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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

LEN is a moderate CYP3A inhibitor with the potential to increase concentrations of fentanyl by inhibiting its metabolism via the CYP3A pathway.[1] Based on in vitro data on fentanyl metabolism combined with calculations using an adapted mechanistic static model, a weak interaction between SC LEN and IV fentanyl (AUC ratio of 1.15) would be predicted. Based on in vitro hepatocyte and enzyme phenotyping data, 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] Please note: in vitro results should not be used to draw clinical conclusions or decision making.

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, sedation, and opioid withdrawal.[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 4 Study[6]

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. 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.

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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