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Section:	Prescription Drugs	**Effective Date:**	January 28, 2026
Subsection:	Anti-Infective Agents	**Original Policy Date:**	August 1, 2025
Subject:	Yeztugo	**Page:**	1 of 5

Last Review Date: December 12, 2025

Yeztugo

Description

Yeztugo (lenacapavir)

Background
Yeztugo (lenacapavir) is a multistage, selective inhibitor of human immunodeficiency virus type 1 (HIV-1) capsid function that directly binds to the interface between capsid protein (p24) subunits in hexamers. Surface plasmon resistance sensorgrams showed dose-dependent and saturable binding of Yeztugo to cross-linked wild-type capsid hexamer with an equilibrium binding constant (K_D) of 1.4 nM. Yeztugo inhibits HIV-1 replication by interfering with multiple essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV-1 proviral DNA (by blocking nuclear import proteins binding to capsid), virus assembly and release (by interfering with Gag/Gag-Pol functioning, reducing production of capsid protein subunits), and capsid core formation (by disrupting the rate of capsid subunit association, leading to malformed capsids) (1).

Regulatory Status
FDA-approved indication: Yeztugo, a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor, 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 Yeztugo (1).

Yeztugo has a boxed warning advising that individuals must be tested before initiation of Yeztugo and at each subsequent injection, using a test cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. Yeztugo should only be initiated on individuals with a negative

infection status for HIV-1 PrEP. Individuals who become infected with HIV-1 while on treatment with Yeztugo must transition to a complete HIV-1 treatment regimen (1).

Yeztugo is contraindicated in individuals with unknown or positive HIV-1 infection status (1).

Yeztugo should be used to reduce the risk of HIV-1 acquisition as part of a comprehensive prevention strategy including adherence to the administration schedule, safer sex practices, including condoms, to reduce the risk of sexually transmitted infections (STIs) (1).

Resistance to Yeztugo may develop. Test before each injection and additionally as clinically appropriate to confirm HIV-1 negative status. Residual concentrations of Yeztugo may remain in systemic circulation for up to 12 months or longer. Improper administration has been associated with serious injection site reactions (1).

Yeztugo dosing schedule consists of a required initiation dosing (subcutaneous injections and oral tablets) followed by once every 6-months continuation dosing (subcutaneous injections) (1).

Healthcare providers should carefully select individuals who agree to the required injection dosing and testing schedule and counsel individuals about the importance of adherence to scheduled dosing visits to help reduce the risk of acquiring HIV-1 infection and development of resistance. Some individuals, such as adolescents, may benefit from additional counseling and appointment reminders to support adherence to the dosing and testing schedule (1).

Healthcare providers should consider the long-acting properties of Yeztugo, as lenacapavir is a moderate CYPA3A inhibitor. Medications metabolized by CYP3A initiated within 9 months after the last subcutaneous dose of Yeztugo could have increased risk of adverse reactions due to increased exposure (1).

The safety and effectiveness of Yeztugo in patients weighing less than 35 kg have not been established (1).

Related policies
Apretude, Cabenuva

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Yeztugo may be considered **medically necessary** if the conditions indicated below are met.

Yeztugo may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 12 years of age or older

Diagnosis

Patient must have the following:

1. Used for pre-exposure prophylaxis (PrEP) of HIV-1 infection
    a. Weight ≥ 35kg
    b. Patient is at risk for sexually acquired HIV-1 infection
    c. Patient is confirmed HIV-1 infection status negative using a test cleared by the FDA for the diagnosis of acute or primary HIV-1 infection
    d. Yeztugo will be administered by a healthcare professional
    e. Prescriber agrees to confirm the patient is HIV-1 infection status negative before each injection
    f. Prescriber agrees to transition patient to a complete HIV-1 treatment regimen if the patient acquires HIV-1 infection during treatment with Yeztugo
    g. Prescriber has counseled the patient regarding the required injection dosing schedule and the importance of adherence to scheduled dosing visits

Prior–Approval *Renewal* Requirements

Same as above

Policy Guidelines

Pre–PA Allowance

None

Prior–Approval Limits

Quantity 4 tablets and 4 vials

Duration 12 months

Prior–Approval *Renewal* Limits

Quantity 4 vials

Duration 12 months

Rationale

Summary
Yeztugo is indicated for the prevention of HIV-1 infection in at-risk adult and adolescent patients weighing 35 kg or more. Patients must be confirmed HIV-1 negative infection status before initiation of Yeztugo and at each subsequent injection. Individuals to receive Yeztugo should be carefully selected and advised of the adherence requirements and injection schedule to reduce the risk of infection with HIV-1. The safety and effectiveness of Yeztugo in patients weighing less than 35 kg have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Yeztugo while maintaining optimal therapeutic outcomes.

References

1. Yeztugo [package insert]. Foster City, CA: Gilead Sciences, Inc.; June 2025.

Policy History

Date	Action
August 2025	Addition to PA
September 2025	Annual review

October 2025	Annual review
January 2026	Per SME, regulatory update to promote effective monitoring and counseling for patient safety

Keywords

This policy was effective with interim approval on January 28, 2026 and will be reviewed by the FEP® Pharmacy and Medical Policy Committee on March 6, 2026.