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Yeztugo® (lenacapavir) Drug Interaction Profile

This document is in response to your request for information regarding the drug interaction profile of Yeztugo® (lenacapavir [LEN]). This is not an exhaustive list of potential drug-drug interactions. Please refer to Section 7 Drug Interactions in the US FDA-approved Prescribing Information for more information.

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.

Summary[1]

There are no contraindications to administering LEN with other drugs.

Based on drug interaction studies conducted with LEN, no clinically significant drug interactions have been observed with: atorvastatin, famotidine, pitavastatin, rosuvastatin, tenofovir alafenamide and voriconazole.

- Table 1: Summary of the Effect of Other Drugs on LEN
- Table 2: Drug-Drug Interaction Study: Effects of Select Drugs on LEN
- Figure 1: Dosing Recommendations for Individuals Receiving LEN and Initiating a Strong or Moderate CYP3A Inducer
- Table 3: Summary of the Effect of LEN on Other Drugs
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Effects of Other Drugs on LEN[1]

LEN is a substrate of P-gp, UGT1A1, and CYP3A.

Table 1. Summary of the Effect of Other Drugs on LEN[1]

Other Drug DDI Profile	How the Other Drug Affects LEN	Prescribing Information Guidance
Strong or Moderate CYP3A Inducer	Coadministration may significantly decrease plasma concentrations of LEN, which may reduce the effectiveness of LEN	Dosage modifications (supplemental doses) of LEN are recommended when initiating strong or moderate CYP3A inducers. See Figure 1 below for dosing.
Combined P-gp, UGT1A1, and strong CYP3A inhibitor	Coadministration may significantly increase plasma concentrations of LEN	Concomitant administration of LEN with these inhibitors is not recommended

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Effects on Exposure of LEN When Coadministered With Select Drugs[1]

In a clinical drug-drug interaction study, select drugs were coadministered with a single dose of LEN 300 mg. The effects of the selected drugs on LEN PK parameters (C_{max}, AUC) are summarized below in Table 2. Please refer to Section 12.3 Pharmacokinetics and Table 11. Effect of Other Drugs on LEN in the Prescribing Information for more information.

Table 2. Drug-Drug Interaction Study: Effects of Select Drugs on LEN[1]

Drug Coadministered with LEN	DDI Mechanism of Coadministered Drug	Effects on LEN[a]
Cobicistat	Inhibitor of CYP3A (strong) and P-gp	↑ Increased LEN exposure
Darunavir/cobicistat	Inhibitor of CYP3A (strong) and inhibitor and inducer of P-gp	
Atazanavir/cobicistat	Inhibitor of CYP3A (strong), UGT1A1, and P-gp	
Rifampin	Inducer of CYP3A (strong), P-gp, and UGT	↓ Decreased LEN exposure
Efavirenz	Inducer of CYP3A (moderate) and P-gp	
Voriconazole	Inhibitor of CYP3A (strong)	↔ No meaningful effect on LEN exposure
Famotidine	NA[b]	

[a]Based on mean ratio of LEN PK parameters of C_{max} and AUC, where no effect = 1.00. Refer to Table 11. Effect of Other Drugs on LEN in the Prescribing Information for more information
[b]Not applicable; was not described in the Prescribing Information.

Dosage Modifications for Coadministration with Strong or Moderate CYP3A Inducers[1]

Supplemental doses of LEN are recommended for individuals initiating therapy with either strong CYP3A inducers or moderate CYP3A inducers.

- **Strong CYP3A inducers** may be initiated starting at least 2 days after LEN is first initiated.
- **Moderate CYP3A inducers** may be started any time after LEN is first initiated.

Dosing recommendations are not available for the **initiation of LEN in individuals already receiving strong or moderate CYP3A inducers**, nor in individuals receiving the weekly oral dosage of LEN.

Figure 1 shows the dosing recommendations for individuals receiving LEN and initiating a strong or moderate CYP3A inducer. Please refer to Section 2.5 Dosage Modifications for Co-administration with Strong or Moderate CYP3A Inducers in the Prescribing Information for more information.

Figure 1. Dosing Recommendations for Individuals Receiving LEN and Initiating a Strong or Moderate CYP3A Inducer[1]

Proceed with scheduled continuation injection dosing of LEN

927 mg by subcutaneous injection
(2 x 1.5 mL injections) every 26 weeks (+/- 2 weeks)

+

Administer Supplemental Doses of LEN as follows:
Wait at least 2 days after LEN initiation before initiating strong CYP3A inducers.
Moderate CYP3A inducers may be started at any time after LEN initiation.

Step 1: On the same day the moderate or strong CYP3A inducer is initiated

Strong CYP3A Inducer:	Moderate CYP3A Inducer:
927 mg by subcutaneous injection (2 x 1.5 mL injections) + 600 mg orally (2 x 300 mg tablets)	463.5 mg by subcutaneous injection (1 x 1.5 mL injections)

Step 2: The day after the CYP3A inducer is initiated

Strong CYP3A Inducer:	Moderate CYP3A Inducer:
600 mg orally (2 x 300 mg tablets)	N/A

Ongoing: If a moderate or strong CYP3A inducer is coadministered >6 months

Strong CYP3A Inducer:	Moderate CYP3A Inducer:
Repeat Step 1 and Step 2 dosing every 26 weeks (+/- 2 weeks) from the initial Step 1 date	Repeat Step 1 dosing every 26 weeks (+/- 2 weeks) from the initial Step 1 date

Stopping: After stopping the moderate or strong CYP3A inducer

Resume usual scheduled dosing

927 mg by subcutaneous injection
(2 x 1.5 mL injections) every 26 weeks (+/- 2 weeks)

Effects of LEN on Other Drugs[1]

LEN is a moderate inhibitor of CYP3A and a P-gp inhibitor.

Table 3. Summary of the Effect of LEN on Other Drugs[1]

Other Drug DDI Profile	How LEN Affects the Other Drug	Prescribing Information Guidance
Sensitive substrates of CYP3A or P-gp	Coadministration may increase the concentrations of these substrates and result in the increased risk of their adverse events	See the prescribing information of these sensitive substrates for dosing recommendations or appropriate monitoring of safety
Primarily metabolized by CYP3A	LEN may increase the exposure of drugs primarily metabolized by CYP3A initiated within 9 months after the last subcutaneous dose of LEN due to the long half-life of LEN following subcutaneous administration	NA

Effects on Exposure of Select Drugs When Coadministered With LEN[1]

In a clinical drug-drug interaction study, select drugs were coadministered following LEN 600 mg twice daily for 2 days. Single 600 mg doses of LEN were administered with each coadministered drug. The effects of LEN on the selected drugs PK parameters (C_{max},AUC) are summarized below in Table 4. Please refer to Section 12.3 Pharmacokinetics and Table 12. Effect of LEN on Other Drugs in the Prescribing Information for more information.

Table 4. Drug-Drug Interaction Study: Effects of LEN on Other Drugs[1]

Drug Coadministered with LEN	DDI Mechanism of Coadministered Drug	Effects on Coadministered Drug[a]
Midazolam	substrate of CYP3A	↑ Increased coadministered drug exposure
1-hydroxymidazolam[b]	substrate of CYP3A	↓ Decreased coadministered drug exposure
Rosuvastatin	substrate of BCRP and OATP	↔ No meaningful effect on coadministered drug exposure
Pitavastatin	substrate of OATP	
Tenofovir[c]	substrate of P-gp	
Tenofovir alafenamide	substrate of P-gp	

[a]Based on mean ratio of coadministered drug PK parameters of C_{max} and AUC, where no effect = 1.00. All no effect boundaries were 70% to 143%. See Table 12. Effect of LEN on Other Drugs in the Prescribing Information for more information.
[b]Major active metabolite of midazolam.
[c]Tenofovir alafenamide is converted to tenofovir *in vivo*.

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Drugs Without Clinically Significant Interactions with LEN[1]

Based on drug interaction studies conducted with LEN, no clinically significant drug interactions have been observed with:

- Atorvastatin
- Famotidine
- Pitavastatin
- Rosuvastatin
- Tenofovir alafenamide
- Voriconazole

Reference

1. Enclosed, Gilead Sciences Inc. YEZTUGO® (lenacapavir) tablets, for oral use. YEZTUGO® (lenacapavir) injection, for subcutaneous use. U.S. Prescribing Information. Foster City, CA.

Abbreviations

AUC=area under the curve
BCRP=breast cancer resistance protein
C_{max}=maximum plasma concentration
DDI=drug-drug interaction
LEN=lenacapavir
NA=not applicable
OATP=organic anion transporting polypeptide
P-gp=P-glycoprotein
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
UGT=uridine 5'-diphospho-glucuronosyltransferase

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

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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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