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Yeztugo® (lenacapavir) Oral Initiation Dosing Requirement

This document is in response to your request for information regarding Yeztugo® (lenacapavir [LEN]) and the oral initiation dosing.

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The full indication, important safety information, and boxed warning are available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_pi.

Summary

Product Labeling[1]

A 2-day oral initiation is required and was used in the PURPOSE 1 and 2 studies as follows to reach the required PK exposure levels. LEN oral tablets may be taken with or without food:

- Day 1: LEN 600 mg orally (two 300 mg tablets) and SUBQ LEN 927 mg (two 1.5 mL injections)
- Day 2: LEN 600 mg orally (two 300 mg tablets)

Continuation dosing is as follows: SUBQ LEN 927 mg (two 1.5 mL injections) every 6 months (26 weeks) ±2 weeks from the date of the last injection.

Clinical Data on Importance of Oral Initiation Dosing of LEN

Due to the slow initial release of SUBQ LEN, an oral initiation regimen is necessary for PK purposes. The oral loading dose on Days 1 and 2 is not due to safety concerns but is required for LEN to achieve adequate concentrations quickly.[2]

- PK data are available from a small Phase 1 study in healthy participants which were used as the basis for dosing in the PURPOSE 1 and PURPOSE 2 studies. PK can vary among individuals, and in this study, 14 individuals who completed the full initiation dosing had a mean plasma LEN concentration thought to be associated with antiretroviral activity, IQ4 (15.5 ng/mL), two hours after the second oral dose on Day 2. These PK data are not correlative of efficacy.[3]

Pharmacokinetic Data on Importance of Oral Initiation Dosing of LEN

In a population PK analysis of pooled data from participants across 13 phase 1 to phase 3 studies, simulations were conducted to support dosing recommendations, which were based on ensuring the 90% CI of mean LEN concentrations remained above IQ4 (15.5 ng/mL).[4]

- Simulations of SUBQ LEN 927 mg without oral loading showed that IQ4 was reached by Day 22.[4]
- With the oral loading regimen (oral LEN 600 mg on Day 1 and Day 2), concentrations exceeded this threshold earlier (within the first day) and were maintained above IQ4

on Day 2 and thereafter, following the administration of the second oral loading dose.[4]

The full initiation dosing of LEN should be followed and consists of taking 2 tablets and 2 injections on Day 1, and 2 tablets on Day 2.[1]

Clinical Data on Importance of Oral Initiation Dosing of LEN

Phase 1 PK Study in Health Volunteers[3]

The LEN regimen consisting of concurrent dosing of SUBQ LEN 927 mg and oral LEN 600 mg on Day 1 and oral LEN 600 mg on Day 2 followed by SUBQ LEN every 6 months thereafter was characterized in a Phase 1, single-center, open-label study. Among 14 healthy participants following LEN administration, mean plasma LEN concentration and its lower 90% confidence interval bound exceeded the target IQ4 (15.5 ng/mL) from 2 hours post-dose on Day 2 and was consistently maintained above the target IQ4 during the dosing interval. These PK data are not correlative of efficacy. Overall, LEN was well tolerated, and there were no serious AEs. Injection site reactions were the most common AEs and no deaths were reported.

Pharmacokinetic Data on Importance of Oral Initiation Dosing of LEN

Population PK Analysis of LEN in People who Want or Need PrEP[4]

In a population PK analysis of pooled data from participants across 13 phase 1 to phase 3 studies (N=1337 participants; N=14,648 samples), LEN exposures were characterized following a stepwise modeling approach of SUBQ, oral, and IV administration. Simulations were conducted to support dosing recommendations, which were based on ensuring the 90% CI of mean LEN concentrations remained above the IQ4 (15.5 ng/mL), which is thought to be associated with significant antiviral activity. Based on model simulations of twice-yearly SUBQ LEN in people who want or need PrEP, the lower bound of the 90% CI of mean trough concentration (C_{trough}) consistently remained above the IQ4 threshold of 15.5 ng/mL, as well as for at least 2 weeks following a missed SUBQ dose.

Simulations of SUBQ LEN 927 mg without oral loading showed that the C_{trough} reached the IQ4 of 15.5 ng/mL by Day 22. With the oral loading regimen (oral LEN 600 mg on Day 1 and Day 2), concentrations exceeded this threshold earlier (within the first day) and were maintained above IQ4 on Day 2 and thereafter, following the administration of the second oral loading dose. Should the oral initiation dose be missed, this PK data supports taking missed oral loading doses as soon as possible to achieve target concentrations. However, do not take Day 1 and Day 2 oral initiation doses on the same day.[1]

References

1. Enclosed, Gilead Sciences Inc. YEZTUGO® (lenacapavir) tablets, for oral use. YEZTUGO® (lenacapavir) injection, for subcutaneous use. U.S. Prescribing Information. Foster City, CA.
2. Begley R, Lutz J, Rhee M, et al. Lenacapavir Sustained Delivery Formulation Supports 6-Month Dosing Interval [Poster PEB0265]. Paper presented at: AIDS 2020: 23rd International AIDS Conference Virtual; 06-10 July, 2020.
3. Jogiraju V, Graham H, West S, et al. Pharmacokinetics of a Simplified Subcutaneous Lenacapavir Regimen Versus Phase 2/3 Regimen [Poster PESUB22]. Paper presented at: AIDS 2022; 29 July-2 August, 2022; Montreal, Quebec, Canada.
4. Imperial M, Hughes E, Panchia R, et al. Population Pharmacokinetic Analysis of Lenacapavir in People Who Want or Need Pre-Exposure Prophylaxisfor HIV [Poster I-109]. Paper presented at: Population Approach Group Europe (PAGE); 4–6 June, 2025; Thessaloniki, Greece.

Abbreviations

C_{trough}=trough concentration
IQ=inhibitory quotient
LEN=lenacapavir
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
SUBQ=subcutaneous(ly)

Product Label

For the full indication, important safety information, and boxed warning, please refer to the Yeztugo US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

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🖱 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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