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GILEAD | Medical Information

Yeztugo® (lenacapavir) Alternative Sites of Administration

This document is in response to your request for information regarding Yeztugo® (lenacapavir [LEN]) and alternative sites of subcutaneous (SUBQ) administration other than the abdomen or thigh.

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Summary

Product Labeling[1]

LEN injection is only for SUBQ administration into the abdomen by a healthcare provider. The thigh can be used as an alternative injection site if preferred. Do NOT administer intradermally due to risk of serious ISRs.

Two 1.5 mL injections are required for a complete dose. If administering in the abdomen, ensure injections are ≥2 inches away from the navel. The second injection should be administered ≥4 inches from the first injection site.

Available Data on Alternative Sites of LEN Administration

An analysis of data from the RBP and OLE phases of PURPOSE 1 and PURPOSE 2 studies assessed the safety and tolerability of LEN SUBQ injections in the thigh, upper arm, and upper buttock compared with the abdomen.[2]

- LEN administration in non-abdominal sites (ie, thigh, upper arm, and upper buttocks) was associated with fewer ISRs than administration in the abdomen.
- ISR nodules and indurations generally resolved more quickly when LEN was administered in non-abdominal sites than in the abdomen, although there was longer follow-up for abdominal injection administered during the RBP.
- LEN administration in non-abdominal sites was generally well tolerated with no serious ISRs or ISRs that led to discontinuation.

A phase 1, open-label, multicohort study evaluating the PK and safety of LEN SUBQ administered in different sites demonstrated that exposure to LEN administered into the thigh, upper arm, abdomen, and gluteal regions were generally similar. Observed PK differences among the different sites were not considered clinically significant.[3,4]

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Product Labeling[1]

Dosage and Administration

Preparation and administration of SUBQ injection

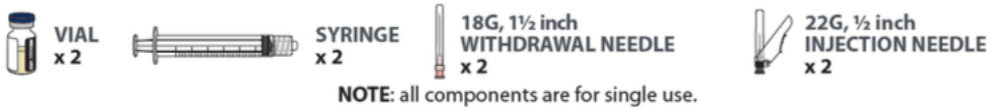
LEN injection is only for SUBQ administration into the abdomen by a healthcare provider. The thigh can be used as an alternative injection site if preferred. Do NOT administer intradermally due to risk of serious ISRs.

Use aseptic technique. Visually inspect the solution in the vials and prepared syringe for particulate matter and discoloration prior to administration. LEN injection is a yellow solution. Do not use LEN injection if the solution is discolored or if it contains particulate matter. Once the solution is withdrawn from the vials, the SUBQ injections should be administered as soon as possible.

Figure 1 identifies the components for use in the administration steps for the withdrawal needle injection kit. The 18-gauge needle is for withdrawal only in this kit.

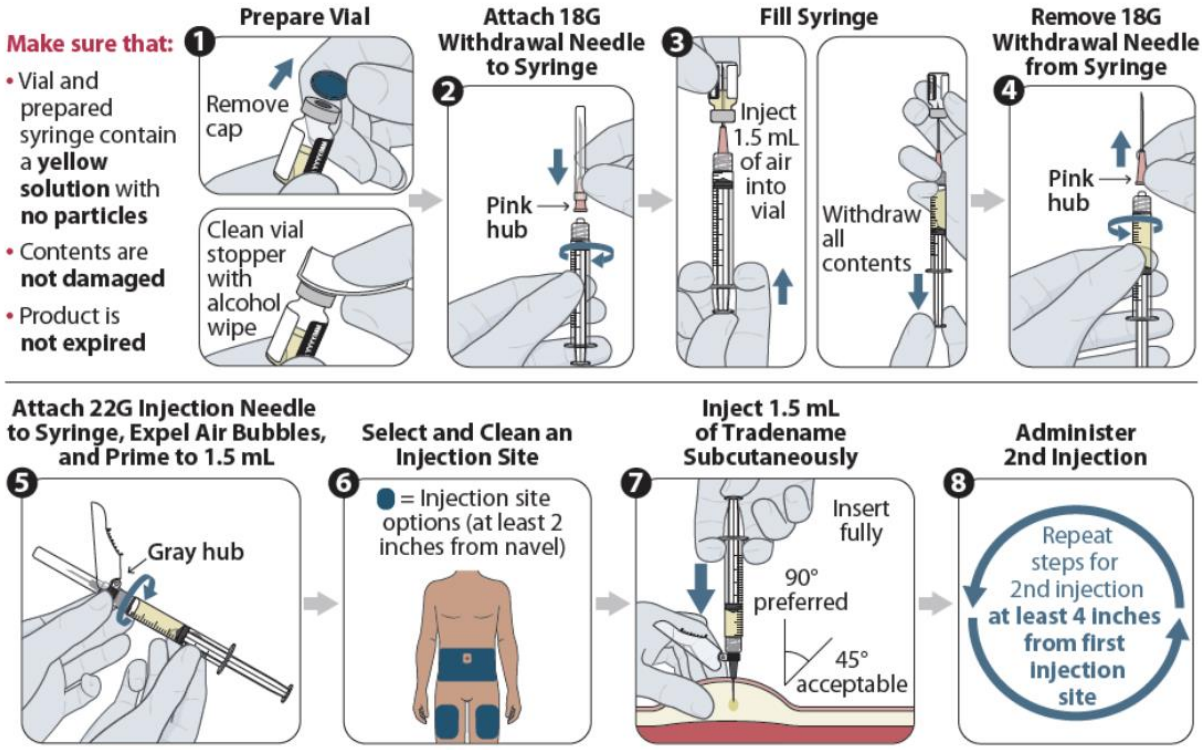
The injection kit components are for single use only. Two 1.5 mL injections are required for a complete dose.

Figure 1. LEN Withdrawal Needle Injection Kit Components[1]



The administration steps are provided in Figure 2. Select and clean the injection sites. If administering in the abdomen, ensure injections are ≥2 inches away from the navel. Administer the second injection ≥4 inches apart from the first injection site.

Figure 2. LEN Injection Steps for Withdrawal Needle Injection Kit[1]



Inform individuals that a SUBQ drug depot forms following LEN injection. Advise that, in some individuals, this may lead to a nodule at the injection site. Improper administration (intradermal injection) of LEN has been associated with serious ISRs, including necrosis and ulcer. Ensure LEN is only administered SUBQ.

Available Data on Alternative Sites of LEN Administration

PURPOSE 1 and PURPOSE 2

Study designs

PURPOSE 1 (NCT04994509) is an ongoing, phase 3, double-blind, randomized, active-controlled study evaluating the efficacy and safety of twice-yearly SUBQ LEN and once-daily oral FTC/TAF or FTC/TDF for HIV-1 PrEP in cisgender women and adolescent girls aged 16 to 25 years across South Africa and Uganda.[5]

PURPOSE 2 (NCT04925752) is an ongoing, phase 3, double-blind, randomized study evaluating the efficacy and safety of twice-yearly SUBQ LEN and once-daily oral FTC/TDF for HIV-1 PrEP in cisgender gay, bisexual, and other men; TGW; TGM; and GNB 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.[6]

In both studies, participants randomly assigned to LEN in the RBP could continue on LEN in the OLE phase; participants randomly assigned to FTC/TAF or FTC/TDF who continued into

the OLE switched to LEN. Participants received LEN SUBQ injections in the abdomen during the RBP; pregnant participants in PURPOSE 1 could choose to receive LEN administration in the thigh. Participants who continued in the OLE phase could choose to receive LEN SUBQ injections in the abdomen, thigh, upper arm, or upper buttocks.[2]

Safety and tolerability of LEN SUBQ injection locations[2]

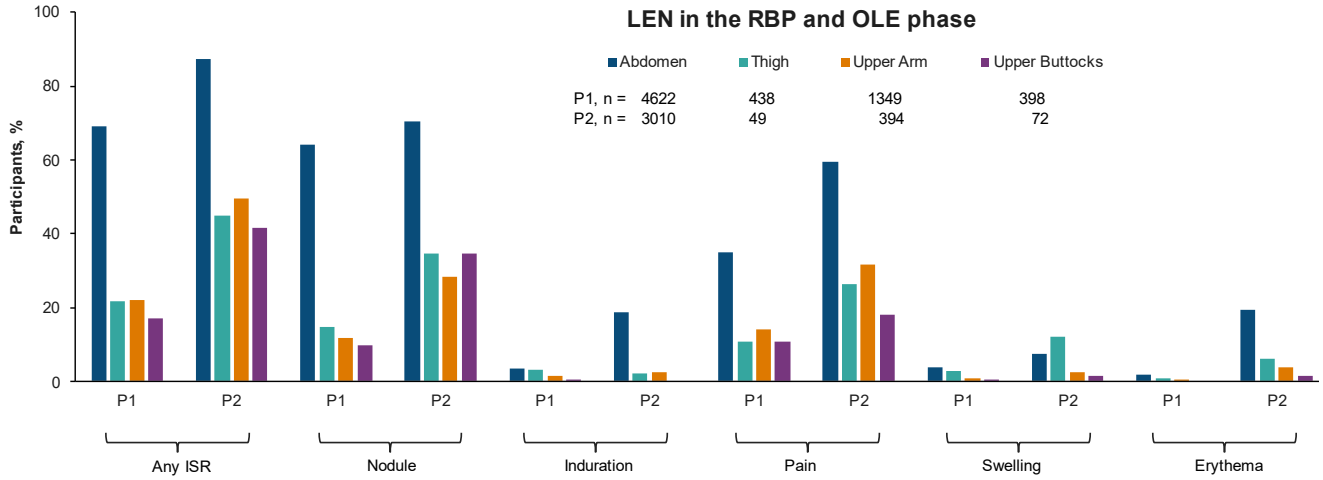
An analysis was conducted to assess the safety and tolerability of LEN SUBQ injections in non-abdominal sites (ie, thigh, upper arm, and upper buttocks) compared with abdominal sites. All participants who received LEN SUBQ in the RBP or OLE phase were included (Table 1). Outcomes included investigator-reported ISRs and AEs that were associated with LEN SUBQ administration across all injection sites.

Table 1. PURPOSE 1 and PURPOSE 2 Analysis: Baseline Demographics[2]

PURPOSE 1	Abdomen (n=4622)	Thigh (n=438)	Upper Arm (n=1349)	Upper Buttocks (n=398)
Female sex at birth, %	100	100	100	100
Body weight, median (IQR), kg	65.2 (55.9–79.5)	63.5 (55.8–75)	69.8 (59–84)	66.8 (56.6–81.6)
BMI, median (IQR), kg/m^2	26 (22.3–31.5)	25.6 (22.6–30)	27.8 (23.6–33.3)	26.8 (23–32)
Pregnant or postpartum at time of injection, n (%)	384 (8.3)	225 (51.4)	126 (9.3)	25 (6.3)
PURPOSE 2	**Abdomen (n=3010)**	**Thigh (n=49)**	**Upper Arm (n=394)**	**Upper Buttocks (n=72)**
Male sex at birth, n (%)	2953 (98.1)	46 (93.9)	390 (99)	72 (100)
Body weight, median (IQR), kg	75.7 (65–89)	77.9 (65.6–88.4)	81.7 (70.5–97.1)	76.5 (68.9–88.2)
BMI, median (IQR), kg/m^2	25.3 (22.1–29.1)	24.5 (22.7–28.9)	26.9 (23.6–31)	25.4 (22.7–28.8)

A smaller percentage of participants across both studies had ISRs in the thigh, upper arm, or upper buttocks than in the abdomen (Figure 3). Note that the sample sizes of thigh, upper arm, and upper buttocks injections were smaller relative to that of abdomen injections in both studies.

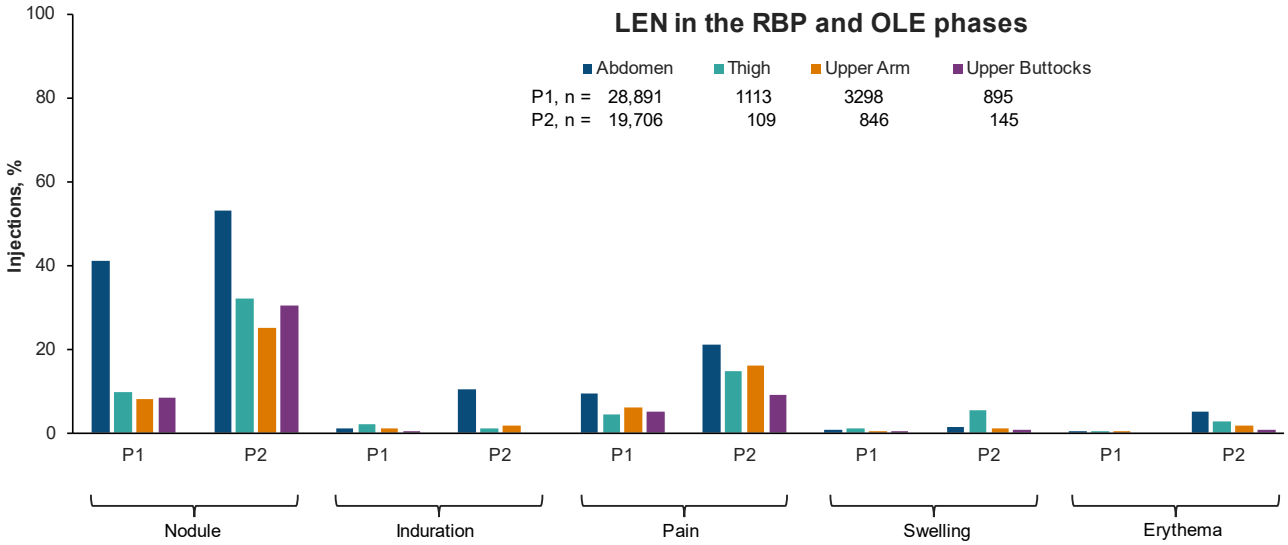
Figure 3. PURPOSE 1 and PURPOSE 2 Analysis: Proportion of Participants in the RBP and OLE Phase With LEN-Related ISRs by Injection Site[2]



A smaller proportion of participants had AEs of injection site nodules and pain with LEN administration in non-abdominal sites than in the abdomen; however, there were fewer

participants who received injections in the thigh, upper arm, and upper buttocks than abdominal injections in both studies (Figure 4).

Figure 4. PURPOSE 1 and PURPOSE 2 Analysis: Proportion of LEN Injections in the RBP and OLE Phase Resulting in ISRs by Injection Site[2]



Note: Each LEN 927 mg SUBQ dose was administered as 2 × 1.5 mL injections. For nodules and indurations, bilateral events from the same injection visit were counted as separate AEs; all other ISRs were not counted separately, and all events with the same AE onset date were counted as one event.

Injection site nodules and indurations generally resolved more quickly when LEN was administered in non-abdominal sites than in the abdomen, although there was longer follow-up for abdominal injections administered during the RBP (Table 2).
LEN administration in the thigh, upper arm, or upper buttocks was generally well tolerated with no serious ISRs or ISRs that led to discontinuation (Table 3).

Table 2. PURPOSE 1 and PURPOSE 2 Analysis: Duration and Resolution of LEN-Related Nodules and Indurations[2]

PURPOSE 1	Abdomen		Thigh	Upper Arm	Upper Buttocks
	All LEN (n=4622)	Switched to LEN OLE (n=2482)	All LEN (n=438)	All LEN (n=1349)	All LEN (n=398)
Total injections, n	28,891	11,082	1113	3298	895
Nodules, n (%)	11,899 (41.2)	4723 (42.6)	108 (9.7)	268 (8.1)	74 (8.3)
Resolved,[a] n (%)	7326 (61.6)	2275 (48.2)	57 (52.8)	80 (29.9)	19 (25.7)
Time to resolution,[b] median (IQR), days	260 (151–364)	182 (91–275)	90 (80–174)	91 (72–142)	90 (86–97)
Indurations, n (%)	276 (1)	79 (0.7)	22 (2)	30 (0.9)	2 (0.2)
Resolved,[a] n (%)	213 (77.2)	47 (59.5)	13 (59.1)	25 (83.3)	1 (50)
Time to resolution,[b] median (IQR), days	87 (15–262)	53 (17–233)	15 (11–49)	29 (10–55)	95 (NR)

PURPOSE 2	Abdomen		Thigh	Upper Arm	Upper Buttocks
	All LEN (n=3010)	Switched to LEN OLE (n=827)	All LEN (n=49)	All LEN (n=394)	All LEN (n=72)
Total injections, n	19,706	3113	109	846	145
Nodules, n (%)	10,430 (52.9)	1839 (59.1)	35 (32.1)	213 (25.2)	44 (30.3)
Resolved,[a] n (%)	6201 (59.5)	597 (32.5)	10 (28.6)	98 (46)	11 (25)
Time to resolution,[b] median (IQR), days	270 (176–367)	183 (106–273)	116 (82–178)	85 (32–96)	182 (168–184)
Indurations, n (%)	2025 (10.3)	398 (12.8)	1 (0.9)	15 (1.8)	0
Resolved,[a] n (%)	1641 (81)	288 (72.4)	1 (100)	12 (80)	N/A
Time to resolution,[b] median (IQR), days	85 (7–191)	11 (6–115)	93	22 (3–95)	N/A

Abbreviation: NR=not reported.
[a]Denominator was the number of nodules or indurations.
[b]Duration was calculated by subtracting the onset date from the stop date and adding 1 day.

Table 3. PURPOSE 1 and PURPOSE 2 Analysis: ISRs[2]

PURPOSE 1, Participants (%)	Abdomen		Thigh	Upper Arm	Upper Buttocks
	All LEN (n=4622)	Switched to LEN OLE (n=2482)	All LEN (n=438)	All LEN (n=1349)	All LEN (n=398)
Any ISR	3188 (69)	1575 (63.5)	95 (21.7)	295 (21.9)	68 (17.1)
Grade 3 or 4 ISR	8 (0.2)	3 (0.1)	3 (0.7)	0	1 (0.3)
Any serious ISR	0	0	0	0	0
ISR that led to LEN discontinuation	6 (0.1)	2 (<0.1)	0	0	0
ISR that led to study discontinuation	1 (<0.1)	1 (<0.1)	0	0	0
PURPOSE 2, Participants (%)	**Abdomen**		**Thigh**	**Upper Arm**	**Upper Buttocks**
	All LEN (n=3010)	**Switched to LEN OLE (n=827)**	**All LEN (n=49)**	**All LEN (n=394)**	**All LEN (n=72)**
Any ISR	2628 (87.3)	723 (87.4)	22 (44.9)	196 (49.7)	30 (41.7)
Grade 3 or 4 ISR	18 (0.6)	3 (0.4)	0	0	0
Any serious ISR	1 (<0.1)	1 (0.1)	0	0	0
ISR that led to LEN discontinuation	27 (0.9)	0	0	0	0
ISR that led to study discontinuation	3 (<0.1)	0	0	0	0

Phase 1 PK Study: Administration in Different Sites[3]

Study design and demographics

A phase 1, open-label, parallel-design, single-dose, multicohort study evaluated the PK and safety of LEN administered SUBQ in different sites.[3,4] Healthy adult volunteers aged 18 to 55 years who had a BMI of 19 to 30 kg/m^2 were enrolled in one of four cohorts (n=10 per cohort). Each cohort of healthy volunteers received a single 927 mg dose of LEN SUBQ administered as two 1.5 mL injections either bilaterally in the thigh, upper arm, or gluteal region or in two different abdominal quadrants, which is the approved administration site and served as a reference. PK samples from plasma were collected post dose at Hours 0, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216, followed by weekly or biweekly assessments between Days 15 and 210 and monthly assessments through to Day 270.[3] Safety evaluations included injection site examinations on Days 1 to 10 and at each study

visit through Day 270 to evaluate the occurrence of ISRs. Baseline demographics were generally similar among cohorts (Table 4).[3]

Table 4. Phase 1 PK Study: Baseline Demographics[3]

Key Demographics	Abdomen (n=10)	Thigh (n=10)	Upper Arm (n=10)	Gluteal Region (n=10)
Male, %	50	50	60	40
Age, mean ± SD, years	44±11.5	44±9.5	43±6.7	40±9.7
Race, White/Black or African American, %	70/30	70/30	80/20	100/0
Weight, mean ± SD, kg	74.7±8.7	77.8±11.5	80.3±13.4	74.4±11.6
BMI, mean ± SD, kg/m^2	27±2.4	27±1.6	27.2±2.9	26.9±2.2

PK results[3]

Exposures to LEN after SUBQ administration into the thigh, upper arm, and gluteal regions were generally similar or slightly higher than those observed after administration into the abdomen; observed PK differences were not considered clinically significant (Table 5). GM C_{max}, $AUC_{6\ mo}$, and AUC_{last} values were 8% to 15% lower after SUBQ administration into the thigh than those observed for the abdomen (reference comparator) cohort; these PK parameters were 5% to 33% higher in the upper-arm cohort and 18% to 26% higher in the gluteal-region cohort than in the abdomen cohort. The GM $C_{6\ mo}$ in each cohort was greater than the IQ4 (target efficacy concentration) of 15.5 ng/mL.

Table 5. Phase 1 PK Study: PK Parameters by Administration Site[3]

Parameters	Abdomen (n=8[a])	Thigh (n=10)	Upper Arm (n=10)	Gluteal Region (n=9[a])
C_{max}, GM (%CV), ng/mL	56.7 (40.7)	52.1 (67.4)	75.6 (57.2)	71.2 (42.7)
T_{max}, median (Q1, Q3), h	2660 (1870, 3250)	2490 (1950, 3120)	1990 (1150, 2490)	2160 (1660, 2580)
$T_{1/2}$, median (Q1, Q3), h	1440 (1180,1920)	1430 (1100, 2080)[b]	1260 (1070, 1500)	1560 (1300, 1810)
$C_{6\ mo}$, GM (%CV), ng/mL	28.6 (60.6)	22.6 (69.9)	18.7 (59.9)	25.2 (68)
$AUC_{6\ mo}$, GM (%CV), ng·h/mL	144,000 (38.2)	122,000 (73.9)[b]	172,000 (45.5)	181,000 (36.9)
AUC_{last}, GM (%CV), ng·h/mL	187,000 (33.3)	164,000 (57.6)[b]	196,000 (43.9)	220,000 (35.9)
AUC_{∞}, GM (%CV), ng·h/mL	223,000 (34.7)	267,000 (26.2)[b]	208,000 (43.8)	247,000 (35.3)

Abbreviations: %CV=geometric % coefficient of variation; AUC_{∞}=area under the concentration-time curve to infinity; Q=quartile; $T_{1/2}$=half-life; T_{max}=time to C_{max}.
[a]Three healthy volunteers (abdomen, n=2; gluteal region, n=1) were lost to follow-up or withdrew prematurely.
[b]AUC_{∞} and $T_{1/2}$, n=6; AUC_{last} and $AUC_{6\ mo}$, n=9.

Safety results[4]

No serious AEs or AEs that resulted in study discontinuation occurred. Treatment-related AEs occurred in 38/40 participants (95%), and all non-ISR treatment-related AEs were Grade 1. Most participants (38/40; 95%) experienced ISRs, and the most common ISRs were pain (90%), induration (73%), erythema (70%), nodules (15%), and swelling (15%; Table 6). All ISRs were Grade ≤2 except for 1 event of erythema in the upper-arm cohort.

Table 6. Phase 1 PK Study: Most Common ISRs by Administration Site[4]

ISR, %	Abdomen (n=10)		Thigh (n=10)		Upper Arm (n=10)			Gluteal Region (n=10)	
	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2
Pain	100	0	90	0	80	0	0	90	0

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ISR, %	Abdomen (n=10)		Thigh (n=10)		Upper Arm (n=10)			Gluteal Region (n=10)	
	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2
Induration	50	30	20	60	20	80	0	30	0
Erythema	50	10	30	60	40	30	10	10	40
Nodules	20	0	40	0	0	0	0	0	0
Swelling	30	10	0	0	0	10	0	0	10

References

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2. Brites C, Losso MH, Gallardo-Cartagena J, et al. Favorable Tolerability of Lenacapavir for PrEP Administered at Participant-Chosen Anatomic Sites in PURPOSE 1 and PURPOSE 2 [Poster TUPEC184]. Paper presented at: The 26th International AIDS Conference (AIDS); July 26-31, 2026; Rio de Janeiro, Brazil.
3. Lat A, Kim A, Zhang H, et al. Impact of Subcutaneous Administration Sites on the Clinical Pharmacokinetics of Lenacapavir , a Long-Acting HIV Capsid Inhibitor: Does Body Site Matter? [Poster Abstract 1542]. Paper presented at: ID Week 2023; October 11-15, 2023; Boston, MA.
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5. Bekker LG, Das M, Abdool Karim Q, et al. Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women. *N Engl J Med.* 2024;391(13):1179-1192.
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.

Abbreviations

AE=adverse event
$AUC_{6\ mo}$=area under the concentration-time curve at 6 months
AUC_{last}=area under the concentration-time curve from dosing to last measurable concentration
$C_{6\ mo}$=concentration at 6 months
C_{max}=maximum concentration
FTC=emtricitabine
GM=geometric mean
GNB=gender nonbinary
IQ4=inhibitory quotient-4
IRR=incident rate ratio
ISR=injection site reaction
LEN=lenacapavir
OLE=open-label extension
P1/2=PURPOSE 1/2
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
RBP=randomized blinded phase
SUBQ=subcutaneous(ly)
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TGM=transgender men
TGW=transgender women

Product Label

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