidine (Pepcid®), pitavastatin (Livalo®,

Zypitamag®), rosuvastatin (Crestor®, Ezallor Sprinkle™), tenofovir alafenamide (Vemlidy®), and voriconazole (Vfend®).

COMMON ADVERSE EFFECTS

The most common adverse effects (≥ 3%) reported with lenacapavir as add on to background regimen, in the CAPELLA week 52 analysis, were ISRs (65%) and nausea (4%). Most (96%) of the adverse reactions were mild or moderate in severity. A small proportion of patients (4%) had severe ISRs (erythema, pain, and swelling) with resolution within 15 days. The most common ISRs were swelling (36%), pain (31%), erythema (31%), nodule (25%), induration (15%), pruritus (6%), extravasation (3%) and mass (3%). The most common grade 3 to 4 laboratory abnormalities occurring in ≥ 4% of lenacapavir-treated patients in CAPELLA at the week 52 analysis were increased creatinine (13%), glycosuria (6%), hyperglycemia (5%), and proteinuria (4%).

SPECIAL POPULATIONS

Pregnancy

Data for lenacapavir in pregnancy are inadequate to advise of maternal or fetal risk. Healthcare professionals (HCPs) are encouraged to enroll patients receiving lenacapavir in the pregnancy exposure registry that monitors pregnancy outcomes in patients receiving lenacapavir.

Pediatrics

Safety and efficacy of lenacapavir has not been established in pediatric patients (< 18 years of age).

Geriatrics

Clinical trials did not include an adequate number of patients ≥ 65 years of age to inform of differences in pharmacokinetics of lenacapavir compared to younger patients.

Hepatic Impairment

A dosage adjustment is not required in patients with mild or moderate (Child-Pugh Class A or B, respectively) hepatic impairment; use has not been evaluated in severe hepatic impairment (Child-Pugh Class C).

Renal Impairment

A dosage adjustment is not required for patients with mild, moderate, or severe renal impairment (estimated creatinine clearance [CrCl] ≥ 15 mL/min). Lenacapavir has not been evaluated in patients with end-stage renal disease (CrCl < 15 mL/min).

DOSAGES

There are 2 recommended dosage options for initiation of lenacapavir. The first option includes a 927 mg SC injection (2 x 1.5 mL injections) and a 600 mg (2 x 300 mg tablets) oral dose on day 1, followed by 600 mg orally (2 x 300 mg tablets) on day 2. This is followed by maintenance dosage of 927 mg by SC injection (2 x 1.5 mL injections) every 6 months (26 weeks +/- 2 weeks) from the date of the prior injection.

The second initiation option is 600 mg (2 x 300 mg tablets) orally on day 1, followed by 600 mg orally on day 2, then 300 mg orally on day 8 (1 x 300 mg tablet), and 927 mg by SC injection (2 x 1.5 mL injections) on day 15. This is followed by 927 mg SC (2 x 1.5 mL injections) every 6 months (26 weeks +/- 2 weeks) from the date of last injection.

Oral tablets can be taken with or without food. The injection is prepared using aseptic technique and is administered into the abdomen by an HCP. If more than 28 weeks have elapsed since the last injection during the maintenance phase, reinitiate with the initiation dosage regimen using either of the options described previously.

CLINICAL TRIALS[2,3,4,5]

A literature search was performed using "lenacapavir" and "human immunodeficiency virus" or "HIV."

FDA approval of lenacapavir was based on data from the randomized, placebo-controlled, multicenter, phase 2/3 CAPELLA study (NCT04150068) evaluating lenacapavir in combination with optimized background therapy in patients with multidrug resistant HIV-1 who are heavily treatment-experienced. Patients enrolled were required to be ≥ 12 years of age and had received a stable failing ARV regimen for ≥ 8 weeks (HIV-1 ribonucleic acid [RNA] level of ≥ 400 copies/mL) with documented resistance to ≥ 2 ARV medications from ≥ 3 of the 4 main classes (nucleoside reverse-transcriptase inhibitors [NRTIs], non–nucleoside reverse-transcriptase inhibitors [NNRTIs], protease inhibitors [PIs], and integrase strand-transfer inhibitors [INSTI]) and have ≤ 2 fully active ARVs remaining from the 4 main classes that can be effectively combined. A total of 72 patients were enrolled and assigned to either cohort 1 (n=36) or cohort 2 (n=36). The cohorts were determined based on the change in plasma HIV-1 RNA level between the screening and cohort-selection visit. Cohort 1 included the first 36 patients with a decrease of < 0.5 $\log_{10}$ copies/mL demonstrating stable viremia due to lack of response to the failing therapy and an HIV-1 RNA level of ≥ 400 copies/mL. Patients in cohort 1 were randomly assigned 2:1 to receive either oral lenacapavir (600 mg on days 1 and 2, 300 mg on day 8) or matching placebo as add on to their failing ARV therapy for 14 days (blinded functional monotherapy phase); starting on day 15 (unblinded maintenance phase), patients in the lenacapavir arm received SC lenacapavir (927 mg as two 1.5-mL injections in the abdomen) once every 6 months and placebo patients received oral lenacapavir (600 mg on days 15 and 16, 300 mg on day 22), followed by SC lenacapavir. Optimized background therapy was given to both groups of patients. Cohort 2 included those who had a decrease of ≥ 0.5 $\log_{10}$ copies/mL between the screening and cohort-selection visits, a viral load of < 400 copies/mL, or both, and patients found to be eligible for cohort 1 following enrollment closure of that cohort could also be included in cohort 2 (n=33). Cohort 2 consisted of patients who received open-label oral lenacapavir as add on to optimized background therapy for days 1 to 14, and SC lenacapavir was administered once every 6 months beginning on day 15. The primary efficacy endpoint was the proportion of patients in cohort 1 with a decrease from baseline of ≥ 0.5 $\log_{10}$ copies/mL in the viral load by day 15. Key secondary endpoints included the proportion of patients with a viral load of < 50 copies/mL and the proportion with a viral load of < 200 copies/mL, both evaluated at week 26 after the initiation of SC lenacapavir in cohort 1.

The median age of all patients enrolled was 52 years (range, 23 to 78 years) with 75% of patients being male. At baseline, demographic characteristics in the randomized cohort 1 patients were similar with the exception of those randomized to lenacapavir had a lower median HIV-1 RNA value than the placebo patients (4.2 $\log_{10}$ copies/mL versus 4.9 $\log_{10}$ copies/mL), and the median CD4+ count was greater in the

lenacapavir group than in the placebo group (172 cells/mm^3 versus 85 cells/mm^3). The median number of prior ARV medications for cohort 1 was 9 therapies, and 47% of patients had resistance to all 4 major ARV classes. Furthermore, many patients had resistance to INSTIs (54%), PIs (42%), or other agents FDA-approved for heavily treatment-experienced adults (ibalizumab: 33%; fostemsavir: 30%), and 17% of patients did not have fully active therapies in their optimized background regimen.

The primary endpoint of ≥ 0.5 $\log_{10}$ copies/mL decrease in viral load by day 15 was achieved by 88% of patients (21 of 24 patients) receiving lenacapavir in cohort 1 compared to 17% of patients (2 of 12 patients) in the placebo group (absolute difference, 71%; 95% confidence interval [CI], 35 to 90; p<0.001). In cohort 1 at week 26, the secondary endpoint of a viral load of < 50 copies/mL occurred in 81% (95% CI, 64 to 92) of patients (29 of 36 patients) and viral load of < 200 copies/mL occurred in 89% (95% CI, 74 to 97) of patients (32 of 36 patients). In cohort 2, the secondary endpoint of viral load < 50 copies/mL occurred in 83% (30 of 36 patients) of patients and a viral load of < 200 copies/mL occurred in 86% of patients (31 of 36 patients). At week 26, there was also an increase in CD4+ counts (measured as least-squares mean) by 75 cells/mm^3 and 104 cells/mm^3 in cohorts 1 and 2, respectively, corresponding with a reduction in the proportion of patients with CD4+ counts < 50 cells/mm^3 (24% to 0 patients). Efficacy was similar regardless of the activity of the optimized background regimen and comparable results were found regardless of whether patients received fully active agents or had resistance to INSTIs. Although 19 patients were found to have resistance across both cohorts and lenacapavir-associated substitutions were found in 8 of these patients (4 did not have fully active agents in their optimized background therapy, 4 had poor adherence to the background therapy), 4 had resuppression of HIV-1 viral RNA to < 50 copies/mL. Of the remaining 4 patients without resuppression, 2 had ongoing viremia, 1 passed away at week 10 (due to cancer), and 1 discontinued lenacapavir at week 4. In the 11 other patients found to have resistance, 7 had resuppression during continued lenacapavir and none of these patients exhibited emerging resistance to background regimen components.

OTHER DRUGS USED FOR CONDITION[6,7,8,9]

Other therapies FDA-approved for *heavily treatment-experienced* adults with *multidrug resistant* HIV-1 infection include the HIV-1 gp120-directed attachment inhibitor fostemsavir (Rukobia™) and the CD4-directed post-attachment HIV-1 inhibitor ibalizumab-uiyk (Trogarzo®).

- Fostemsavir is indicated in combination with other ARVs for HIV-1 infection in adults failing their current ARV regimen due to resistance, intolerance, or safety issues and is supplied as an extended-release tablet taken twice daily.
- Ibalizumab is indicated in combination with other ARVs for HIV-1 infection in adults failing their current ARV regimen and is administered as an intravenous (IV) maintenance dose of 800 mg every 2 weeks.

Although not indicated specifically for patients with multidrug resistant HIV-1 infection, enfuvirtide (Fuzeon®), an HIV-1 gp41 fusion inhibitor, is indicated for use in combination with other ARV agents for the treatment of HIV-1 infection in *treatment-experienced* patients with HIV-1 replication despite ongoing ARV therapy. Enfuvirtide is administered SC twice daily and is indicated for use in adults and pediatric patients weighing ≥ 11 kg.

PLACE IN THERAPY[10,11,12,13,14,15]

It is estimated 1.2 million individuals in the United States (US) have HIV with 13% of these individuals unaware they are infected. Although the prevalence of persons with HIV with limited treatment options has declined to < 1% in recent years due to increased virologic control with more potent ARV drugs/classes, new therapies are crucial to continue improvements in outcomes for these patients. The 2022 ARV Drugs for Treatment and Prevention of HIV Infection in Adults Recommendations of the International Antiviral Society-USA Panel define virologic failure as HIV RNA level > 200 copies/mL and requires confirmation by a repeat viral load measurement. Following confirmation, genotype resistance testing is required, ideally while patients continue the failing therapy.

Dolutegravir (Tivicay®, Tivicay PD®) plus 2 NRTIs (with ≥ 1 active NRTI) is recommended after failure with an NNRTI + 2 NRTIs (evidence rating: A [strong panel support]; Ia [highest quality of evidence]). If no active NRTIs are identified and a boosted PI and INSTI are fully active, treatment could include boosted darunavir (Prezista®) + TXF (tenofovir alafenamide or tenofovir disoproxil fumarate)/XTC (emtricitabine or lamivudine) (evidence rating: AIa) or dolutegravir + a boosted PI +/- additional agents (evidence rating: B [moderate panel support]; III [based on accumulated evidence]). For management of INSTI resistance, an expert in HIV drug resistance should select the optimal regimen. If resistance to INSTI is relatively limited and the new ARV regimen will include an INSTI, dolutegravir should be taken twice daily. At least 1, but preferably 2 other fully active drugs from classes not previously used are recommended. Examples include fostemsavir (except for treatment of HIV subtype CRF01_AE), lenacapavir, maraviroc (Selzentry®) (if the patient's virus is documented to be R5 tropic when tested), ibalizumab, or enfuvirtide. For patients with both a high-level of INSTI resistance as well as reduced PI susceptibility, a multidrug regimen with ≥ 2 fully active agents from these novel classes are recommended, along with recycled NRTIs (evidence rating: AIII).

Lenacapavir (Sunlenca) is an HIV-1 antiretroviral agent that is a multistage, selective HIV-1 capsid inhibitor. It acts by binding to the area between capsid protein subunits in hexamers and interferes with multiple required steps of the viral lifecycle. HIV-1 replication is inhibited by interference with (1) capsid-mediated nuclear uptake of HIV-1 proviral DNA, (2) virus assembly and release, and (3) capsid core formation. The CAPELLA trial demonstrated a significant reduction in viral load with lenacapavir compared to continuation of the patient's current failing regimen (primary endpoint at day 15, cohort 1) in patients with multidrug-resistant HIV-1 infection. When added on to optimized background regimen, lenacapavir therapy resulted in virologic suppression and increases in CD4+ counts. Notably, studies have demonstrated sustained decreases in HIV-1 RNA levels for 16 to 24 weeks are associated with a decreased risk of disease progression and death. Apart from ISRs, the most common adverse effects in the clinical study were gastrointestinal (nausea, constipation, diarrhea) and were deemed not related to lenacapavir. Despite the small number of patients in the CAPELLA study and relatively short duration of follow-up, trial data demonstrate a decrease from baseline in viral load with lenacapavir in difficult-to-treat patients with multidrug-resistant HIV-1 infection. Lenacapavir provides a novel, multistage mechanism of action with every 6 month maintenance dosing, for use in combination with other ARVs in heavily treatment-experienced adults with multi-drug resistant HIV-1 infection, a population of patients with currently limited treatment options.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	HIV/AIDS
Clinical Edit	**Initial Approval Criteria** ▪ Patient is ≥ 18 years old; **AND** ▪ Patient has a diagnosis of human immunodeficiency virus type 1 (HIV-1) infection; **AND** ▪ Patient is heavily treatment-experienced with multidrug resistance HIV-1 infection (has documented resistance to ≥ 2 antiretroviral [ARV] medications from each of ≥ 3 of the 4 main classes [nucleoside reverse-transcriptase inhibitors [NRTIs], non–nucleoside reverse-transcriptase inhibitors [NNRTIs], protease inhibitors [PIs], and integrase strand-transfer inhibitors [INSTI]); **AND** ▪ Patient has ≤ 2 fully active ARVs remaining from the 4 main classes that can be effectively combined; **AND** ▪ Patient has HIV-1 RNA level of > 200 copies/mL; **AND** ▪ Patient has no history of treatment failure or known or suspected resistance to lenacapavir; **AND** ▪ Patient will complete oral induction of lenacapavir with initiation of subcutaneous maintenance lenacapavir; **AND** ▪ Patient will be taking with other antiretrovirals (optimized background regimen); **AND** ▪ Patient will NOT receive concomitant therapy with strong CYP3A inducers that can result in decreases of lenacapavir activity (e.g. rifampin, carbamazepine, St. John's wort, phenytoin); **AND** ▪ Prescribed by or in consultation with an infectious disease specialist. **Renewal Criteria** ▪ Patient must continue to meet the above criteria; **AND** ▪ Patient has been adherent to their ARV treatment regimen; **AND** ▪ Patient has NOT experienced virologic failure of lenacapavir and has documented clinical improvement and/or stabilization (e.g., disease response as indicated by a decrease in viral load from pretreatment baseline*; increased or stabilized CD4+ counts); **AND** ▪ Patient has NOT experienced any treatment-restricting adverse effects (e.g., immune reconstitution syndrome; severe injection site reactions). ** Note: increases in viral load from nadir and/or less than anticipated reduction from baseline should prompt resistance testing for susceptibility and optimization of the background regimen.*

Quantity Limit	300 mg tablets: 5 tablets per initiation regimen 463.5 mg/1.5 mL SDVs: 2 vials per initiation regimen 463.5 mg/1.5 mL SDVs: 2 vials per 6 months for maintenance dosing
Duration of Approval	Initial: 12 months Renewal: 12 months
Drug to Disease Hard Edit	N/A

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