

YEZTUGO (lenacapavir)

RATIONALE FOR INCLUSION IN PA PROGRAM

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 resonance 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



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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 (1).

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

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.