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## Subject: Lenacapavir (Yeztugo) SQ Injection and Tablet

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

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### DESCRIPTION:

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral medication to prevent infection with the human immunodeficiency virus (HIV). PrEP is for people without HIV who may be exposed to HIV through sex or injection drug use. According to the Centers for Disease Control and Prevention, PrEP, when taken as prescribed, reduces the risk of acquiring HIV from sex by approximately 99% and from injection drug use by at least 74%. Until recently, three FDA-approved PrEP medications were available and included emtricitabine and tenofovir disoproxil fumarate (Truvada) tablets, emtricitabine and tenofovir alafenamide (Descovy) tablets, and cabotegravir (Apretude) injection. On June 18, 2025, the FDA approved lenacapavir (Yeztugo), a capsid inhibitor, for PrEP in adults and adolescents weighing at least 35 kg who are at risk for HIV acquisition. Lenacapavir (Yeztugo) is administered every six months as two subcutaneous injections with four oral tablets co-administered with the first dose (i.e., two tablets with the injection and two tablets the day after the injection).

According to the prescribing information, the efficacy and safety of lenacapavir (Yeztugo) was evaluated in two randomized, double-blind, active-controlled, multinational trials (PURPOSE 1 and PURPOSE 2). PURPOSE 1 was in cisgender adolescent girls and young women between 16 and 25 years of age in South Africa and Uganda who had unknown HIV-1 status at screening and who were at risk of acquiring HIV-1 based on sexual activity with male partners. Participants who tested negative for HIV-1 at screening and baseline were randomized to receive lenacapavir (Yeztugo) (N=2134), once daily emtricitabine and tenofovir alafenamide (Descovy) (N=2136), or once daily emtricitabine and tenofovir disoproxil fumarate (Truvada) (N=1068) in a 2:2:1 ratio. The median age of participants was 21 years (range: 16-26 years) and 99.9% were Black. Baseline characteristics in the randomized participants were similar to the screened population. Over 99% of lenacapavir (Yeztugo) injections were administered into

the abdomen and each dose was administered in two locations. A total of 32 pregnant participants received lenacapavir (Yeztugo) injections into the thigh and each dose was administered bilaterally (i.e., one injection in the right thigh and one injection in the left thigh). The efficacy endpoint was the rate of incident HIV-1 infections per 100 person-years in participants randomized to lenacapavir (Yeztugo) compared with the rate of incident HIV-1 infections per 100 person-years in participants randomized to emtricitabine and tenofovir disoproxil fumarate (Truvada). The results of PURPOSE 1 are listed in Table 1.

**Table 1: Overall HIV-1 Infection Outcomes in PURPOSE 1<sup>a</sup>**

	<b>Lenacapavir (Yeztugo) N=2134</b>	<b>Emtricitabine + tenofovir disoproxil fumarate (Truvada) N=1068</b>	<b>Rate Ratio (95% CI)</b>
<b>Person-years</b>	1939	949	
<b>HIV-1 infections (incidence rate per 100 person years)</b>	0 (0.00)	16 (1.69)	Yeztugo/Truvada 0.000 (0.000, 0.101) p < 0.0001
CI = confidence interval			
<sup>a</sup> The determination of efficacy was based on planned interim analyses (which became the final analyses) following sequential testing of HIV-1 incidence for lenacapavir (Yeztugo) compared to background followed by lenacapavir (Yeztugo) compared to emtricitabine + tenofovir disoproxil fumarate (Truvada), all at alpha level of 0.0026 when 50% of randomized participants completed at least 52 weeks of follow-up or prematurely discontinued from the study. Lenacapavir (Yeztugo) also demonstrated superiority in the risk of incident HIV-1 infection over background HIV-1 incidence.			

PURPOSE 2 was in cisgender men, transgender women, transgender men, and gender nonbinary individuals 16 years of age and older who had unknown HIV-1 status at screening and who were at risk of acquiring HIV-1 based on sexual activity with male partners. PURPOSE 2 enrolled participants in Argentina, Brazil, Mexico, Peru, South Africa, Thailand, and the United States. Participants who tested negative for HIV-1 at screening and baseline were randomized to receive lenacapavir (Yeztugo) (N=2179) or once daily emtricitabine and tenofovir disoproxil fumarate (Truvada) (N=1086) in a 2:1 ratio. The median age of participants was 29 years (range: 17-74 years). Sixty-seven percent were non-white, and 63% were Hispanic/Latine. Twenty-two percent identified as gender-diverse (transgender women, transgender men, and gender nonbinary people). Baseline characteristics in the randomized participants were similar to the screened population. Lenacapavir (Yeztugo) injections were administered into the abdomen and each dose was administered in two locations. The efficacy endpoint was the rate of incident HIV-1 infections per 100 person-years in participants randomized to lenacapavir (Yeztugo) compared with the rate of incident HIV-1 infections per 100 person-years in participants randomized to emtricitabine and tenofovir disoproxil fumarate (Truvada). The results of PURPOSE 2 are listed in Table 2.

**Table 2: Overall HIV-1 Infection Outcomes in PURPOSE 2<sup>a</sup>**

	<b>Lenacapavir (Yeztugo) N=2179</b>	<b>Emtricitabine + tenofovir disoproxil fumarate (Truvada) N=1086</b>	<b>Rate Ratio (95% CI)</b>
<b>Person-years</b>	1938	967	
<b>HIV-1 infections (incidence rate per 100 person years)</b>	2 (0.1)	9 (0.93)	Yeztugo/Truvada 0.111 (0.024, 0.513) p = 0.00245
CI = confidence interval <sup>a</sup> The determination of efficacy was based on planned interim analyses (which became the final analyses) following sequential testing of HIV-1 incidence for lenacapavir (Yeztugo) compared to background followed by lenacapavir (Yeztugo) compared to emtricitabine + tenofovir disoproxil fumarate (Truvada), all at alpha level of 0.0026 when 50% of randomized participants completed at least 52 weeks of follow-up or prematurely discontinued from the study. Lenacapavir (Yeztugo) also demonstrated superiority in the risk of incident HIV-1 infection over background HIV-1 incidence.			

The most common adverse reactions with lenacapavir (Yeztugo) (incidence greater than or equal to 5%, all grades) are injection site reactions, headache, and nausea.

**POSITION STATEMENT:**

Lenacapavir (Yeztugo) administered every 6 months for all indications including, but not limited to, pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 **does not meet the definition of medical necessity**, as **medical necessity** is **not** primarily for the member’s convenience, the family’s convenience, the caregiver’s convenience or that of the physician or other health care provider (such as extended dosing intervals).

Lenacapavir (Yeztugo) was granted FDA approval for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg who are at risk for HIV-1 acquisition and is clinically similar to other commercially available products. According to the Centers for Disease Control and Prevention, all commercially available PrEP products, when taken as prescribed, both oral [i.e., emtricitabine and tenofovir disoproxil fumarate (Truvada) tablets or emtricitabine and tenofovir alafenamide (Descovy) tablets daily] and injectable [i.e., cabotegravir (Apretude) injection every other month] reduce the risk of acquiring HIV from sex by about 99% and from injection drug use by at least 74%.

**DOSAGE/ADMINISTRATION:**

**THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER’S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.**

**FDA-approved**

- Lenacapavir (Yeztugo) is a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor and is indicated for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg who are at risk for HIV-1 acquisition.
- Individuals must have a negative HIV-1 test prior to initiating and prior to each injection of lenacapavir (Yeztugo).
- Initiation dosing:
  - Day 1: 927 mg by subcutaneous injection (2 x 1.5 mL injections) and 600 mg orally (2 x 300 mg tablets)
  - Day 2: 600 mg orally (2 x 300 mg tablets)
- Continuation dosing: 927 mg by subcutaneous injection (2 x 1.5 mL injections) every 6-months (26 weeks) from the date of the last injection +/-2 weeks

### **Dose Adjustments**

- If a scheduled injection is anticipated to be delayed by more than 2 weeks, lenacapavir (Yeztugo) tablets may be used on an interim basis (for up to 6 months if needed) until injections resume. Dosing schedule for delayed injection is 300 mg orally once every 7 days.
- If more than 28 weeks have elapsed since the last injection and tablets have not been taken, restart initiation from Day 1 if clinically appropriate.
- Dosage modifications (supplemental doses) of lenacapavir (Yeztugo) are recommended when initiating strong or moderate CYP3A inducers.

### **Drug Availability**

- Lenacapavir (Yeztugo) tablets, 300 mg are beige, capsule-shaped, and film-coated with “GSI” debossed on one side and “62L” on the other side. Each bottle contains 4 tablets (NDC 61958-3401-1), a silica gel desiccant, polyester coil, and is closed with a child resistant closure. Do not remove the desiccant packet. Dispense and store only in original container.
- Lenacapavir (Yeztugo) injection is packaged in a dosing kit (NDC 61958-3402-1) containing two single-dose clear glass vials [each containing sufficient volume to allow withdrawal of 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir], two disposable syringes, two withdrawal needles (18-gauge, 1½ inch), and two injection safety needles for subcutaneous injection (22-gauge, ½ inch). The injection solution is sterile, preservative-free, clear, and yellow with no visible particles. Vials are sealed with a stopper and aluminum overseal with flip-off cap. The vial stoppers are not made with natural rubber latex.

## **PRECAUTIONS:**

### **Boxed Warning**

- Risk of Drug Resistance with Use of Lenacapavir (Yeztugo) for HIV-1 Pre-Exposure Prophylaxis (PrEP) in Undiagnosed HIV-1 Infection: Individuals must be tested for HIV-1 infection prior to

initiating lenacapavir (Yeztugo), and with each subsequent injection, using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. Drug-resistant HIV-1 variants have been identified with use of lenacapavir (Yeztugo) by individuals with undiagnosed HIV-1 infection. Do not initiate lenacapavir (Yeztugo) unless negative infection status is confirmed. Individuals who acquire HIV-1 while receiving lenacapavir (Yeztugo) must transition to a complete HIV-1 treatment regimen.

**Contraindications**

- Unknown or positive HIV-1 status

**Precautions/Warnings**

- Comprehensive management to reduce the risk of HIV-1 acquisition.
- Potential risk of developing resistance to lenacapavir if an individual acquires HIV-1 either before or when receiving lenacapavir (Yeztugo) or following discontinuation of lenacapavir (Yeztugo). Test before each injection and additionally as clinically appropriate to confirm HIV-1 negative status.
- Residual concentrations of lenacapavir may remain in systemic circulation for up to 12 months or longer.
- Improper administration (intra-dermal injection) has been associated with serious injection site reactions.

**BILLING/CODING INFORMATION:**

The following codes may be used to describe:

**HCPCS Coding**

J0738	Injection, lenacapavir, 1 mg, fda approved prescription, only for use as hiv pre-exposure prophylaxis (not for use as treatment for hiv)
J0752	Oral, lenacapavir, 300 mg, fda approved prescription, only for use as hiv pre-exposure prophylaxis (not for use as treatment for hiv)

**ICD-10 Diagnosis Codes That Support Medical Necessity**

Z29.81	Encounter for HIV pre-exposure prophylaxis
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**REIMBURSEMENT INFORMATION:**

Refer to section entitled [POSITION STATEMENT](#).

**PROGRAM EXCEPTIONS:**

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Part D:** Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

**Medicare Advantage:** The following National Coverage Determination (NCD) was reviewed on the last guideline revised date: Self-administered Drug List (A54770). No Local Coverage Determination (LCD) was found at the time of the last guideline revised date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at [Coverage Protocol Exemption Request](#).

### DEFINITIONS:

None

### RELATED GUIDELINES:

None

### OTHER:

None

### REFERENCES:

1. Centers for Disease Control and Prevention. Clinical Guidance for PrEP. <https://www.cdc.gov/hivnexus/hcp/prep/index.html>. Accessed July 30, 2025.
2. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2025. Available at: <https://www.clinicalkey.com/pharmacology/>. Accessed 7/30/25.
3. DRUGDEX System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2025 July 30].
4. Yeztugo (lenacapavir) [package insert]. Foster City, CA: Gilead Sciences, Inc.; June 2025.

### COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 08/13/25.

### GUIDELINE UPDATE INFORMATION:

10/01/25	New Medical Coverage Guideline: Lenacapavir (Yeztugo) administered every 6 months for all indications including, but not limited to, pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 does not meet the definition of medical necessity, as medical necessity is not primarily for convenience (such as extended dosing intervals).
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