IOWA | Health and Human Services

Iowa PDL New Drug Review

Proprietary Name: Yeztugo®
Common Name: lenacapavir
PDL Category: Antiretrovirals

Pharmacology/Usage: Yeztugo® is an HIV-1 antiretroviral agent with long-acting properties. Lenacapavir sodium, the active ingredient of Yeztugo®, is a capsid inhibitor. It is a multistage, selective inhibitor of HIV1 capsid function that directly binds to the interface between capsid protein (p24) subunits in hexamers. Lenacapavir inhibits HIV1 replication by interfering with multiple essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV1 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).

Indication: For pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults and adolescents weighing at least 35kg who are at risk for HIV-1 acquisition. Individuals must have a negative HIV-1 test prior to starting Yeztugo®.

There is no pregnancy category for this medication; however, the risk summary indicates that available data from a trial with Yeztugo® use during pregnancy have not identified a drug-associated risk for miscarriage, or adverse maternal or fetal outcomes when compared to the active control. The rate of major birth defects in Yeztugo®-exposed pregnancies did not exceed the background prevalence rates. There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to Yeztugo® during pregnancy. There are clinical considerations. The safety and efficacy of use in the pediatric population weighing less than 35kg have not been established.

Dosage Form: Available as:

- Tablets: 300mg lenacapavir (306.8mg of lenacapavir sodium)
- Single-dose Vial for Injection: 463.5mg/1.5ml lenacapavir (473.1mg/1.5ml of lenacapavir sodium). Preservative-free.

Recommended Dosage: Screen all individuals for HIV-1 infection before starting Yeztugo®, prior to each subsequent injection of Yeztugo®, and additionally as clinically appropriate, using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. When screening for HIV-1 infection prior to starting Yeztugo®, if an antigen/antibody-specific test is used and provides negative results, then such negative results should be confirmed using an RNA-specific assay, even if the results of the RNA-assay are available after Yeztugo® initiation. When screening for HIV-1 infection prior to continuing Yeztugo®, negative results from a rapid, point-of-care antigen/antibody test should be confirmed using a more sensitive assay.

Prior to starting Yeztugo®, healthcare providers should select individuals who agree to the required testing and every 6 month injection dosing schedule, and counsel individuals about the importance of adherence to scheduled Yeztugo® dosing visits to help reduce the risk of acquiring HIV-1 infection and development of resistance.

The dosing schedule consists of a required initiation dosing (subcutaneous [SC] injections and oral tablets) followed by once every 6 months continuation dosing (SC injections). Yeztugo® oral tablets may be taken with or without food. Yeztugo® injection is only for SC 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 the risk of serious injection site reactions. Refer to the table below for the dosing schedule of Yeztugo® for initiation and continuation in adults and adolescents weighing at least 35kg, which was adapted from the prescribing information.

Time	
Dosage of Yeztugo®: Initiation	
Day 1	927mg SC injection & 600mg PO (2 X 1.5ml injections & 2 X 300mg tablets)
Day 2	600mg PO (2 X 300mg tablets)
Dosage of Yeztugo®: Continuation	
Every 6 months (26 weeks) +/- 2 weeks	927mg SC injection (2 X 1.5ml injections)

If the day 2 oral initiation dose is missed, take it as soon as possible. Do not take day 1 and day 2 oral initiation doses on the same day.

Refer to the prescribing information for additional information on anticipated delayed injections and missed injections.

Dosage adjustments are not recommended with mild, moderate, or severe renal impairment; however, Yeztugo® has not been studied in individuals with end-stage renal disease (ESRD). Dosage adjustments are not recommended with mild or moderate hepatic impairment; however, Yeztugo® has not been studied in individuals with severe hepatic impairment.

Drug Interactions: Lenacapavir is a substrate of P-gp, UGT1A1, and CYP3A.

Drugs that are strong or moderate inducers of CYP3A may significantly decrease plasma concentrations of lenacapavir, which may reduce the efficacy of Yeztugo®. Thus, dosage modifications (supplemental doses) of Yeztugo® are recommended when starting strong or moderate CYP3A inducers.

Combined P-gp, UGT1A1, and strong CYP3A inhibitors may significantly increase Yeztugo® plasma concentrations. Concomitant administration of Yeztugo® with these inhibitors is not recommended.

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

The coadministration of Yeztugo® with sensitive substrates of CYP3A or P-gp 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.

Due to the long half-life of lenacapavir after SC administration, Yeztugo® may increase the exposure of drugs mainly metabolized by CYP3A started within 9 months after the last SC Yeztugo® dose.

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

Box Warning: This product has a box warning regarding risk of drug resistance with use of Yeztugo® for HIV-1 pre-exposure prophylaxis (PrEP) in undiagnosed HIV-1 infection. Individuals must be tested for HIV-1 infection prior to starting Yeztugo®, and with each subsequent injection of Yeztugo®, 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 Yeztugo® by individuals with undiagnosed HIV-1 infection. Do not start Yeztugo® unless negative infection status is confirmed. Individuals who acquire HIV-1 while receiving Yeztugo® must transition to a complete HIV1 treatment regimen.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Yeztugo®) minus reported % incidence for Truvada® in study PURPOSE 1. Please note that an incidence of 0% means the incidence was the same as or less than comparator.* The most frequently reported adverse events included injection site reactions (35%), headache (0%), nausea (0%), dizziness (0%), vomiting (0%), and diarrhea (0%).

Listed % incidence for adverse drug reactions= reported % incidence for drug (Yeztugo®) minus reported % incidence for Truvada® in study PURPOSE 2. Please note that an incidence of 0% means the incidence was the same as or less than comparator. The most frequently reported adverse events included injection site reactions (14%), headache (0%), nausea (0%), dizziness (0%), vomiting (0%), and diarrhea (0%).

Use Yeztugo® to reduce the risk of HIV1 acquisition as part of a comprehensive prevention strategy including adherence to the administration schedule and safer sex practices, including condoms, to reduce the risk of sexually transmitted infections (STIs). Yeztugo® is not always effective in preventing HIV-1 acquisition. The time from initiation of Yeztugo® for HIV-1 PrEP to maximal protection against HIV-1 infection is not known.

Due to the long-acting properties of Yeztugo®, alternative forms of PrEP should be considered following discontinuation of Yeztugo® for those individuals with HIV-1 negative status who are at continuing risk of HIV-1 acquisition and initiated within 28 weeks of the last Yeztugo® injection.

Healthcare providers should take the long-acting properties of Yeztugo® into consideration when Yeztugo® is prescribed. Residual concentrations of lenacapavir may remain in the systemic circulation of individuals for prolonged periods (up to 12 months or longer after the last SC dose). It is important to select individuals who agree to the required injection dosing schedule because non-adherence to every 6 month injections or missed doses could lead to HIV-1 acquisition and development of resistance.

Improper administration (intradermal injection) of lenacapavir has been associated with serious injection site reactions, including necrosis and ulcer. Ensure Yeztugo® is only administered SC.

Contraindications: In individuals with unknown or positive HIV-1 status.

Manufacturer: Gilead Sciences, Inc.

Analysis: The safety and efficacy of Yeztugo® for reducing the risk of HIV-1 acquisition were assessed in two randomized, double-blind, active-controlled, multinational studies (PURPOSE 1 and PURPOSE 2).

PURPOSE 1 included 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. Patients who tested negative for HIV-1 at screening and baseline were randomized to receive Yeztugo® (N=2134), once daily Descovy® (N=2136), or once daily Truvada® (N=1068).

In this study, the median age of included participants was 21 years (range 16 to 26), while 99.9% were Black. Over 99% of Yeztugo® injections were administered into the abdomen and each dose was administered in two locations. A total of 32 pregnant patients received Yeztugo® injections into the thigh and each dose was administered bilaterally.

The efficacy endpoint was the rate of incident HIV-1 infections per 100 person-years in participants randomized to Yeztugo® compared with the rate of incident HIV-1 infections per 100 person-years in participants randomized to Truvada®. Results suggested that Yeztugo® demonstrated superiority with a 100% reduction in the risk of incident HIV-1 infection over Truvada®. Results are presented in the table below, which was adapted from the prescribing information.

	Yeztugo® (N=2134)	Truvada® (N=1068)	Rate Ratio; p-value
Person-Years (PY)	1939	949	
HIV-1 infections (incidence rate per 100 PY)	0 (0.00)	16 (1.69)	0.000; p<0.0001

*Note that the determination of efficacy was based on planned interim analyses (which became the final analyses) following sequential testing of HIV-1 incidence for Yeztugo® compared to background followed by Yeztugo® compared to 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. Yeztugo® also demonstrated superiority in the risk of incident HIV-1 infection over background HIV-1 incidence.

PURPOSE 2 included 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. This study 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 Yeztugo® (N=2179) or once daily Truvada® (N=1086).

In this study, the median age of participants was 29 years (range 17 to 74), while 67% were non White and 22% identified as gender-diverse (transgender women, transgender men, and gender nonbinary people). 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 Yeztugo® compared with the rate of incident HIV-1 infections per 100 person-years in participants randomized to Truvada®. Results suggested that Yeztugo® demonstrated superiority with an 89% reduction in the risk of incident HIV-1 infection over Truvada®. Results are presented in the table below, which was adapted from the prescribing information.

	Yeztugo® (N=2179)	Truvada® (N=1086)	Rate Ratio; p-value
Person-Years (PY)	1938	967	
HIV-1 infections (incidence rate per 100 PY)	2 (0.1)	9 (0.93)	0.111; p=0.00245

*Note that the determination of efficacy was based on planned interim analyses (which became the final analyses) following sequential testing of HIV-1 incidence for Yeztugo® compared to background followed by Yeztugo® compared to 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. Yeztugo® also demonstrated superiority in the risk of incident HIV-1 infection over background HIV-1 incidence.

Place in Therapy: Yeztugo®, a 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 35kg who are at risk for HIV-1 acquisition. Individuals must have a negative HIV-1 test prior to starting Yeztugo®. It carries a box warning regarding risk of drug resistance with use for HIV-1 PrEP in undiagnosed HIV-1 infection. Individuals must be tested for HIV-1 infection prior to starting Yeztugo® treatment and with each subsequent injection. Drug-resistant HIV-1 variants have been identified with the use of Yeztugo® by individuals with undiagnosed HIV-1 infection. Do not start Yeztugo® unless negative infection status is confirmed. Individuals who acquire HIV-1 while receiving Yeztugo® must transition to a complete HIV-1 treatment regimen.

There are currently two oral options for PrEP, including tenofovir disoproxil fumarate-emtricitabine (TDF-FTC; Truvada) and tenofovir alafenamide-emtricitabine (TAF-FTC; Descovy®). Cabotegravir (Apretude®) is a long-acting injectable available.[2]

The safety and efficacy of Yeztugo® were assessed in two randomized, double-blind, active-controlled studies. In study 1, Yeztugo® demonstrated superiority with a 100% reduction in the risk of incident HIV-1 infection over

Truvada® (p<0.0001). In study 2, Yeztugo® demonstrated superiority with an 89% reduction in the risk of incident HIV-1 infection over Truvada® (p=0.00245).

Summary

There is some evidence to suggest from two phase 3 trials that Yeztugo® may be more effective than Truvada® for reduction in the risk of incident HIV-1 infection; however, there is no evidence to suggest that Yeztugo® is safer or more effective than other currently preferred, more cost-effective medications. It is therefore recommended that Yeztugo® be placed on the RDL as non-recommended.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended**

References

[1] Yeztugo [package insert]. Foster City, CA: Gilead Sciences, Inc; 2025.
[2] UpToDate online. HIV pre-exposure prophylaxis. Accessed September 2025.

Prepared By: Iowa Medicaid Date: 09/22/2025