GILEAD | Medical Information

Yeztugo® (lenacapavir) Coadministration With Fentanyl

This document is in response to your request for information regarding Yeztugo® (lenacapavir [LEN]) and coadministration with fentanyl.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

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

PK DDI Evaluation

Based on the PK profile of LEN and fentanyl, a weak PK interaction would be predicted. Narcotic analgesics metabolized by CYP3A, such as fentanyl, that are coadministered with LEN, a moderate inhibitor of CYP3A, may result in increased concentrations of fentanyl; however, the clinical interaction potential between SUBQ LEN and IV fentanyl is predicted to be low.[1,2] PK/pharmacodynamic modeling predicts that any change in fentanyl exposure from coadministration with LEN would not significantly increase the risk of respiratory depression. Fentanyl is not a sensitive clinical CYP3A substrate due to its diverse elimination involving multiple enzymes (eg, CYP2D6, CES2, UGT1A4), which helps to potentially explain its modest interactions with potent CYP3A inhibitors.[2]

Refer to the product labeling of fentanyl for more information on the coadministration with moderate CYP3A inhibitors. Dose adjustments may be required; monitor for therapeutic effects and adverse reactions, including respiratory depression.[3]

LEN PK

Table 1. LEN DDI Potential[1,4]

DDI Mechanism		LEN
Drug Transporters	OCT2	N/A
	MATE1	N/A
	P-gp	Substrate[a] and weak inhibitor
	BCRP	Weak inhibitor
	OATP1B1	N/A
	OATP1B3	N/A
Drug Metabolizing Enzymes	CYP3A	Substrate[a,b] and moderate inhibitor
	UGT1A1	Substrate[a]

Abbreviations: BCRP=breast cancer resistance protein; MATE=multidrug and toxin extrusion protein; OATP=organic anion transporting polypeptide; OCT=organic cation transporter.
[a]Combined P-gp, UGT1A1, and strong CYP3A inhibitors may significantly increase plasma concentrations of LEN. Concomitant administration of LEN with these inhibitors is not recommended.
[b]Drugs that are strong or moderate inducers of CYP3A may significantly decrease plasma concentrations of LEN, which may result in reduced effectiveness of LEN. Therefore, dosage modifications (supplemental doses) of LEN are recommended when initiating strong or moderate CYP3A inducers. Please refer to Section 2.5, *Dosage Modifications for Coadministration With Strong or Moderate CYP3A Inducers*, of the LEN US Prescribing Information for more information.

Relevant LEN Label Information[1]

Drug Interactions

Effect of LEN on other drugs: CYP3A and P-gp substrates

LEN is a moderate inhibitor of CYP3A and a P-gp inhibitor. The coadministration of LEN with sensitive substrates of CYP3A or P-gp may increase the concentrations of these substrates and result in the increased risk of their AEs. See the prescribing information for these sensitive substrates for dosing recommendations or appropriate monitoring of safety.

Due to the long half-life of LEN following subcutaneous administration, LEN may increase the exposure of drugs primarily metabolized by CYP3A initiated within 9 months after the last SUBQ dose of LEN.

Clinical Data on Coadministration of LEN and Fentanyl

PURPOSE 1 and PURPOSE 2 Studies

In the phase 3 studies evaluating the efficacy and safety of LEN for HIV-1 PrEP, 4 participants in PURPOSE 1 and one participant in PURPOSE 2 received fentanyl. There were no reports of AEs due to concomitant use.[5]

PURPOSE 2 Study

PURPOSE 2 (NCT04925752) is an ongoing, phase 3, double-blind, randomized study evaluating the efficacy and safety of twice-yearly SUBQ LEN (n=2179) and once-daily oral FTC/TDF (n=1086) for HIV-1 PrEP in cisgender gay, bisexual, and other men, transgender women, transgender men, and gender nonbinary individuals aged ≥16 years in Argentina, Brazil, Mexico, Peru, South Africa, Thailand, and the US who have condomless receptive anal sex with partners assigned male at birth (N=3265). The primary efficacy endpoint is the incidence of HIV among randomized participants.[6]

DDIs between LEN and fentanyl[7]

A subanalysis included participants who self-reported drug use (ie, oral use, injection, or inhalation use of cocaine, amphetamine-type stimulants, inhalants, sedatives or sleeping pills, hallucinogens, opioids, or prescription drugs for nonprescription purposes; cannabis was excluded) in the past 12 weeks and assessed any potential DDI between LEN and fentanyl. Among the participants treated with LEN, 37.2% (767/2061) reported drug use, including cocaine or amphetamine-type stimulant use (409/2058 [19.9%]), opioid use (33/2086 [1.6%]), and injection drug use (17/2092 [0.8%]).

According to a preliminary physiologically based PK model, there was no clinically meaningful interaction between SUBQ LEN and fentanyl. No substance use-related overdoses were reported.

PURPOSE 4 Study[8]

The interaction between LEN and fentanyl is being evaluated in PURPOSE 4 (NCT06101342), an ongoing phase 2 study evaluating LEN and FTC/TDF for PrEP among people who inject drugs in the US. The study will include participants who screen positive for misuse of any drug, including, but not limited to, fentanyl.

References

1. YEZTUGO®, Gilead Sciences Inc. YEZTUGO® (lenacapavir) tablets, for oral use. YEZTUGO® (lenacapavir) injection, for subcutaneous use. U.S. Prescribing Information. Foster City, CA. Revised: June. 2025.
2. Sun HL, Le H, Salerno SN, Murray BP. Low Potential for Drug Interaction Between Lenacapavir and Fentanyl [Poster PI-019]. Paper presented at: American Society for Clinical Pharmacology & Therapeutics (ASCPT); 28–31 May, 2025; Washington, DC.
3. FENTANYL CITRATE, Hospira Inc. FENTANYL CITRATE Injection, for Intravenous or Intramuscular use. U.S. Prescribing Information. Lake Forest, IL. Revised October. 2019.
4. Lutz J. CLINICAL EVALUATION OF DRUG INTERACTIONS WITH ORAL LENACAPAVIR AND PROBE DRUGS [Presentation]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); March 6-10, 2021; Virtual.
5. Gilead Sciences Inc. Data on File.
6. Kelley CF, Acevedo-Quinones M, Agwu AL, et al. Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons. *N Engl J Med.* 2025;392(13):1261-1276.
7. Clark J, Agwu AL, Buchbinder S, et al. Favorable Adherence and Safety of Twice-Yearly Subcutaneous Lenacapavir for PrEP Among PURPOSE 2 Participants Who Used Substances. [Presentation]. Paper presented at: IDWeek; October 19–22, 2025; Atlanta, GA.
8. Gilead Sciences. Study of Lenacapavir and Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF) for Prevention of HIV in People Who Inject Drugs (HPTN-103) (PURPOSE-4) Available at:

https://clinicaltrials.gov/study/NCT06101342?intr=lenacapavir&rank=5 Accessed: 07 November 2023. 2023.

Abbreviations

AE=adverse event
CES2=carboxylesterase 2
CYP=cytochrome P450
DDI=drug-drug interaction
FTC=emtricitabine
LEN=lenacapavir
P-gp=P-glycoprotein
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
SUBQ=subcutaneous(ly)
TDF= tenofovir disoproxil fumarate
UGT1A4/1=uridine 5'-diphospho-glucuronosyltransferase family 1 member A4/1

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:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 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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