YEZTUGO® (lenacapavir) for HIV-1 PrEP

Navigating the US Prescribing Information

Approved for Use on 18 Aug 2025

Disclaimers

This non-promotional, proactive deck is intended to be used by Gilead Medical Affairs as educational material only.

This deck should only be presented by a Gilead employee, not a third-party speaker.

These slides provide only a summary and select sections of the FDA-approved YEZTUGO® US Prescribing Information.

Please see full Prescribing Information for YEZTUGO, including Boxed Warning, available at Gilead.com.

Approved for Use on 18 Aug 2025

SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

Boxed Warning

WARNING: RISK OF DRUG RESISTANCE WITH USE OF YEZTUGO FOR HIV-1 PrEP IN UNDIAGNOSED HIV-1 INFECTION

Individuals must be tested for HIV-1 infection prior to initiating 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 initiate YEZTUGO unless negative infection status is confirmed. Individuals who acquire HIV-1 while receiving YEZTUGO must transition to a complete HIV-1 treatment regimen.

[see Dosage and Administration (2.1), Contraindications (4) and Warnings and Precautions (5.1, 5.2)]

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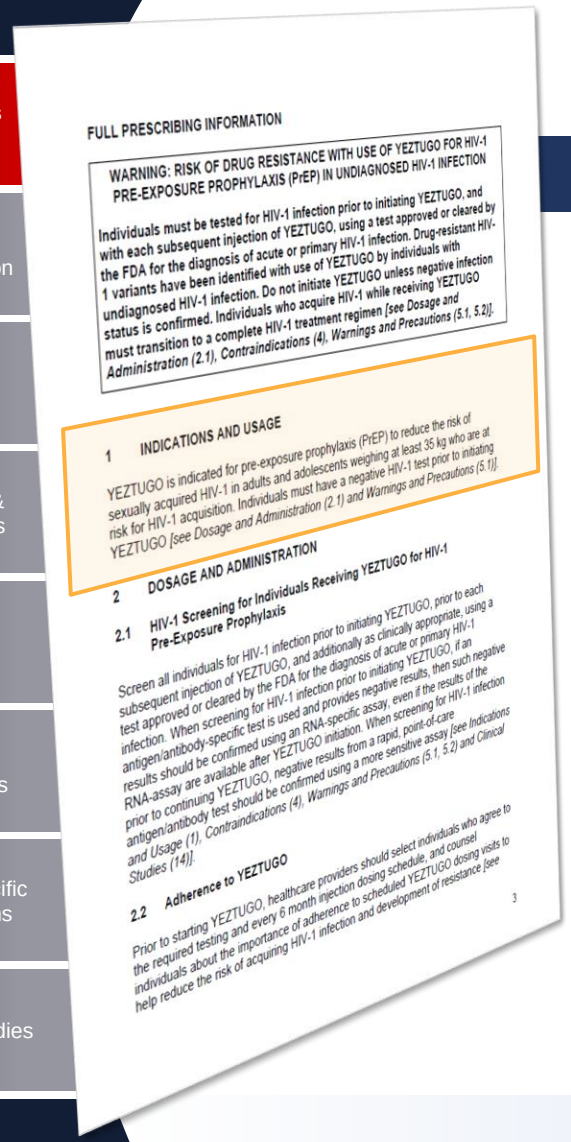
SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

1. Indications and Usage



FULL PRESCRIBING INFORMATION

WARNING: 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 initiating 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 initiate YEZTUGO unless negative infection status is confirmed. Individuals who acquire HIV-1 while receiving YEZTUGO must transition to a complete HIV-1 treatment regimen *[see Dosage and Administration (2.1), Contraindications (4), Warnings and Precautions (5.1, 5.2)]*.

1 INDICATIONS AND USAGE

YEZTUGO 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 *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 HIV-1 Screening for Individuals Receiving YEZTUGO for HIV-1 Pre-Exposure Prophylaxis

Screen all individuals for HIV-1 infection prior to initiating 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 initiating 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 *[see Indications and Usage (1), Contraindications (4), Warnings and Precautions (5.1, 5.2) and Clinical Studies (14)]*.

2.2 Adherence to YEZTUGO

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 *[see*

3

1 Indications and Usage

YEZTUGO is **indicated for PrEP** to reduce the risk of sexually acquired HIV-1 in adults and adolescents weighing ≥35 kg who are at risk for HIV-1 acquisition.

Individuals must have a **negative HIV-1 test result** prior to initiating YEZTUGO.

[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]

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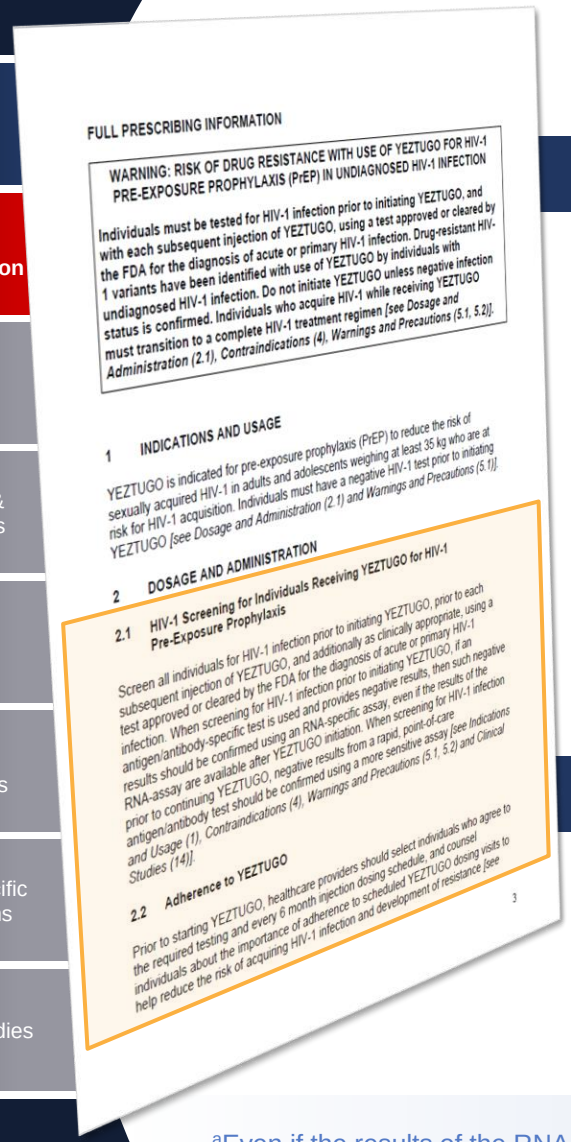
SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

2. Dosage and Administration



FULL PRESCRIBING INFORMATION

WARNING: 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 initiating 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 initiate YEZTUGO unless negative infection status is confirmed. Individuals who acquire HIV-1 while receiving YEZTUGO must transition to a complete HIV-1 treatment regimen [see Dosage and Administration (2.1), Contraindications (4), Warnings and Precautions (5.1, 5.2)].

1 INDICATIONS AND USAGE

YEZTUGO 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 [see Dosage and Administration (2.1) and Warnings and Precautions (5.1)].

2 DOSAGE AND ADMINISTRATION

2.1 HIV-1 Screening for Individuals Receiving YEZTUGO for HIV-1 Pre-Exposure Prophylaxis

Screen all individuals for HIV-1 infection prior to initiating 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 initiating 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 [see Indications and Usage (1), Contraindications (4), Warnings and Precautions (5.1, 5.2) and Clinical Studies (14)].

2.2 Adherence to YEZTUGO

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 [see

3

2.1 HIV-1 Screening for Individuals Receiving YEZTUGO

Screen all individuals for HIV-1 prior to initiating 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. [see Indications and Usage (1), Contraindications (4) and Warnings and Precautions (5.1, 5.2) and Clinical Studies (14)]

Prior to initiating YEZTUGO: Negative result from an Ag/Ab-specific test should be confirmed using an RNA-specific assay.[a]

Prior to continuing YEZTUGO: Negative result from a rapid, point-of-care Ag/Ab test should be confirmed using a more sensitive assay.

2.2 Adherence to YEZTUGO

Prior to starting YEZTUGO, healthcare providers should select individuals who agree to the required testing and Q6M injection dosing schedule, and counsel individuals about the importance of adherence to scheduled YEZTUGO dosing visits.

[see Dosage and Administration (2.1), Warnings and Precautions (5.1, 5.2) and Microbiology (12.4)]

[a]Even if the results of the RNA-assay are available after YEZTUGO initiation

Ag/Ab, antigen/antibody; Q6M, every 6 months

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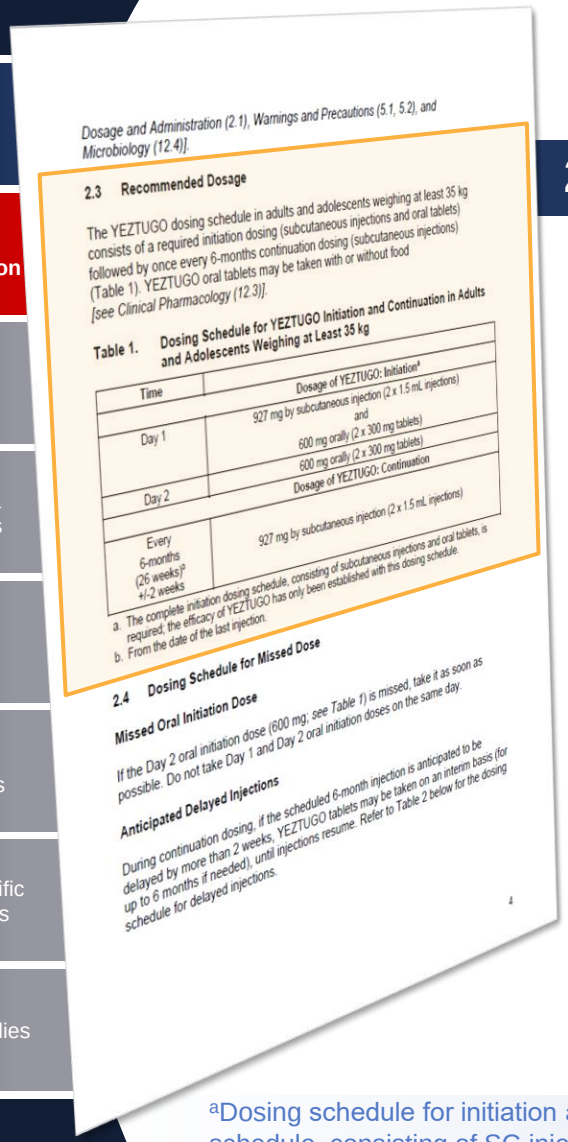
2. Dosage and Administration



Dosage and Administration (2.1), Warnings and Precautions (5.1, 5.2), and Microbiology (12.4)].

2.3 Recommended Dosage

The YEZTUGO dosing schedule in adults and adolescents weighing at least 35 kg consists of a required initiation dosing (subcutaneous injections and oral tablets) followed by once every 6-months continuation dosing (subcutaneous injections) (Table 1). YEZTUGO oral tablets may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Table 1. Dosing Schedule for YEZTUGO Initiation and Continuation in Adults and Adolescents Weighing at Least 35 kg

Time	Dosage of YEZTUGO: Initiation[a]
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)
	Dosage of YEZTUGO: Continuation
Every 6-months (26 weeks)[b] +/-2 weeks	927 mg by subcutaneous injection (2 x 1.5 mL injections)

a. The complete initiation dosing schedule, consisting of subcutaneous injections and oral tablets, is required, the efficacy of YEZTUGO has only been established with this dosing schedule.
b. From the date of the last injection.

2.4 Dosing Schedule for Missed Dose

Missed Oral Initiation Dose

If the Day 2 oral initiation dose (600 mg, *see Table 1*) is missed, take it as soon as possible. Do not take Day 1 and Day 2 oral initiation doses on the same day.

Anticipated Delayed Injections

During continuation dosing, if the scheduled 6-month injection is anticipated to be delayed by more than 2 weeks, YEZTUGO tablets may be taken on an interim basis (for up to 6 months if needed), until injections resume. Refer to Table 2 below for the dosing schedule for delayed injections.

4

2.3 Recommended Dosage

The YEZTUGO dosing schedule in adults and adolescents weighing ≥35 kg consists of a required initiation dosing (SC injections and oral tablets) followed by Q6M continuation dosing (SC injections) (**Table 1**).

YEZTUGO oral tablets may be taken with or without food.

[see Clinical Pharmacology (12.3)]

Table 1. Dosing Schedule for YEZTUGO Initiation and Continuation[a]

Time	
	Dosage of YEZTUGO: Initiation[b]
Day 1	927 mg by SC injection (2 × 1.5 mL injections) 600 mg orally (2 × 300 mg tablets)
Day 2	600 mg orally (2 × 300 mg tablets)
	Dosage of YEZTUGO: Continuation
Q6M (Q26W)[c] ±2 weeks	927 mg by SC injection (2 × 1.5 mL injections)

[a]Dosing schedule for initiation and continuation in adults and adolescents weighing ≥35 kg; [b]The complete initiation dosing schedule, consisting of SC injections and oral tablets, is required. The efficacy of YEZTUGO has only been established with this dosing schedule; [c]From date of last injection

Q6M, every 6 months; Q26W, every 26 weeks

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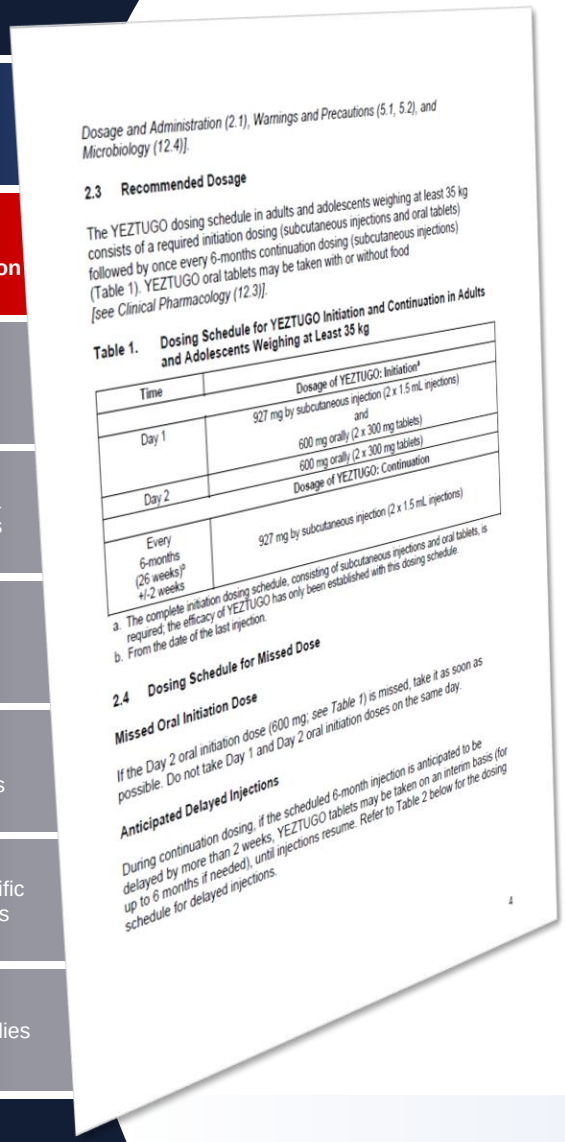
2. Dosage and Administration



Dosage and Administration (2.1), Warnings and Precautions (5.1, 5.2), and Microbiology (12.4)].

2.3 Recommended Dosage

The YEZTUGO dosing schedule in adults and adolescents weighing at least 35 kg consists of a required initiation dosing (subcutaneous injections and oral tablets) followed by once every 6-months continuation dosing (subcutaneous injections) (Table 1). YEZTUGO oral tablets may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Table 1. Dosing Schedule for YEZTUGO Initiation and Continuation in Adults and Adolescents Weighing at Least 35 kg

Time	Dosage of YEZTUGO: Initiation[a]
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)
	Dosage of YEZTUGO: Continuation
Every 6-months (26 weeks)[b] +/-2 weeks	927 mg by subcutaneous injection (2 x 1.5 mL injections)

a. The complete initiation dosing schedule, consisting of subcutaneous injections and oral tablets, is required, the efficacy of YEZTUGO has only been established with this dosing schedule.
b. From the date of the last injection.

2.4 Dosing Schedule for Missed Dose

Missed Oral Initiation Dose

If the Day 2 oral initiation dose (600 mg, *see Table 1*) is missed, take it as soon as possible. Do not take Day 1 and Day 2 oral initiation doses on the same day.

Anticipated Delayed Injections

During continuation dosing, if the scheduled 6-month injection is anticipated to be delayed by more than 2 weeks, YEZTUGO tablets may be taken on an interim basis (for up to 6 months if needed), until injections resume. Refer to Table 2 below for the dosing schedule for delayed injections.

4

QUESTION 1

The indicated dosage for YEZTUGO is 927 mg by 2 × 1.5 mL SC injections and 600 mg orally on Day 1; 600 mg orally on Day 2; and 927 mg by 2 × 1.5 mL SC injections every 6 months thereafter

TRUE OR FALSE

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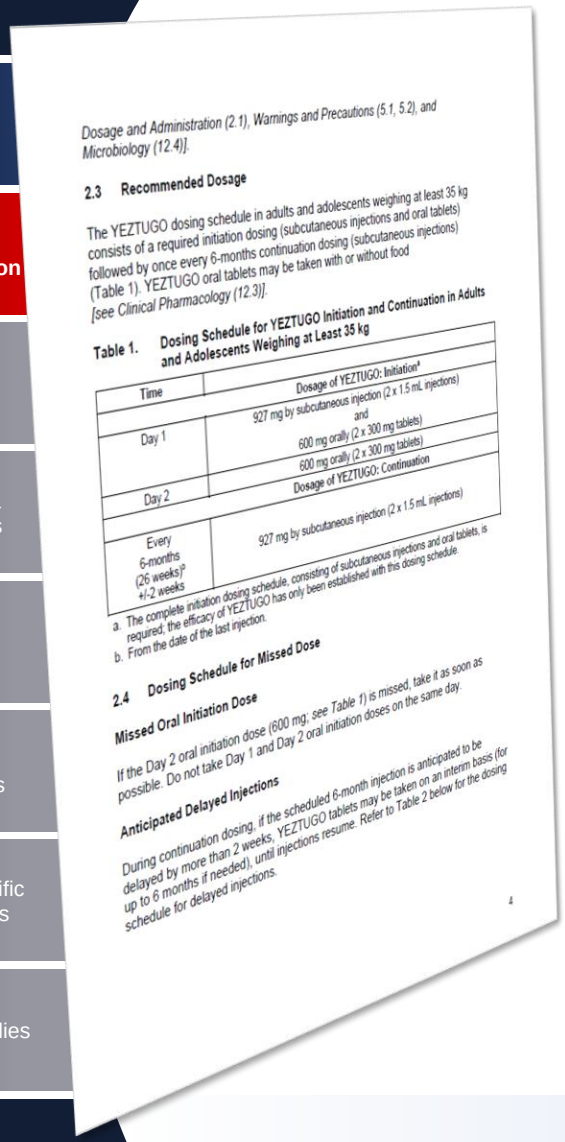
2. Dosage and Administration



Dosage and Administration (2.1), Warnings and Precautions (5.1, 5.2), and Microbiology (12.4)].

2.3 Recommended Dosage

The YEZTUGO dosing schedule in adults and adolescents weighing at least 35 kg consists of a required initiation dosing (subcutaneous injections and oral tablets) followed by once every 6-months continuation dosing (subcutaneous injections) (Table 1). YEZTUGO oral tablets may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Table 1. Dosing Schedule for YEZTUGO Initiation and Continuation in Adults and Adolescents Weighing at Least 35 kg

Time	Dosage of YEZTUGO: Initiation[a]
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)
	Dosage of YEZTUGO: Continuation
Every 6-months (26 weeks)[b] +/-2 weeks	927 mg by subcutaneous injection (2 x 1.5 mL injections)

a. The complete initiation dosing schedule, consisting of subcutaneous injections and oral tablets, is required; the efficacy of YEZTUGO has only been established with this dosing schedule.
b. From the date of the last injection.

2.4 Dosing Schedule for Missed Dose

Missed Oral Initiation Dose

If the Day 2 oral initiation dose (600 mg; *see Table 1*) is missed, take it as soon as possible. Do not take Day 1 and Day 2 oral initiation doses on the same day.

Anticipated Delayed Injections

During continuation dosing, if the scheduled 6-month injection is anticipated to be delayed by more than 2 weeks, YEZTUGO tablets may be taken on an interim basis (for up to 6 months if needed), until injections resume. Refer to Table 2 below for the dosing schedule for delayed injections.

4

QUESTION 1

The indicated dosage for YEZTUGO is 927 mg by 2 × 1.5 mL SC injections and 600 mg orally on Day 1; 600 mg orally on Day 2; and 927 mg by 2 × 1.5 mL SC injections every 6 months thereafter

TRUE

TRUE. *Please refer to section 2.3 of the USPI for further information*

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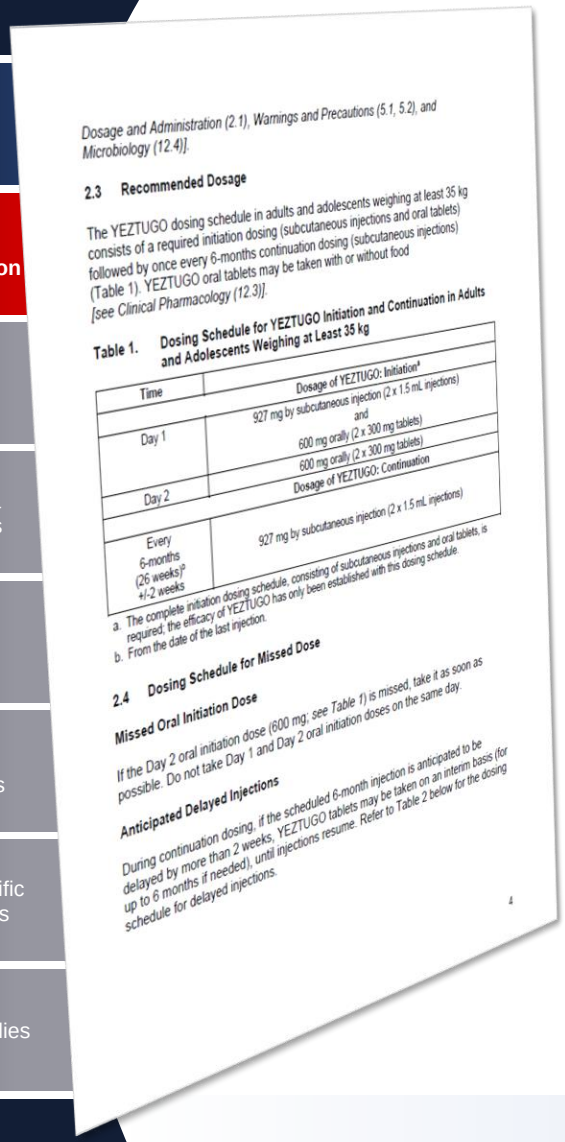
2. Dosage and Administration



Dosage and Administration (2.1), Warnings and Precautions (5.1, 5.2), and Microbiology (12.4)].

2.3 Recommended Dosage

The YEZTUGO dosing schedule in adults and adolescents weighing at least 35 kg consists of a required initiation dosing (subcutaneous injections and oral tablets) followed by once every 6-months continuation dosing (subcutaneous injections) (Table 1). YEZTUGO oral tablets may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Table 1. Dosing Schedule for YEZTUGO Initiation and Continuation in Adults and Adolescents Weighing at Least 35 kg

Time	Dosage of YEZTUGO: Initiation[a]
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)
	Dosage of YEZTUGO: Continuation
Every 6-months (26 weeks)[b] +/-2 weeks	927 mg by subcutaneous injection (2 x 1.5 mL injections)

a. The complete initiation dosing schedule, consisting of subcutaneous injections and oral tablets, is required, the efficacy of YEZTUGO has only been established with this dosing schedule.
b. From the date of the last injection.

2.4 Dosing Schedule for Missed Dose

Missed Oral Initiation Dose

If the Day 2 oral initiation dose (600 mg, *see Table 1*) is missed, take it as soon as possible. Do not take Day 1 and Day 2 oral initiation doses on the same day.

Anticipated Delayed Injections

During continuation dosing, if the scheduled 6-month injection is anticipated to be delayed by more than 2 weeks, YEZTUGO tablets may be taken on an interim basis (for up to 6 months if needed), until injections resume. Refer to Table 2 below for the dosing schedule for delayed injections.

4

QUESTION 2

This dose is indicated in adults and adolescents weighing ≥25 kg

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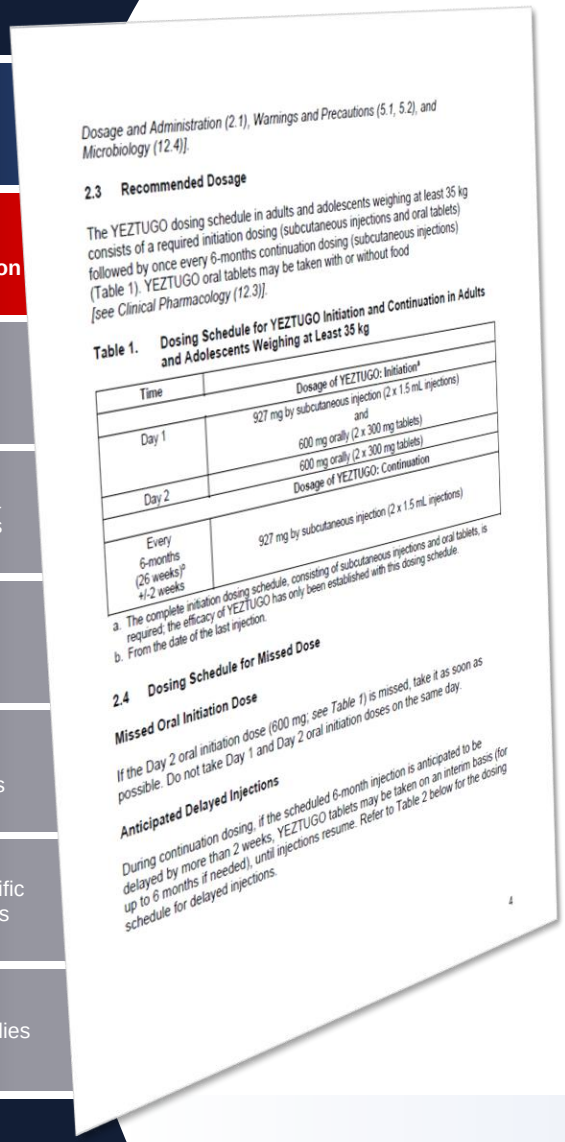
2. Dosage and Administration



Dosage and Administration (2.1), Warnings and Precautions (5.1, 5.2), and Microbiology (12.4)].

2.3 Recommended Dosage

The YEZTUGO dosing schedule in adults and adolescents weighing at least 35 kg consists of a required initiation dosing (subcutaneous injections and oral tablets) followed by once every 6-months continuation dosing (subcutaneous injections) (Table 1). YEZTUGO oral tablets may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Table 1. Dosing Schedule for YEZTUGO Initiation and Continuation in Adults and Adolescents Weighing at Least 35 kg

Time	Dosage of YEZTUGO: Initiation[a]
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)
	Dosage of YEZTUGO: Continuation
Every 6-months (26 weeks)[b] +/-2 weeks	927 mg by subcutaneous injection (2 x 1.5 mL injections)

a. The complete initiation dosing schedule, consisting of subcutaneous injections and oral tablets, is required, the efficacy of YEZTUGO has only been established with this dosing schedule.
b. From the date of the last injection.

2.4 Dosing Schedule for Missed Dose

Missed Oral Initiation Dose

If the Day 2 oral initiation dose (600 mg, *see Table 1*) is missed, take it as soon as possible. Do not take Day 1 and Day 2 oral initiation doses on the same day.

Anticipated Delayed Injections

During continuation dosing, if the scheduled 6-month injection is anticipated to be delayed by more than 2 weeks, YEZTUGO tablets may be taken on an interim basis (for up to 6 months if needed), until injections resume. Refer to Table 2 below for the dosing schedule for delayed injections.

4

QUESTION 2

This dose is indicated in adults and adolescents weighing ≥25 kg

FALSE

FALSE. This dose is indicated in adults and adolescents weighing ≥35 kg

Please refer to section 2.3 of the USPI for further information

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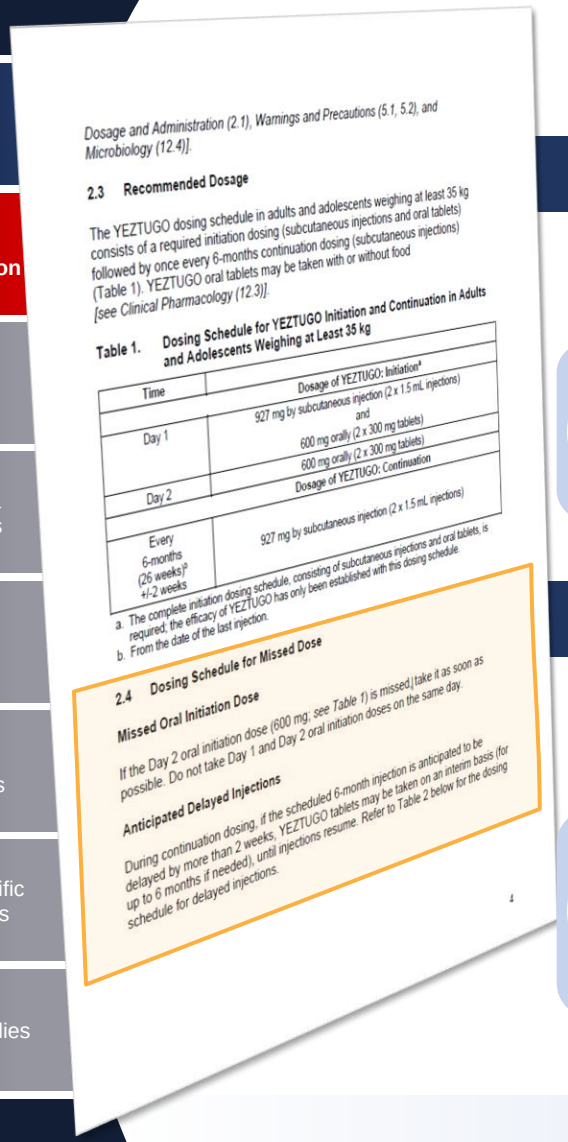
SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

2. Dosage and Administration



Dosage and Administration (2.1), Warnings and Precautions (5.1, 5.2), and Microbiology (12.4)].

2.3 Recommended Dosage

The YEZTUGO dosing schedule in adults and adolescents weighing at least 35 kg consists of a required initiation dosing (subcutaneous injections and oral tablets) followed by once every 6-months continuation dosing (subcutaneous injections) (Table 1). YEZTUGO oral tablets may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Table 1. Dosing Schedule for YEZTUGO Initiation and Continuation in Adults and Adolescents Weighing at Least 35 kg

Time	Dosage of YEZTUGO: Initiation[a]
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)
	Dosage of YEZTUGO: Continuation
Every 6-months (26 weeks)[b] +/-2 weeks	927 mg by subcutaneous injection (2 x 1.5 mL injections)

a. The complete initiation dosing schedule, consisting of subcutaneous injections and oral tablets, is required; the efficacy of YEZTUGO has only been established with this dosing schedule.
b. From the date of the last injection.

2.4 Dosing Schedule for Missed Dose

Missed Oral Initiation Dose

If the Day 2 oral initiation dose (600 mg; see Table 1) is missed, take it as soon as possible. Do not take Day 1 and Day 2 oral initiation doses on the same day.

Anticipated Delayed Injections

During continuation dosing, if the scheduled 6-month injection is anticipated to be delayed by more than 2 weeks, YEZTUGO tablets may be taken on an interim basis (for up to 6 months if needed), until injections resume. Refer to Table 2 below for the dosing schedule for delayed injections.

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2.4 Missed Oral Initiation Dose

If the Day 2 oral initiation dose (600 mg; see **Table 1**) is missed:

Take it as soon as possible. Do not take Day 1 and Day 2 oral initiation doses on the same day.

2.4 Anticipated Delayed Injections

During continuation dosing, if the scheduled 6-month injection is anticipated to be delayed by more than 2 weeks:

Oral dosing of YEZTUGO tablets may be taken on an interim basis (300 mg Q7D, for up to 6 months if needed), until injections resume. Continuation injection dosage should be resumed within 7 days after the last oral dose.

Q7D, every 7 days

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2. Dosage and Administration

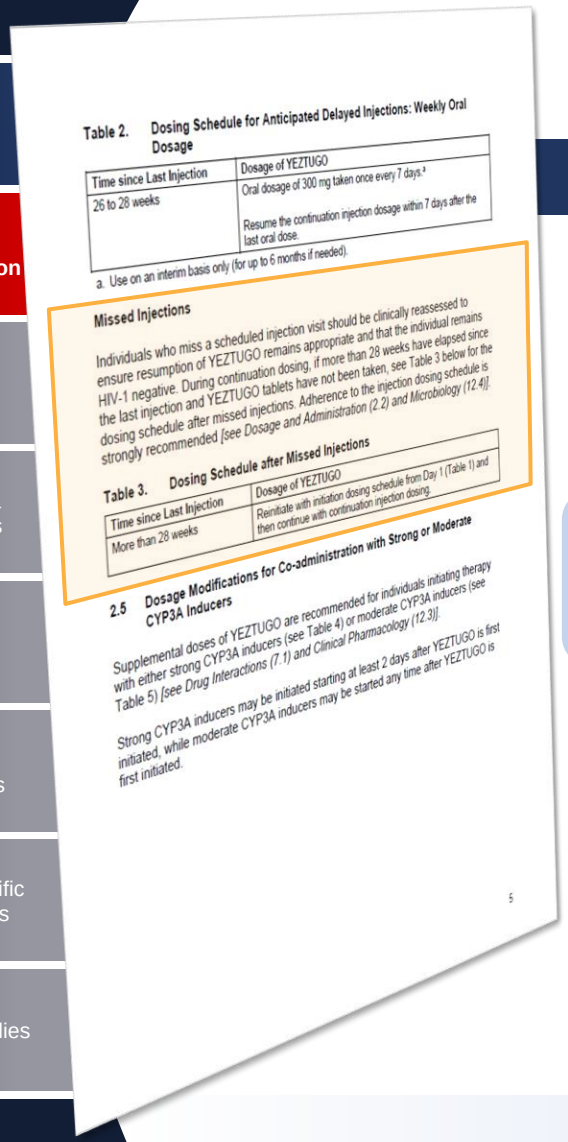

Table 2. Dosing Schedule for Anticipated Delayed Injections: Weekly Oral Dosage

Time since Last Injection	Dosage of YEZTUGO
26 to 28 weeks	Oral dosage of 300 mg taken once every 7 days.[a] Resume the continuation injection dosage within 7 days after the last oral dose.

a. Use on an interim basis only (for up to 6 months if needed).

Missed Injections

Individuals who miss a scheduled injection visit should be clinically reassessed to ensure resumption of YEZTUGO remains appropriate and that the individual remains HIV-1 negative. During continuation dosing, if more than 28 weeks have elapsed since the last injection and YEZTUGO tablets have not been taken, see Table 3 below for the dosing schedule after missed injections. Adherence to the injection dosing schedule is strongly recommended *[see Dosage and Administration (2.2) and Microbiology (12.4)]*.

Table 3. Dosing Schedule after Missed Injections

Time since Last Injection	Dosage of YEZTUGO
More than 28 weeks	Reinitiate with initiation dosing schedule from Day 1 (Table 1) and then continue with continuation injection dosing.

2.5 Dosage Modifications for Co-administration with Strong or Moderate CYP3A Inducers

Supplemental doses of YEZTUGO are recommended for individuals initiating therapy with either strong CYP3A inducers (see Table 4) or moderate CYP3A inducers (see Table 5) *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

Strong CYP3A inducers may be initiated starting at least 2 days after YEZTUGO is first initiated, while moderate CYP3A inducers may be started any time after YEZTUGO is first initiated.

5

2.4 Missed Injections

Individuals who miss a scheduled injection visit should be clinically reassessed to ensure that the individual remains HIV-1 negative and resumption of YEZTUGO remains appropriate.

During continuation dosing, if more than 28 weeks have elapsed since the last injection and YEZTUGO tablets have not been taken:

Reinitiate with initiation dosing schedule from Day 1 (**Table 1**) and then continue with continuation injection dosing.
[see Dosage and Administration (2.2) and Microbiology (12.4)]

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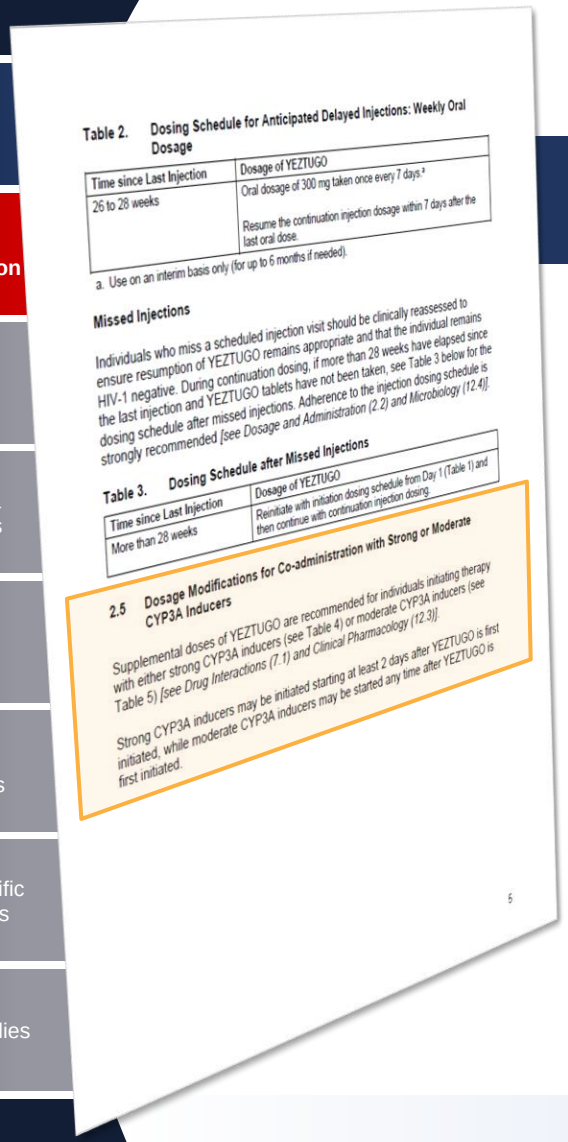
2. Dosage and Administration



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a. Use on an interim basis only (for up to 6 months if needed).

Missed Injections

Individuals who miss a scheduled injection visit should be clinically reassessed to ensure resumption of YEZTUGO remains appropriate and that the individual remains HIV-1 negative. During continuation dosing, if more than 28 weeks have elapsed since the last injection and YEZTUGO tablets have not been taken, see Table 3 below for the dosing schedule after missed injections. Adherence to the injection dosing schedule is strongly recommended [see Dosage and Administration (2.2) and Microbiology (12.4)].

Table 3. Dosing Schedule after Missed Injections

Time since Last Injection	Dosage of YEZTUGO
More than 28 weeks	Reinitiate with initiation dosing schedule from Day 1 (Table 1) and then continue with continuation injection dosing.

2.5 Dosage Modifications for Co-administration with Strong or Moderate CYP3A Inducers

Supplemental doses of YEZTUGO are recommended for individuals initiating therapy with either strong CYP3A inducers (see Table 4) or moderate CYP3A inducers (see Table 5) [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].

Strong CYP3A inducers may be initiated starting at least 2 days after YEZTUGO is first initiated, while moderate CYP3A inducers may be started any time after YEZTUGO is first initiated.

5

2.5 Dosage Modifications for Co-administration with Strong or Moderate CYP3A Inducers

Supplemental doses of YEZTUGO are recommended for individuals initiating therapy with either strong or moderate CYP3A inducers (Table 4 and Table 5).

[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]

Strong CYP3A inducers may be initiated starting **at least 2 days after** YEZTUGO is first initiated

Moderate CYP3A inducers may be started **any time after** YEZTUGO is first initiated

CYP3A, cytochrome (P450) 3A

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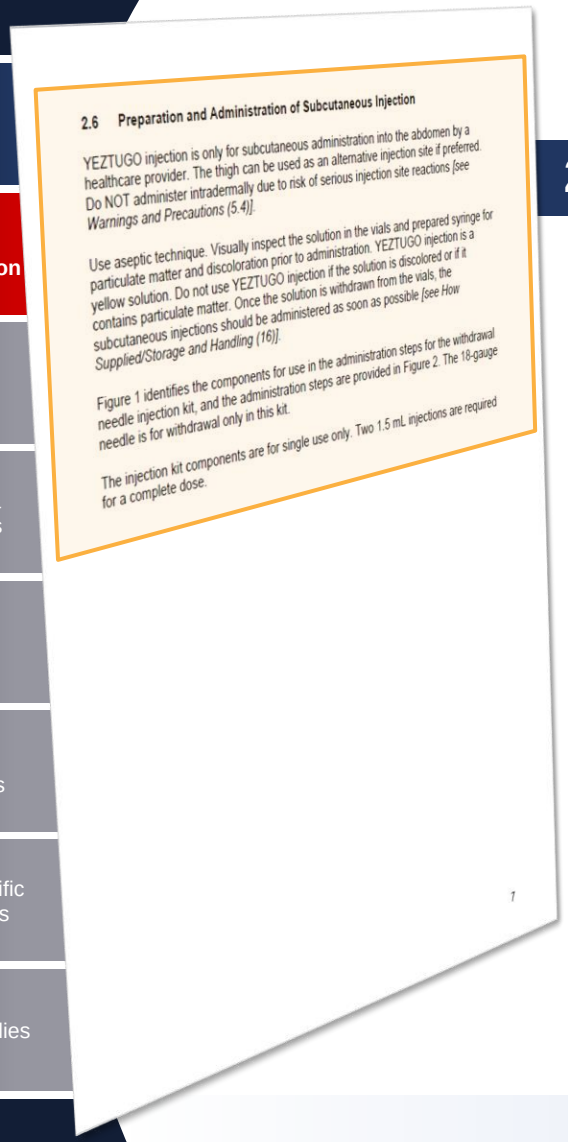
SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

2. Dosage and Administration



2.6 Preparation and Administration of Subcutaneous Injection

YEZTUGO injection is only for subcutaneous 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 injection site reactions [see Warnings and Precautions (5.4)].

Use aseptic technique. Visually inspect the solution in the vials and prepared syringe for particulate matter and discoloration prior to administration. YEZTUGO injection is a yellow solution. Do not use YEZTUGO injection if the solution is discolored or if it contains particulate matter. Once the solution is withdrawn from the vials, the subcutaneous injections should be administered as soon as possible [see How Supplied/Storage and Handling (16)].

Figure 1 identifies the components for use in the administration steps for the withdrawal needle injection kit, and the administration steps are provided in Figure 2. The 18-gauge needle is for withdrawal only in this kit.

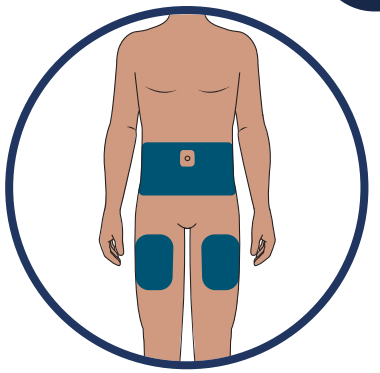
The injection kit components are for single use only. Two 1.5 mL injections are required for a complete dose.

1

2.6 Preparation and Administration of Subcutaneous Injection

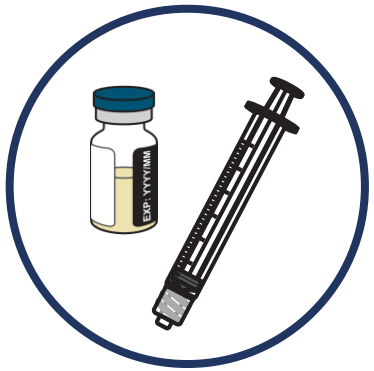
YEZTUGO injection is only for SC administration into the **abdomen** by a healthcare provider. The thigh can be used as an alternative injection site if preferred. Do NOT administer intradermally due to risk of serious ISRs.

[see Warnings and Precautions (5.4)]



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

[see How Supplied/Storage and Handling (16)]



ISR, injection-site reaction

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2. Dosage and Administration

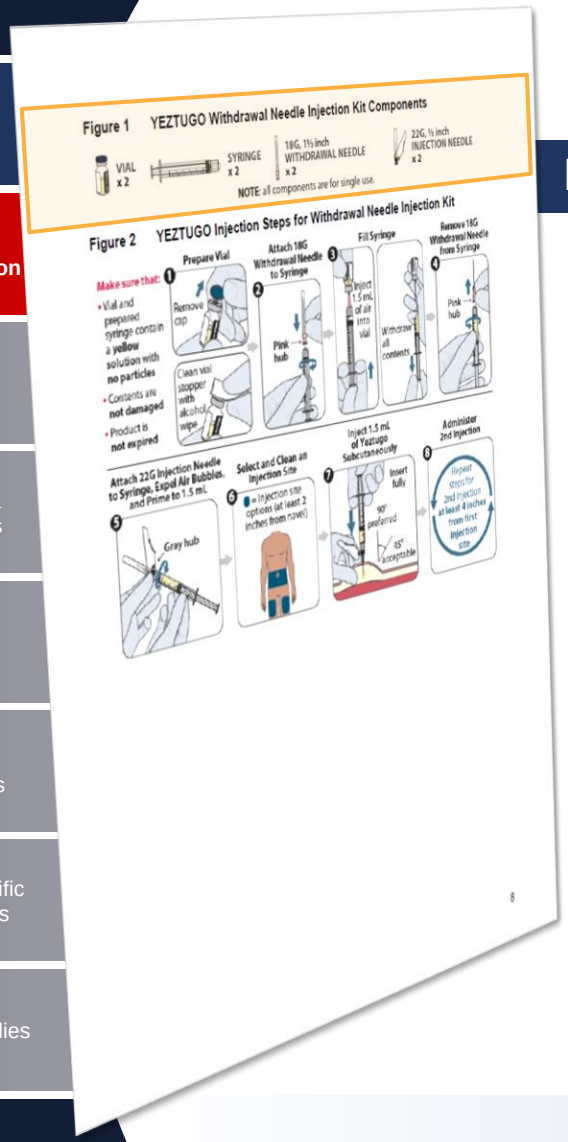
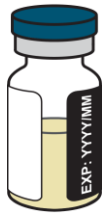


Figure 1 ▸ YEZTUGO Withdrawal Needle Injection Kit Components

Figure 1 identifies the components for use in the administration steps for the withdrawal needle injection kit, and the administration steps are provided in **Figure 2** (next slide).
The 18-gauge needle is for withdrawal only in this kit. Two 1.5 mL injections are required for a complete dose.



VIAL ×2

SYRINGE ×2

18G, 1½ inch WITHDRAWAL NEEDLE ×2

22G, ½ inch INJECTION NEEDLE ×2

NOTE: All components are for single use.

G, gauge

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SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

2. Dosage and Administration

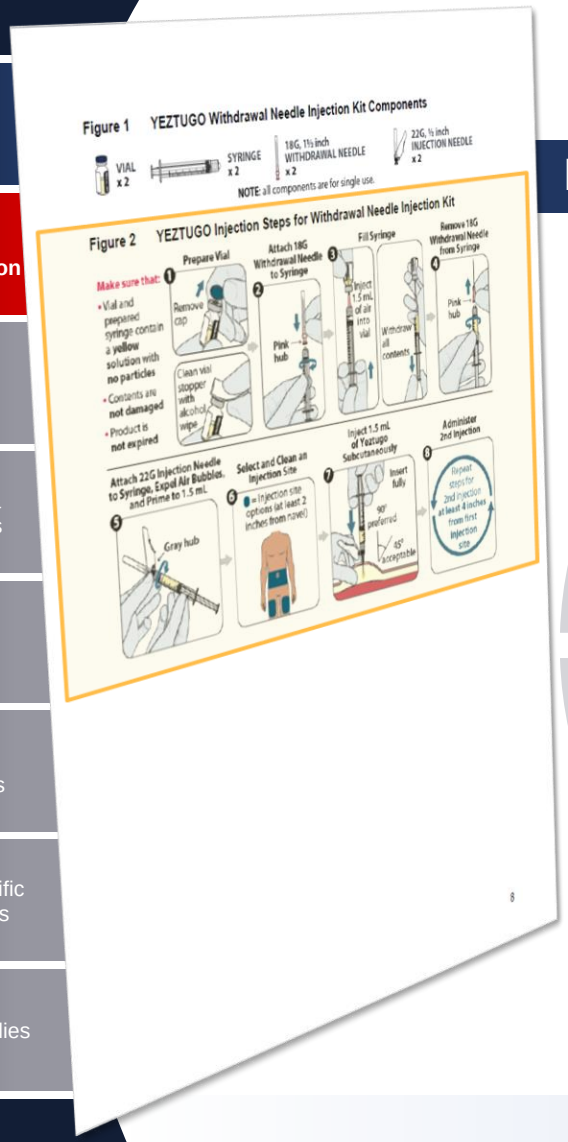
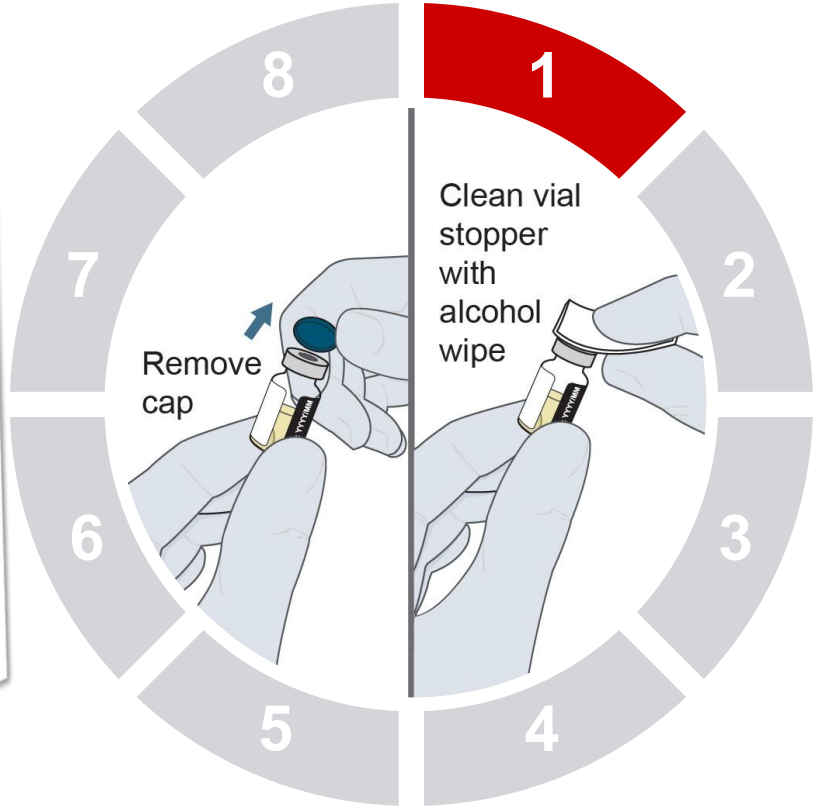


Figure 2 ▸ YEZTUGO Injection Steps for Withdrawal Needle Injection Kit



1. Prepare vial

G, gauge

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2. Dosage and Administration

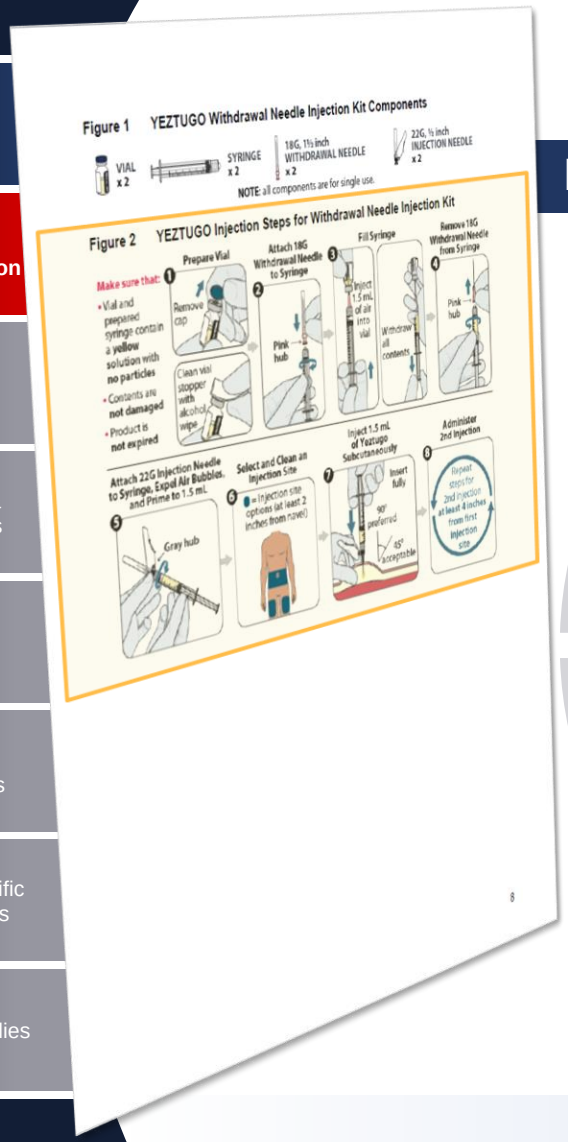
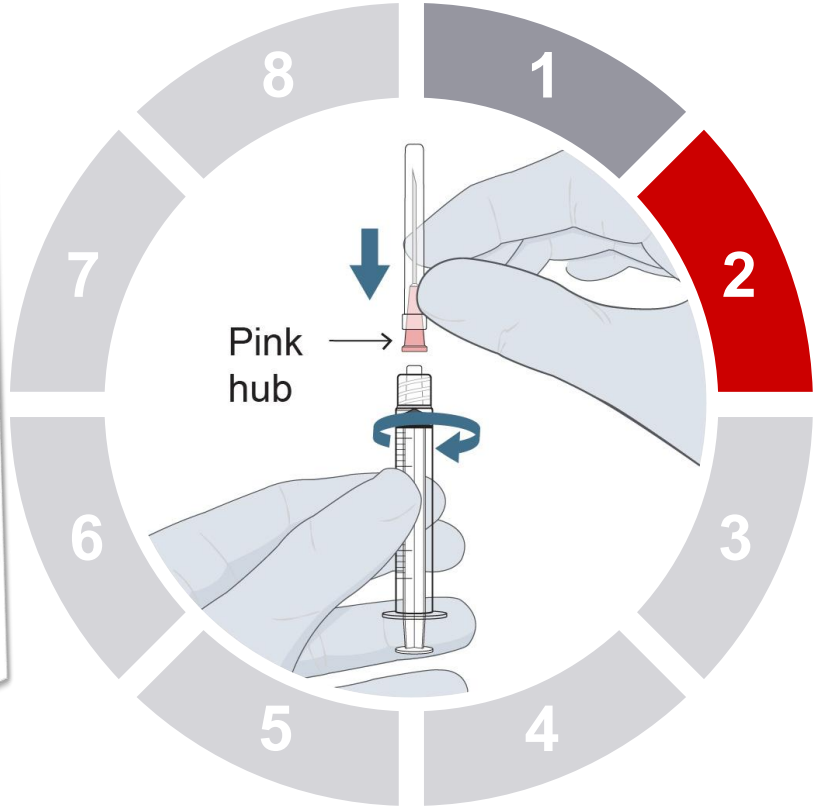


Figure 2 ▸ YEZTUGO Injection Steps for Withdrawal Needle Injection Kit



1. Prepare vial
2. Attach 18G withdrawal needle to syringe

G, gauge

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2. Dosage and Administration

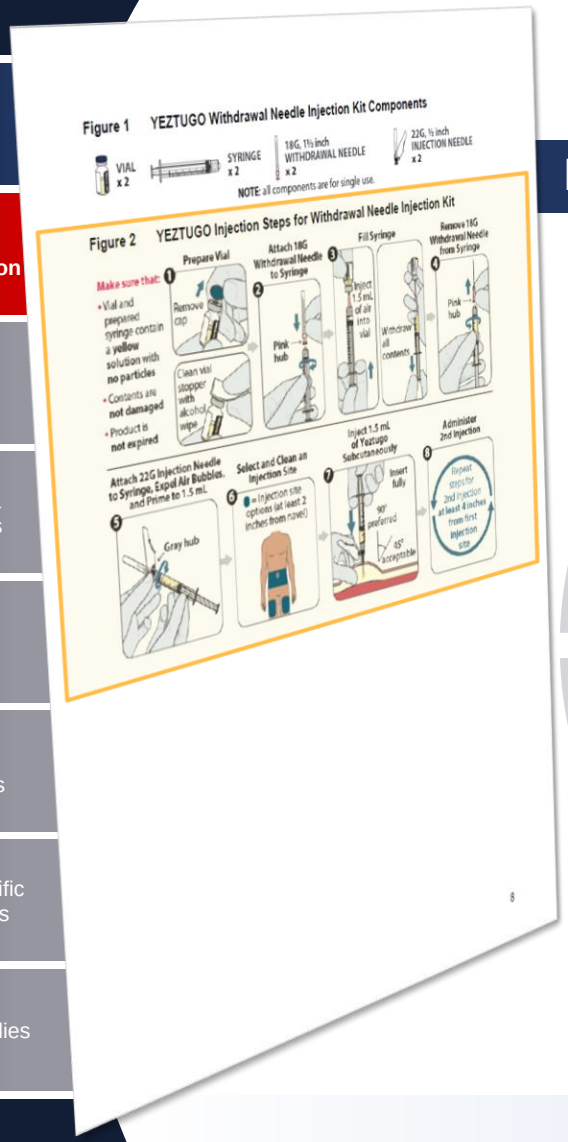
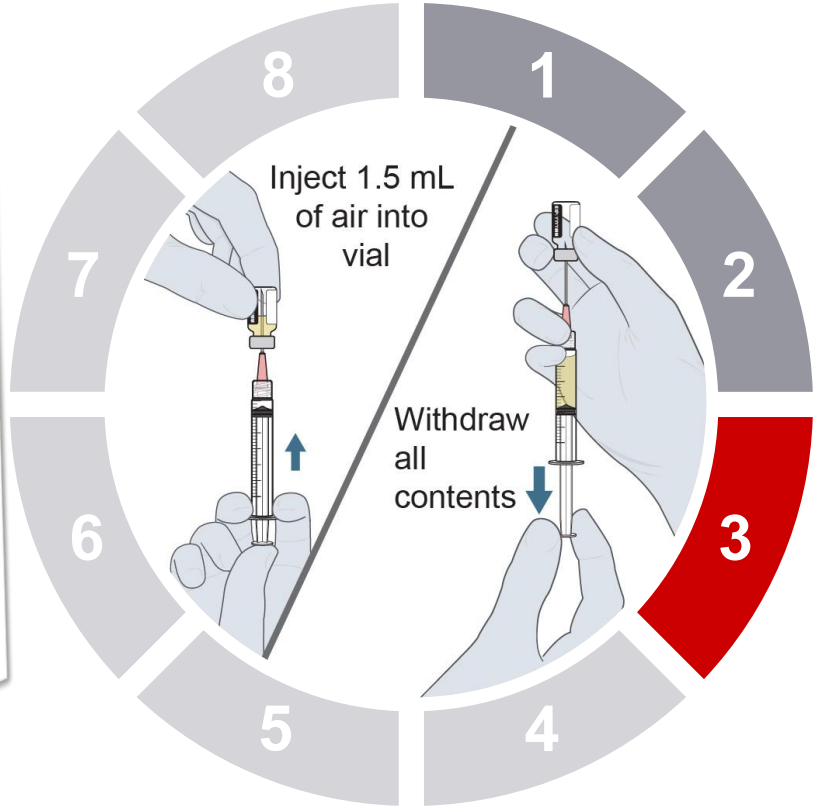


Figure 2 ▸ YEZTUGO Injection Steps for Withdrawal Needle Injection Kit



1. Prepare vial
2. Attach 18G withdrawal needle to syringe
3. Fill syringe

G, gauge

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2. Dosage and Administration

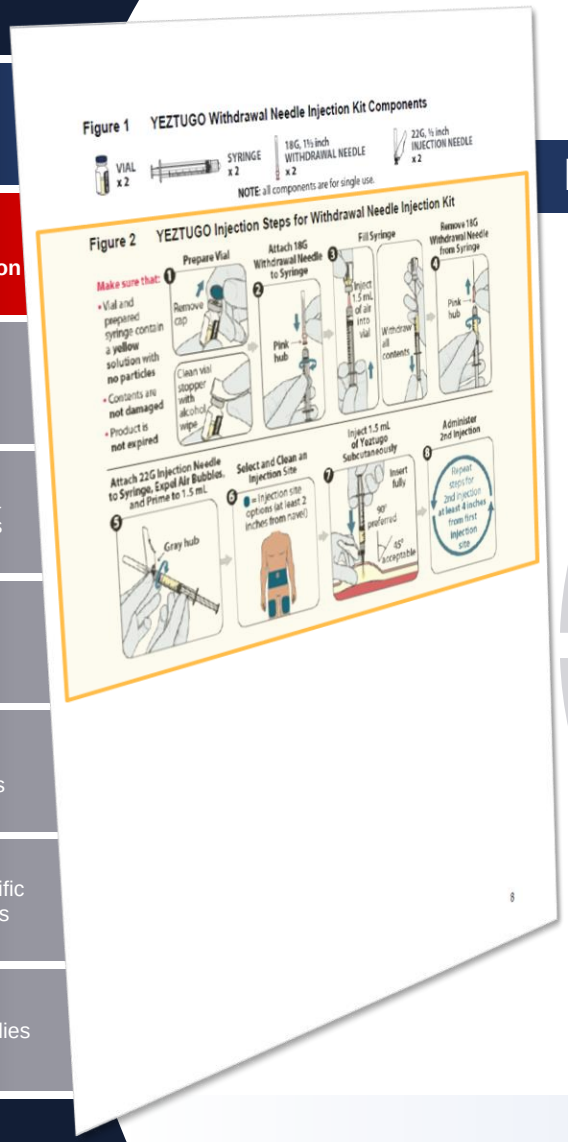
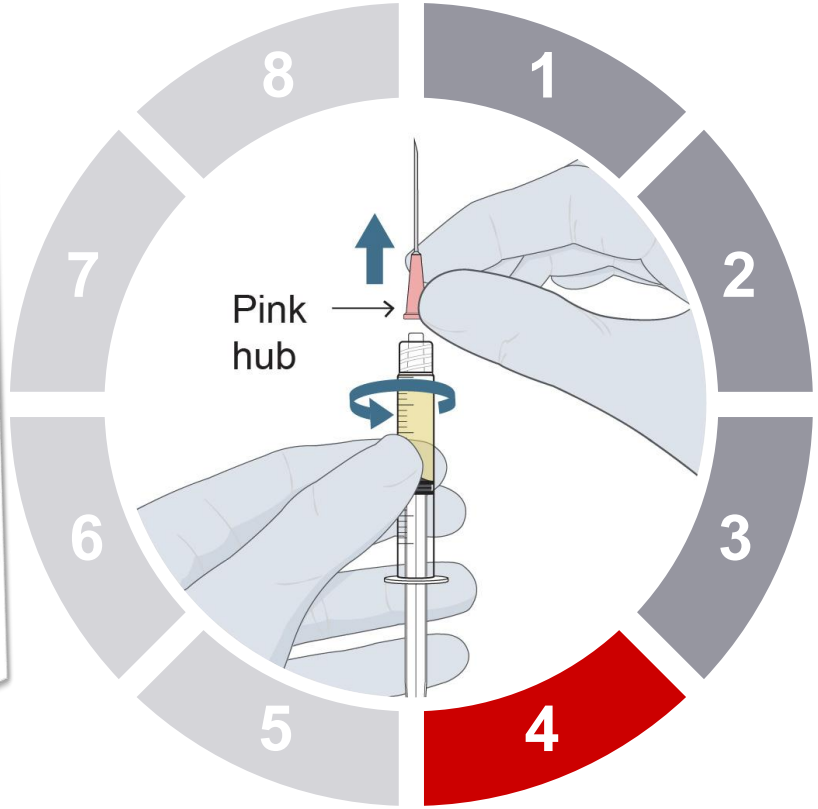


Figure 2 ▸ YEZTUGO Injection Steps for Withdrawal Needle Injection Kit



1. Prepare vial
2. Attach 18G withdrawal needle to syringe
3. Fill syringe
4. Remove 18G withdrawal needle from syringe

G, gauge

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SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

2. Dosage and Administration

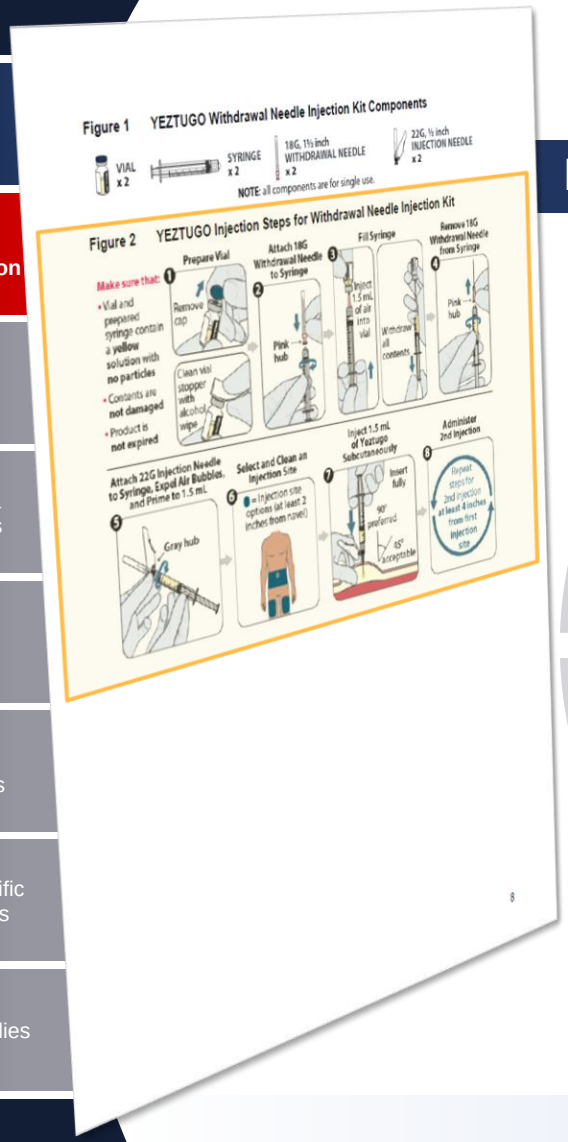
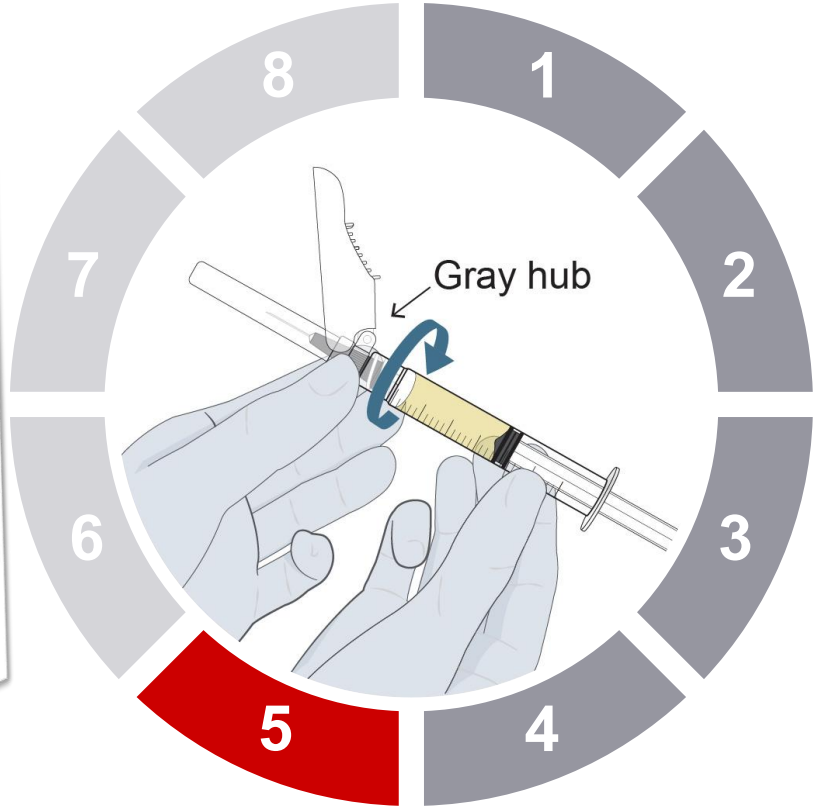


Figure 2 ▸ YEZTUGO Injection Steps for Withdrawal Needle Injection Kit



1. Prepare vial
2. Attach 18G withdrawal needle to syringe
3. Fill syringe
4. Remove 18G withdrawal needle from syringe
5. Attach 22G injection needle to syringe, expel air bubbles, and prime to 1.5 mL

G, gauge

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SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

2. Dosage and Administration

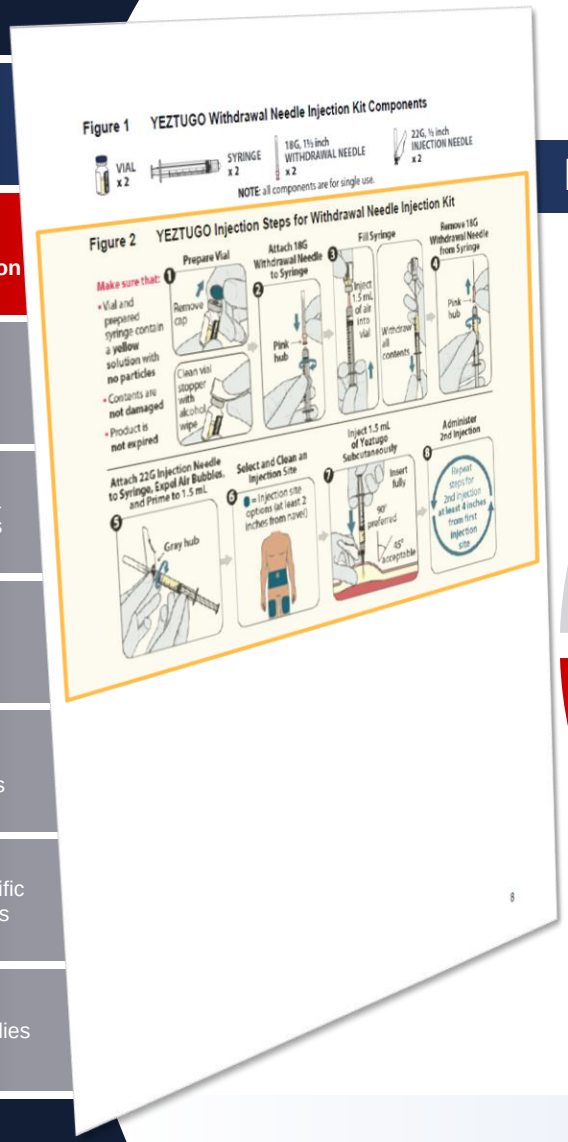
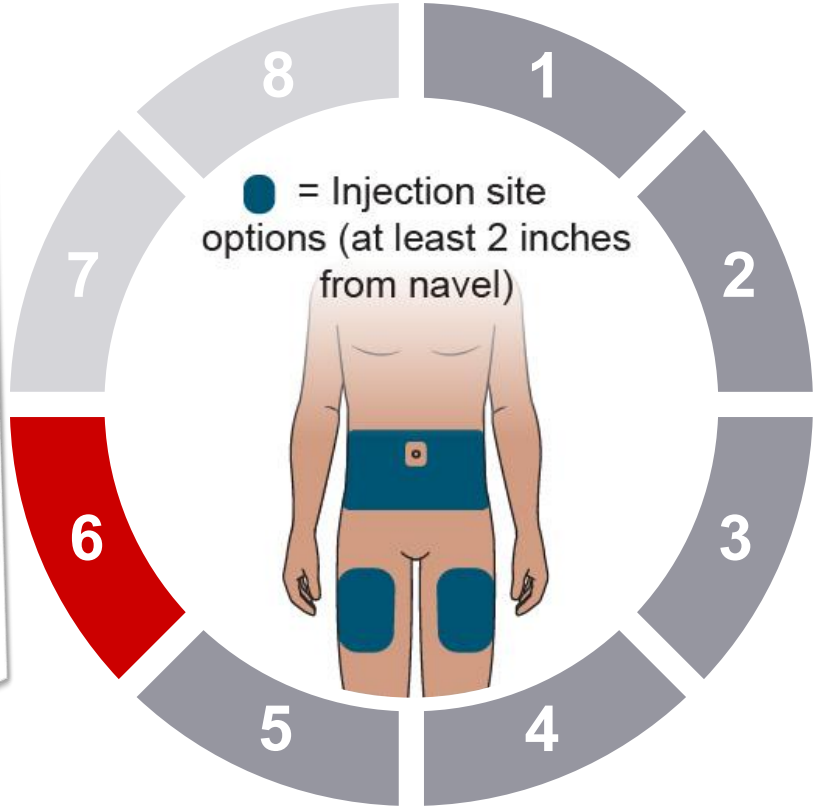


Figure 2 ▸ YEZTUGO Injection Steps for Withdrawal Needle Injection Kit



1. Prepare vial
2. Attach 18G withdrawal needle to syringe
3. Fill syringe
4. Remove 18G withdrawal needle from syringe
5. Attach 22G injection needle to syringe, expel air bubbles, and prime to 1.5 mL
6. Select and clean an injection site

G, gauge

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SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

2. Dosage and Administration

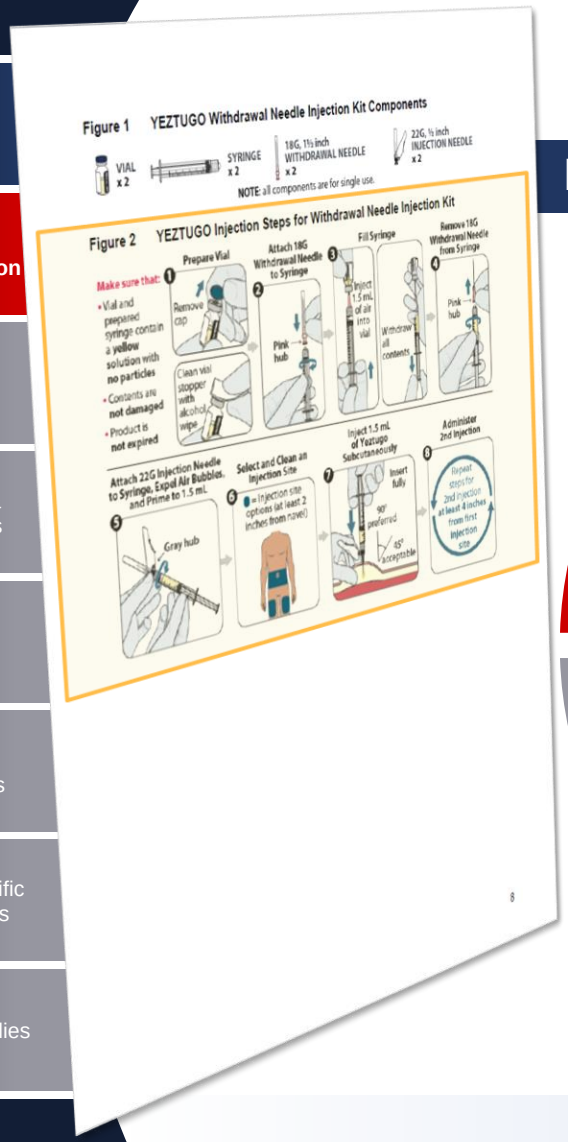
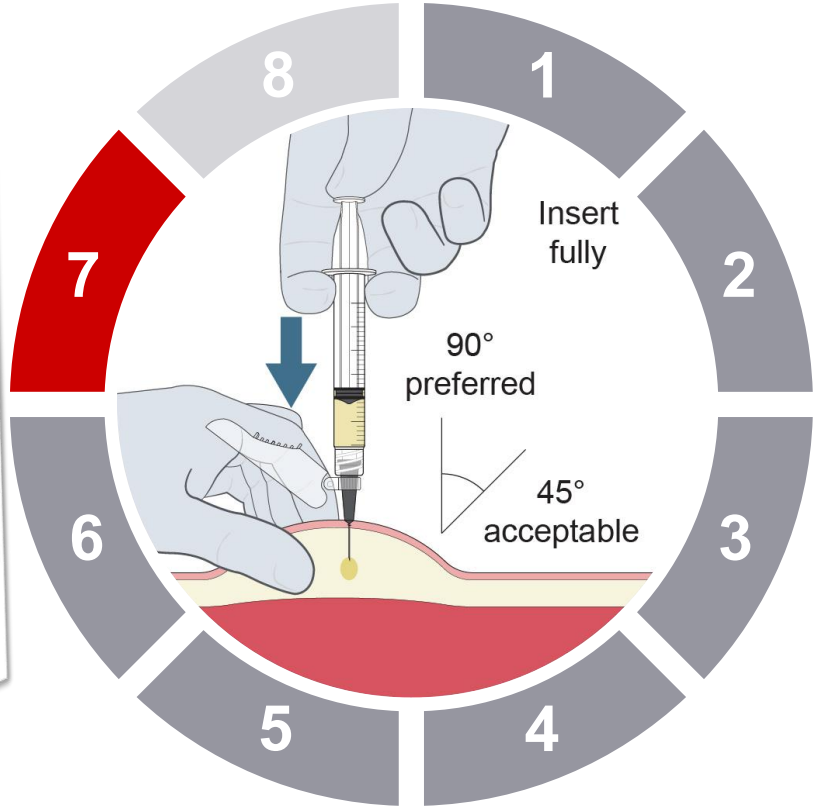


Figure 2 ▸ YEZTUGO Injection Steps for Withdrawal Needle Injection Kit



1. Prepare vial
2. Attach 18G withdrawal needle to syringe
3. Fill syringe
4. Remove 18G withdrawal needle from syringe
5. Attach 22G injection needle to syringe, expel air bubbles, and prime to 1.5 mL
6. Select and clean an injection site
7. Inject 1.5 mL of YEZTUGO subcutaneously (needle angle to skin: 45–90°, 90° preferred)

G, gauge

Approved for Use on 18 Aug 2025

SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

2. Dosage and Administration

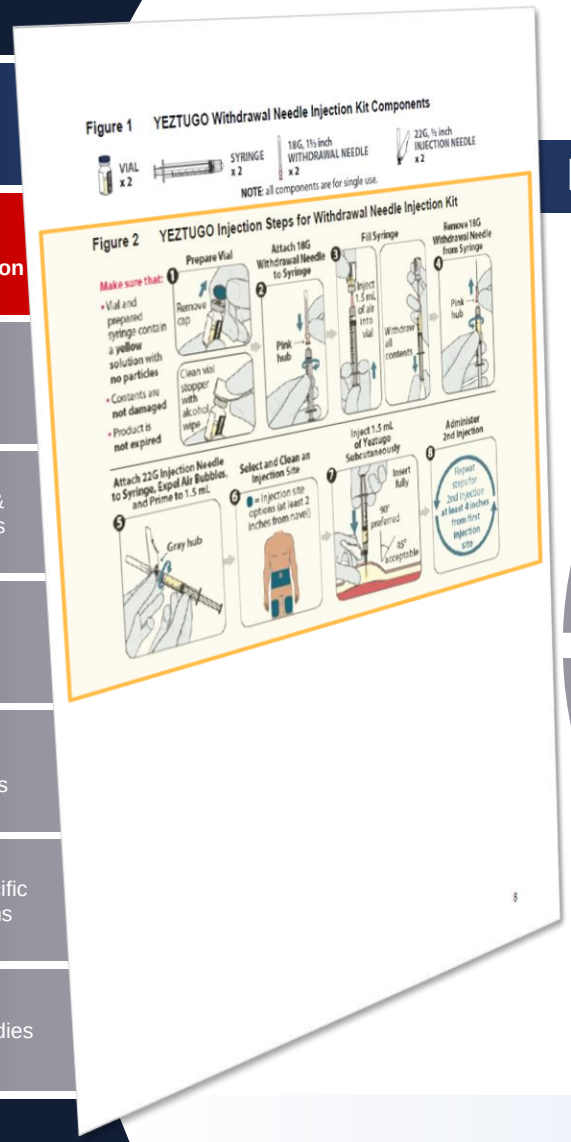


Figure 2 ▸ YEZTUGO Injection Steps for Withdrawal Needle Injection Kit

1. Prepare vial
2. Attach 18G withdrawal needle to syringe
3. Fill syringe
4. Remove 18G withdrawal needle from syringe
5. Attach 22G injection needle to syringe, expel air bubbles, and prime to 1.5 mL
6. Select and clean an injection site
7. Inject 1.5 mL of YEZTUGO subcutaneously (needle angle to skin: 45–90°, 90° preferred)
8. Administer second injection

G, gauge

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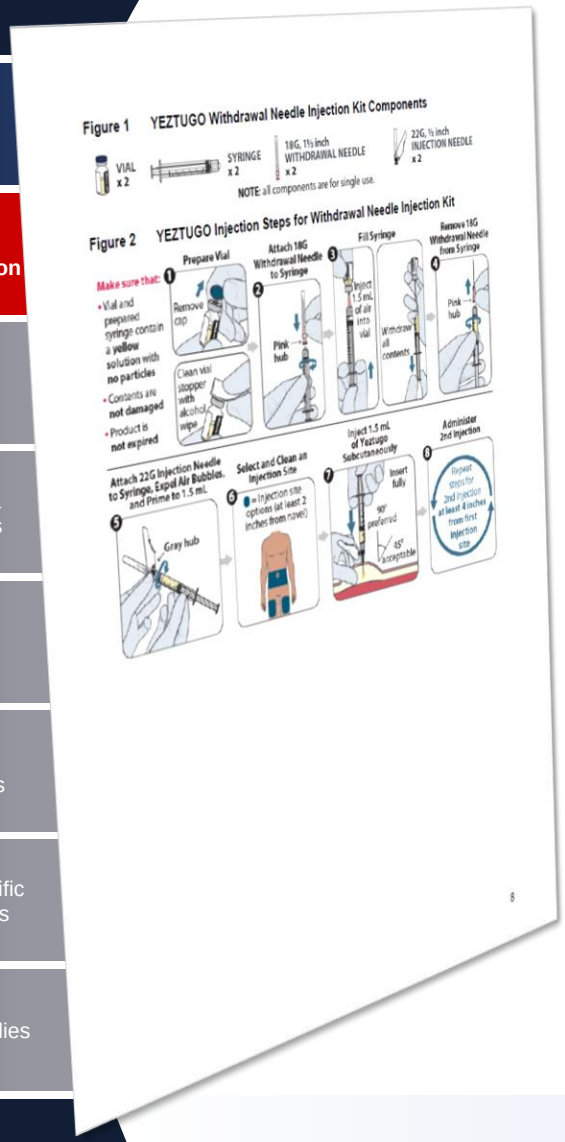
SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

2. Dosage and Administration



QUESTION 1

YEZTUGO should be injected into the subcutaneous space at a 45–90° angle (preferably 90°)

TRUE OR FALSE

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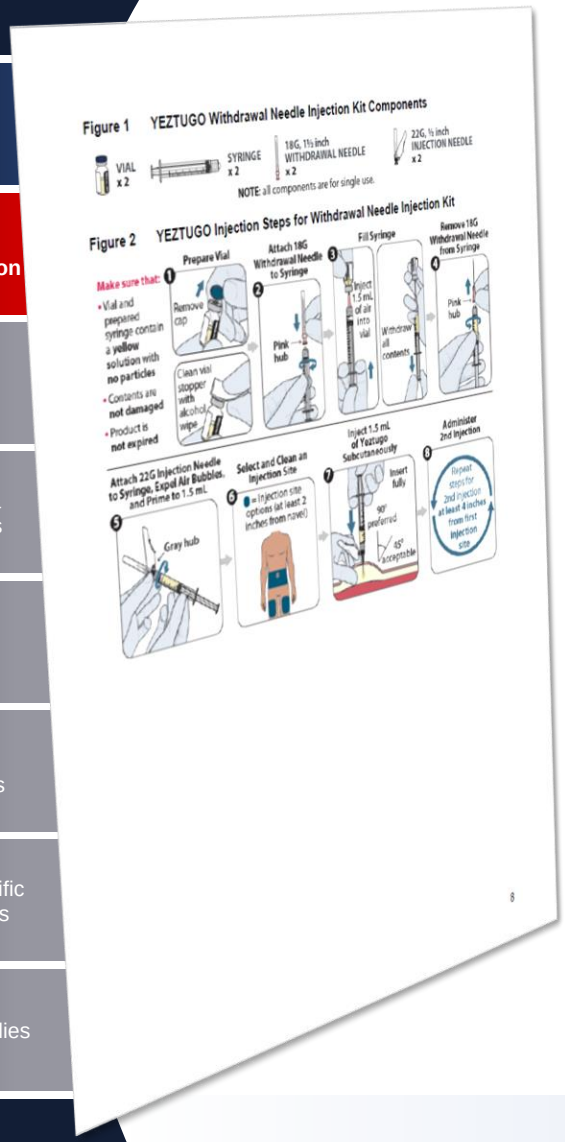
2. Dosage and Administration



QUESTION 1

YEZTUGO should be injected into the subcutaneous space at a 45–90° angle (preferably 90°)

TRUE

TRUE. YEZTUGO injection is only for **SC administration into the abdomen by a healthcare provider,** and a **90-degree** angle is preferred. The thigh can be used as an alternative injection site if preferred. Do **NOT** administer intradermally due to risk of serious ISRs

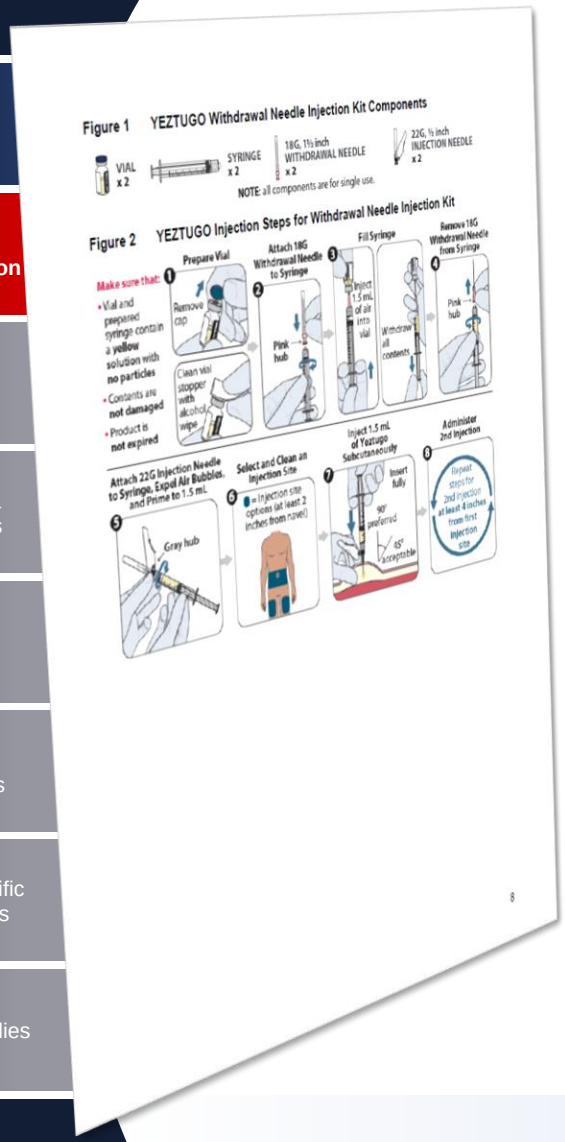
Please refer to section 2.6 of the USPI for further information

ISR, injection-site reaction

Approved for Use on 18 Aug 2025

SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

2. Dosage and Administration



QUESTION 2

Two different needles are provided in the YEZTUGO kit. One is for withdrawal and one is for injection

TRUE OR FALSE

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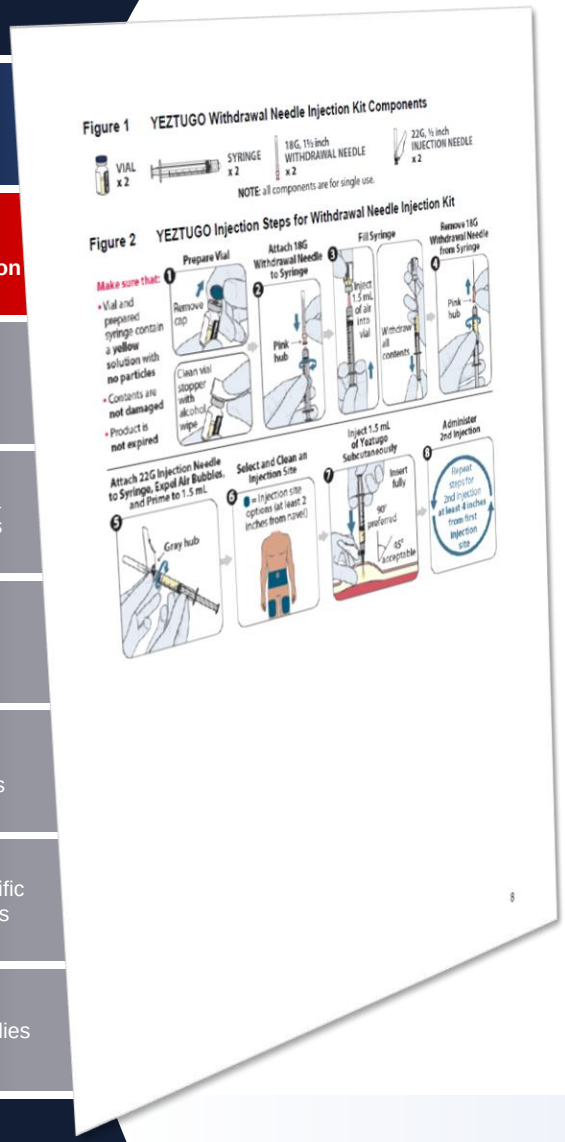
SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

2. Dosage and Administration



QUESTION 2

Two different needles are provided in the YEZTUGO kit. One is for withdrawal and one is for injection

TRUE

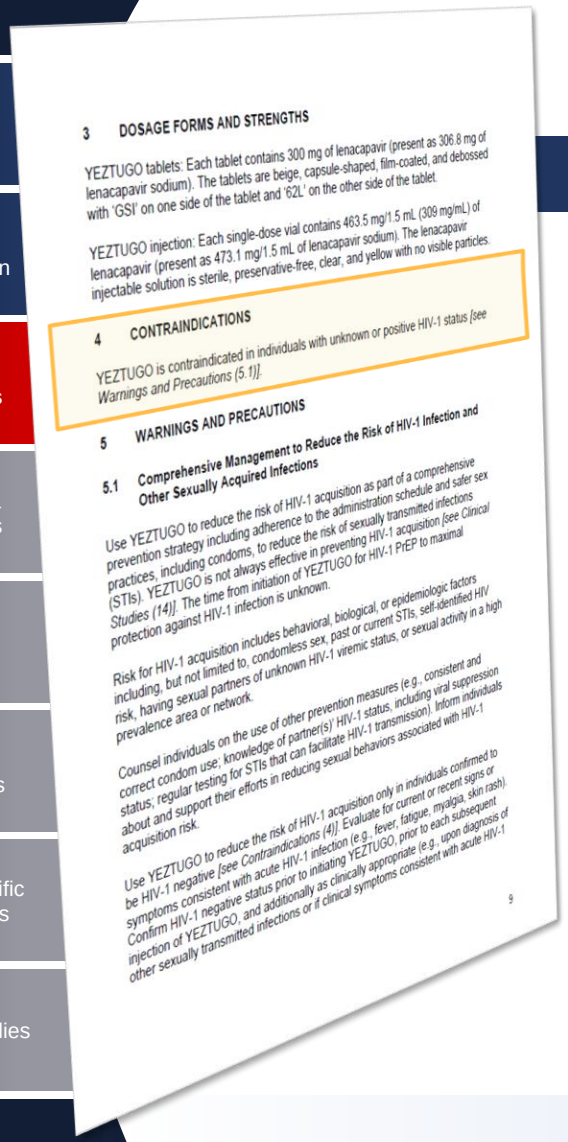
TRUE. The 18-gauge needle is used for withdrawal and a 22-gauge needle is used for injection

Please refer to section 2.6 of the USPI for further information

Approved for Use on 18 Aug 2025

SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

4. Contraindications



3 DOSAGE FORMS AND STRENGTHS

YEZTUGO tablets: Each tablet contains 300 mg of lenacapavir (present as 306.8 mg of lenacapavir sodium). The tablets are beige, capsule-shaped, film-coated, and debossed with 'GSI' on one side of the tablet and '62L' on the other side of the tablet.

YEZTUGO injection: Each single-dose vial contains 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir (present as 473.1 mg/1.5 mL of lenacapavir sodium). The lenacapavir injectable solution is sterile, preservative-free, clear, and yellow with no visible particles.

4 CONTRAINDICATIONS

YEZTUGO is contraindicated in individuals with unknown or positive HIV-1 status *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Comprehensive Management to Reduce the Risk of HIV-1 Infection and Other Sexually Acquired Infections

Use YEZTUGO to reduce the risk of HIV-1 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 *[see Clinical Studies (14)]*. The time from initiation of YEZTUGO for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.

Risk for HIV-1 acquisition includes behavioral, biological, or epidemiologic factors including, but not limited to, condomless sex, past or current STIs, self-identified HIV risk, having sexual partners of unknown HIV-1 viremic status, or sexual activity in a high prevalence area or network.

Counsel individuals on the use of other prevention measures (e.g., consistent and correct condom use; knowledge of partner(s)' HIV-1 status, including viral suppression status; regular testing for STIs that can facilitate HIV-1 transmission). Inform individuals about and support their efforts in reducing sexual behaviors associated with HIV-1 acquisition risk.

Use YEZTUGO to reduce the risk of HIV-1 acquisition only in individuals confirmed to be HIV-1 negative *[see Contraindications (4)]*. Evaluate for current or recent signs or symptoms consistent with acute HIV-1 infection (e.g., fever, fatigue, myalgia, skin rash). Confirm HIV-1 negative status prior to initiating YEZTUGO, prior to each subsequent injection of YEZTUGO, and additionally as clinically appropriate (e.g., upon diagnosis of other sexually transmitted infections or if clinical symptoms consistent with acute HIV-1

9

4 ▸ Contraindications

YEZTUGO is contraindicated in individuals:

With **unknown or positive HIV-1 status**.
[see Warnings and Precautions (5.1)]

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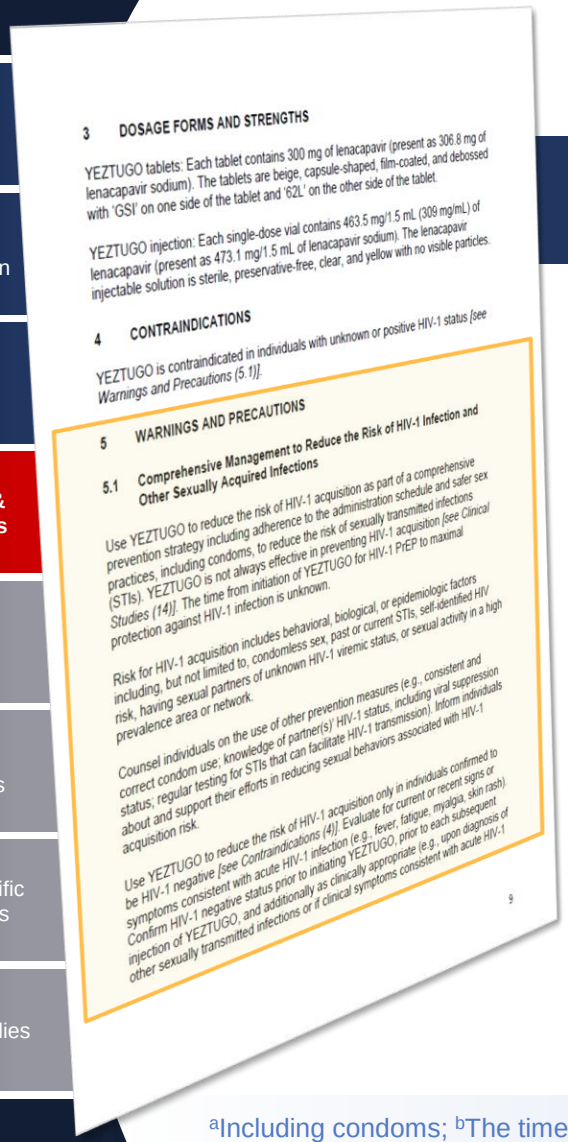
SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

5. Warnings and Precautions



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4 CONTRAINDICATIONS

YEZTUGO is contraindicated in individuals with unknown or positive HIV-1 status *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Comprehensive Management to Reduce the Risk of HIV-1 Infection and Other Sexually Acquired Infections

Use YEZTUGO to reduce the risk of HIV-1 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 *[see Clinical Studies (14)]*. The time from initiation of YEZTUGO for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.

Risk for HIV-1 acquisition includes behavioral, biological, or epidemiologic factors including, but not limited to, condomless sex, past or current STIs, self-identified HIV risk, having sexual partners of unknown HIV-1 viremic status, or sexual activity in a high prevalence area or network.

Counsel individuals on the use of other prevention measures (e.g., consistent and correct condom use; knowledge of partner(s)' HIV-1 status, including viral suppression status; regular testing for STIs that can facilitate HIV-1 transmission). Inform individuals about and support their efforts in reducing sexual behaviors associated with HIV-1 acquisition risk.

Use YEZTUGO to reduce the risk of HIV-1 acquisition only in individuals confirmed to be HIV-1 negative *[see Contraindications (4)]*. Evaluate for current or recent signs or symptoms consistent with acute HIV-1 infection (e.g., fever, fatigue, myalgia, skin rash). Confirm HIV-1 negative status prior to initiating YEZTUGO, prior to each subsequent injection of YEZTUGO, and additionally as clinically appropriate (e.g., upon diagnosis of other sexually transmitted infections or if clinical symptoms consistent with acute HIV-1

9

5.1 Comprehensive Management to Reduce the Risk of HIV-1 Infection and Other Sexually Acquired Infections

Use YEZTUGO to reduce the risk of HIV-1 acquisition as part of a comprehensive prevention strategy including adherence to the administration schedule and safer sex practices[a] to reduce the risk of STIs. YEZTUGO is not always effective in preventing HIV-1 acquisition.[b]
[see Clinical Studies (14)]

Counsel individuals on the use of other prevention measures (e.g., consistent and correct condom use; knowledge of partner(s)' HIV-1 status, including viral suppression status; regular testing for STIs that can facilitate HIV-1 transmission). Inform individuals about and support their efforts in reducing sexual behaviors associated with HIV-1 acquisition risk.

Counsel and support individuals on adhering to the YEZTUGO administration schedule, on the use of other measures to reduce the risk of STIs and on the importance of routine testing for HIV-1 and other STIs.

[a]Including condoms; [b]The time from initiation of YEZTUGO for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown

STI, sexually transmitted infection

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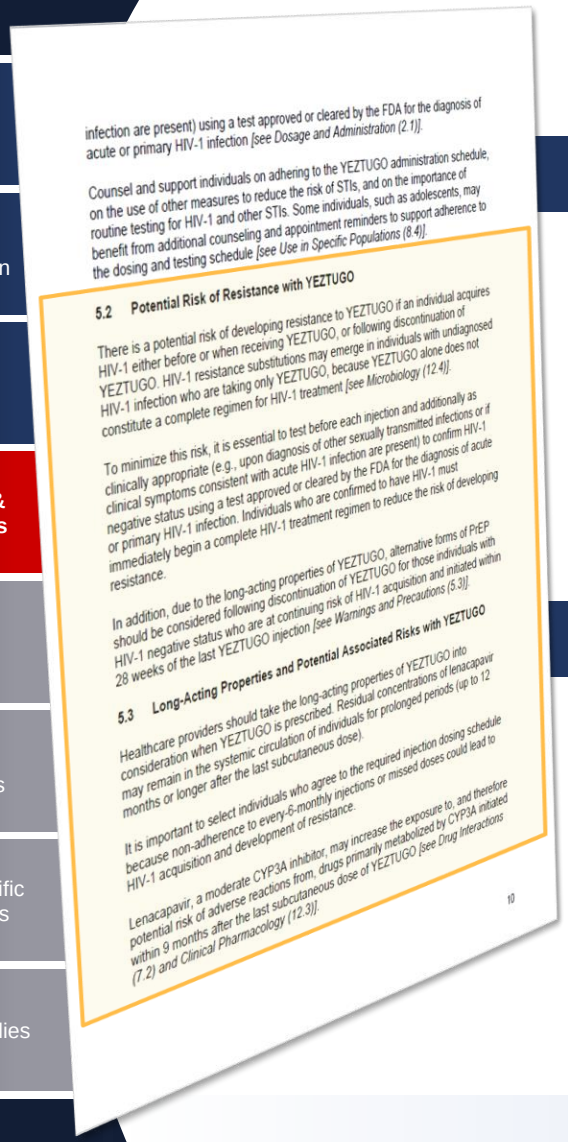
SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

5. Warnings and Precautions



infection are present) using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection [see Dosage and Administration (2.1)].

Counsel and support individuals on adhering to the YEZTUGO administration schedule, on the use of other measures to reduce the risk of STIs, and on the importance of routine testing for HIV-1 and other STIs. Some individuals, such as adolescents, may benefit from additional counseling and appointment reminders to support adherence to the dosing and testing schedule [see Use in Specific Populations (8.4)].

5.2 Potential Risk of Resistance with YEZTUGO

There is a potential risk of developing resistance to YEZTUGO if an individual acquires HIV-1 either before or when receiving YEZTUGO, or following discontinuation of YEZTUGO. HIV-1 resistance substitutions may emerge in individuals with undiagnosed HIV-1 infection who are taking only YEZTUGO, because YEZTUGO alone does not constitute a complete regimen for HIV-1 treatment [see Microbiology (12.4)].

To minimize this risk, it is essential to test before each injection and additionally as clinically appropriate (e.g., upon diagnosis of other sexually transmitted infections or if clinical symptoms consistent with acute HIV-1 infection are present) to confirm HIV-1 negative status using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. Individuals who are confirmed to have HIV-1 must immediately begin a complete HIV-1 treatment regimen to reduce the risk of developing resistance.

In addition, 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 [see Warnings and Precautions (5.3)].

5.3 Long-Acting Properties and Potential Associated Risks with YEZTUGO

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 subcutaneous dose).

It is important to select individuals who agree to the required injection dosing schedule because non-adherence to every-6-monthly injections or missed doses could lead to HIV-1 acquisition and development of resistance.

Lenacapavir, a moderate CYP3A inhibitor, may increase the exposure to, and therefore potential risk of adverse reactions from, drugs primarily metabolized by CYP3A initiated within 9 months after the last subcutaneous dose of YEZTUGO [see Drug Interactions (7.2) and Clinical Pharmacology (12.3)].

10

5.2 Potential Risk of Resistance with YEZTUGO

There is a potential risk of developing resistance to YEZTUGO if an individual acquires HIV-1 either before or when receiving YEZTUGO, or following discontinuation of YEZTUGO. HIV-1 resistance substitutions may emerge in individuals with undiagnosed HIV-1 infection who are taking only YEZTUGO, because YEZTUGO alone does not constitute a complete regimen for HIV-1 treatment. [see Microbiology (12.4)] Test before each injection and additionally as clinically appropriate to confirm HIV-1 negative status.

5.3 Long-Acting Properties and Potential Associated Risks

Healthcare providers should take the long-acting properties of YEZTUGO into consideration when YEZTUGO is prescribed. Residual concentrations of LEN 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 nonadherence to Q6M injections or missed doses could lead to HIV-1 acquisition and development of resistance.

Q6M, every 6 months

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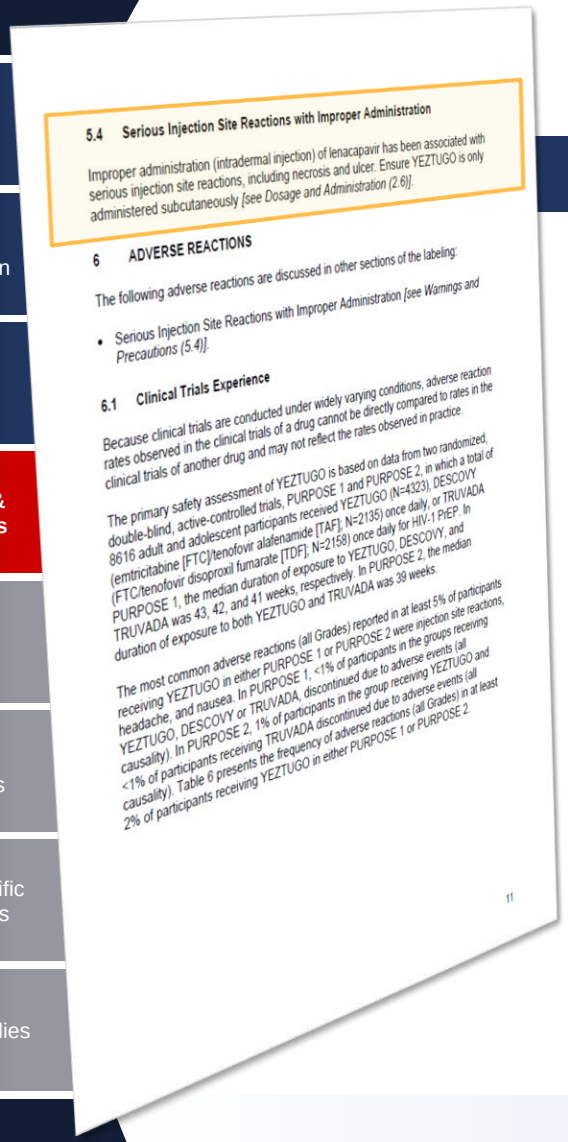
5. Warnings and Precautions



5.4 Serious Injection Site Reactions with Improper Administration

Improper administration (intradermal injection) of lenacapavir has been associated with serious injection site reactions, including necrosis and ulcer. Ensure YEZTUGO is only administered subcutaneously [see Dosage and Administration (2.6)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Serious Injection Site Reactions with Improper Administration [see Warnings and Precautions (5.4)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The primary safety assessment of YEZTUGO is based on data from two randomized, double-blind, active-controlled trials, PURPOSE 1 and PURPOSE 2, in which a total of 8616 adult and adolescent participants received YEZTUGO (N=4323), DESCOVY (emtricitabine [FTC]/tenofovir alafenamide [TAF]; N=2135) once daily, or TRUVADA (FTC/tenofovir disoproxil fumarate [TDF]; N=2158) once daily for HIV-1 PrEP. In PURPOSE 1, the median duration of exposure to YEZTUGO, DESCOVY, and TRUVADA was 43, 42, and 41 weeks, respectively. In PURPOSE 2, the median duration of exposure to both YEZTUGO and TRUVADA was 39 weeks.

The most common adverse reactions (all Grades) reported in at least 5% of participants receiving YEZTUGO in either PURPOSE 1 or PURPOSE 2 were injection site reactions, headache, and nausea. In PURPOSE 1, <1% of participants in the groups receiving YEZTUGO, DESCOVY or TRUVADA, discontinued due to adverse events (all causality). In PURPOSE 2, 1% of participants in the group receiving YEZTUGO and <1% of participants receiving TRUVADA discontinued due to adverse events (all causality). Table 6 presents the frequency of adverse reactions (all Grades) in at least 2% of participants receiving YEZTUGO in either PURPOSE 1 or PURPOSE 2.

11

5.4 Serious Injection-Site Reactions With Improper Administration

Improper administration (intradermal injection) of LEN has been associated with **serious ISRs, including necrosis and ulcer**. Ensure YEZTUGO is only administered subcutaneously.

[see Dosage and Administration (2.6)]

ISR, injection-site reaction

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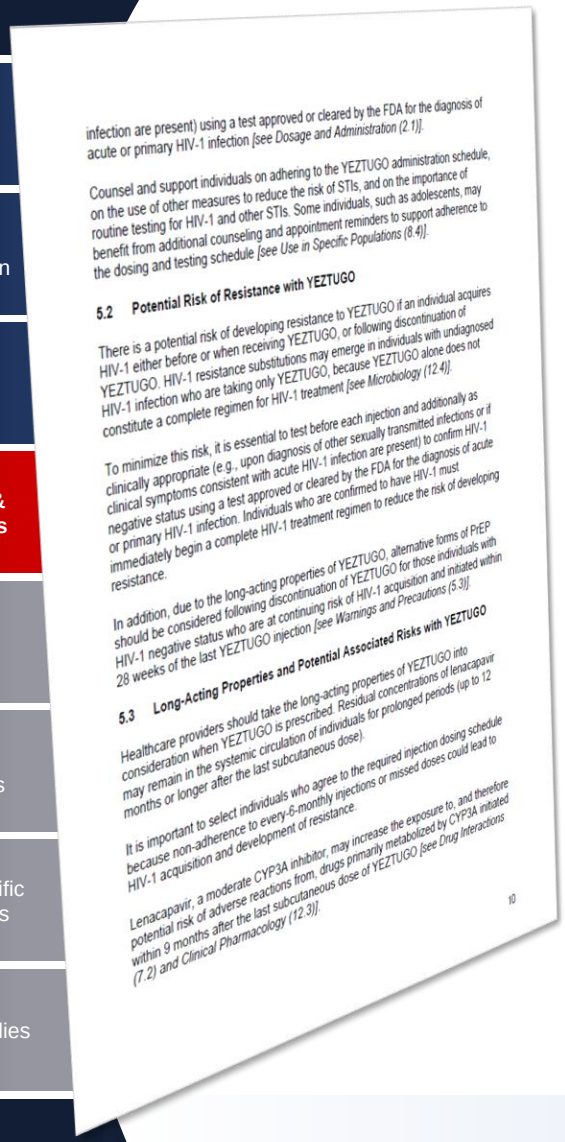
5. Warnings and Precautions



infection are present) using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection *[see Dosage and Administration (2.1)]*.

Counsel and support individuals on adhering to the YEZTUGO administration schedule, on the use of other measures to reduce the risk of STIs, and on the importance of routine testing for HIV-1 and other STIs. Some individuals, such as adolescents, may benefit from additional counseling and appointment reminders to support adherence to the dosing and testing schedule *[see Use in Specific Populations (8.4)]*.

5.2 Potential Risk of Resistance with YEZTUGO

There is a potential risk of developing resistance to YEZTUGO if an individual acquires HIV-1 either before or when receiving YEZTUGO, or following discontinuation of YEZTUGO. HIV-1 resistance substitutions may emerge in individuals with undiagnosed HIV-1 infection who are taking only YEZTUGO, because YEZTUGO alone does not constitute a complete regimen for HIV-1 treatment *[see Microbiology (12.4)]*.

To minimize this risk, it is essential to test before each injection and additionally as clinically appropriate (e.g., upon diagnosis of other sexually transmitted infections or if clinical symptoms consistent with acute HIV-1 infection are present) to confirm HIV-1 negative status using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. Individuals who are confirmed to have HIV-1 must immediately begin a complete HIV-1 treatment regimen to reduce the risk of developing resistance.

In addition, 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 *[see Warnings and Precautions (5.3)]*.

5.3 Long-Acting Properties and Potential Associated Risks with YEZTUGO

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 subcutaneous dose).

It is important to select individuals who agree to the required injection dosing schedule because non-adherence to every-6-monthly injections or missed doses could lead to HIV-1 acquisition and development of resistance.

Lenacapavir, a moderate CYP3A inhibitor, may increase the exposure to, and therefore potential risk of adverse reactions from, drugs primarily metabolized by CYP3A initiated within 9 months after the last subcutaneous dose of YEZTUGO *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

10

QUESTION 1

YEZTUGO alone does **not** constitute a complete regimen for HIV-1 **treatment**

TRUE OR **FALSE**

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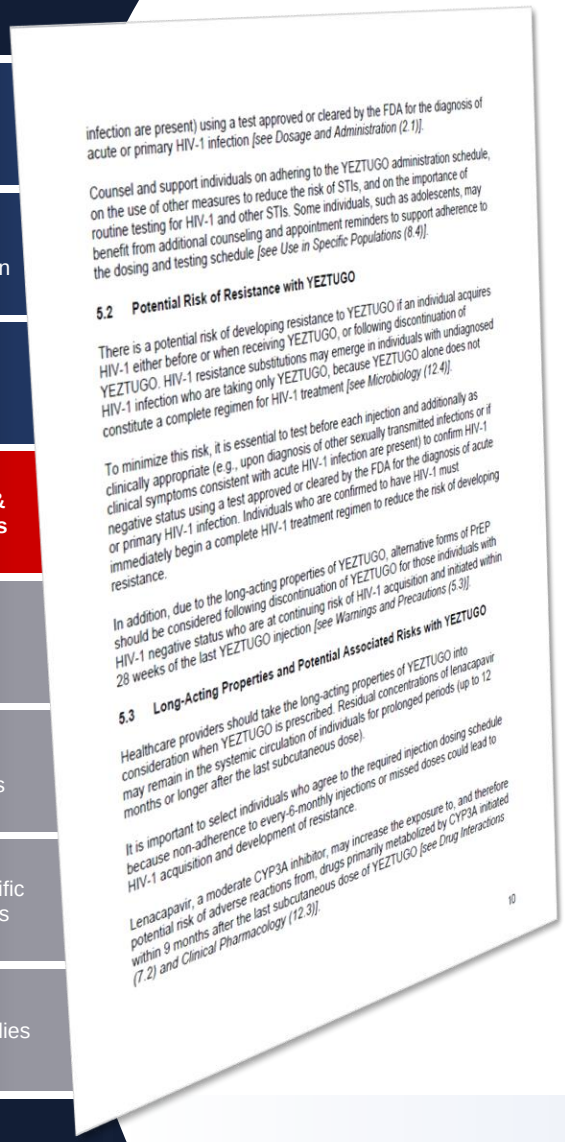
5. Warnings and Precautions



infection are present) using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection *[see Dosage and Administration (2.1)]*.

Counsel and support individuals on adhering to the YEZTUGO administration schedule, on the use of other measures to reduce the risk of STIs, and on the importance of routine testing for HIV-1 and other STIs. Some individuals, such as adolescents, may benefit from additional counseling and appointment reminders to support adherence to the dosing and testing schedule *[see Use in Specific Populations (8.4)]*.

5.2 Potential Risk of Resistance with YEZTUGO

There is a potential risk of developing resistance to YEZTUGO if an individual acquires HIV-1 either before or when receiving YEZTUGO, or following discontinuation of YEZTUGO. HIV-1 resistance substitutions may emerge in individuals with undiagnosed HIV-1 infection who are taking only YEZTUGO, because YEZTUGO alone does not constitute a complete regimen for HIV-1 treatment *[see Microbiology (12.4)]*.

To minimize this risk, it is essential to test before each injection and additionally as clinically appropriate (e.g., upon diagnosis of other sexually transmitted infections or if clinical symptoms consistent with acute HIV-1 infection are present) to confirm HIV-1 negative status using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. Individuals who are confirmed to have HIV-1 must immediately begin a complete HIV-1 treatment regimen to reduce the risk of developing resistance.

In addition, 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 *[see Warnings and Precautions (5.3)]*.

5.3 Long-Acting Properties and Potential Associated Risks with YEZTUGO

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 subcutaneous dose).

It is important to select individuals who agree to the required injection dosing schedule because non-adherence to every-6-monthly injections or missed doses could lead to HIV-1 acquisition and development of resistance.

Lenacapavir, a moderate CYP3A inhibitor, may increase the exposure to, and therefore potential risk of adverse reactions from, drugs primarily metabolized by CYP3A initiated within 9 months after the last subcutaneous dose of YEZTUGO *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

10

QUESTION 1

YEZTUGO alone does **not** constitute a complete regimen for HIV-1 **treatment**

TRUE

TRUE. Individuals who are confirmed to have HIV-1 must immediately begin a complete HIV-1 treatment regimen to reduce the risk of developing resistance

Please refer to section 5.2 of the USPI for further information

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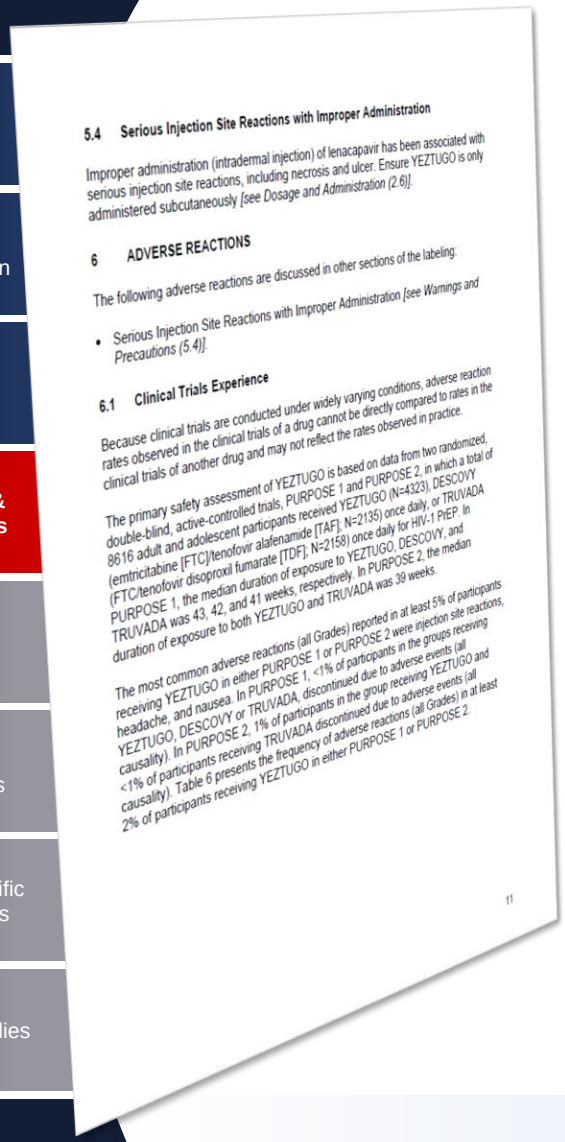
5. Warnings and Precautions



5.4 Serious Injection Site Reactions with Improper Administration

Improper administration (intradermal injection) of lenacapavir has been associated with serious injection site reactions, including necrosis and ulcer. Ensure YEZTUGO is only administered subcutaneously *[see Dosage and Administration (2.6)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Serious Injection Site Reactions with Improper Administration *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The primary safety assessment of YEZTUGO is based on data from two randomized, double-blind, active-controlled trials, PURPOSE 1 and PURPOSE 2, in which a total of 8616 adult and adolescent participants received YEZTUGO (N=4323), DESCOVY (emtricitabine [FTC]/tenofovir alafenamide [TAF]; N=2135) once daily, or TRUVADA (FTC/tenofovir disoproxil fumarate [TDF]; N=2158) once daily for HIV-1 PrEP. In PURPOSE 1, the median duration of exposure to YEZTUGO, DESCOVY, and TRUVADA was 43, 42, and 41 weeks, respectively. In PURPOSE 2, the median duration of exposure to both YEZTUGO and TRUVADA was 39 weeks.

The most common adverse reactions (all Grades) reported in at least 5% of participants receiving YEZTUGO in either PURPOSE 1 or PURPOSE 2 were injection site reactions, headache, and nausea. In PURPOSE 1, <1% of participants in the groups receiving YEZTUGO, DESCOVY or TRUVADA, discontinued due to adverse events (all causality). In PURPOSE 2, 1% of participants in the group receiving YEZTUGO and <1% of participants receiving TRUVADA discontinued due to adverse events (all causality). Table 6 presents the frequency of adverse reactions (all Grades) in at least 2% of participants receiving YEZTUGO in either PURPOSE 1 or PURPOSE 2.

11

QUESTION 2

Improper administration (ex. intradermal injection) of LEN has been associated with serious ISRs, including necrosis and ulcer

TRUE OR FALSE

ISR, injection-site reaction

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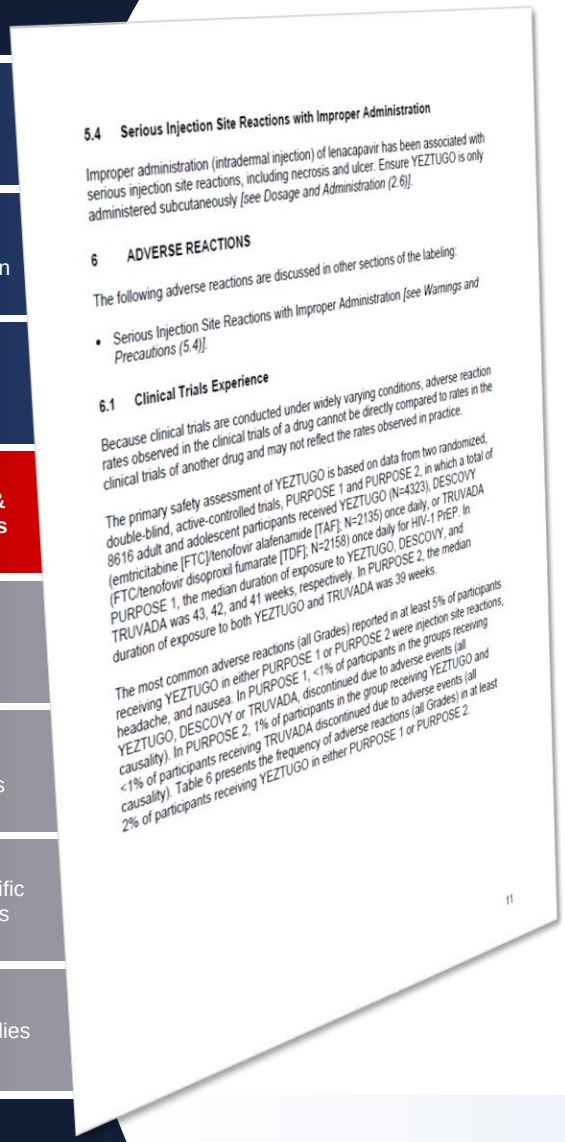
5. Warnings and Precautions



5.4 Serious Injection Site Reactions with Improper Administration

Improper administration (intradermal injection) of lenacapavir has been associated with serious injection site reactions, including necrosis and ulcer. Ensure YEZTUGO is only administered subcutaneously *[see Dosage and Administration (2.6)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Serious Injection Site Reactions with Improper Administration *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The primary safety assessment of YEZTUGO is based on data from two randomized, double-blind, active-controlled trials, PURPOSE 1 and PURPOSE 2, in which a total of 8616 adult and adolescent participants received YEZTUGO (N=4323), DESCOVY (emtricitabine [FTC]/tenofovir alafenamide [TAF]; N=2135) once daily, or TRUVADA (FTC/tenofovir disoproxil fumarate [TDF]; N=2158) once daily for HIV-1 PrEP. In PURPOSE 1, the median duration of exposure to YEZTUGO, DESCOVY, and TRUVADA was 43, 42, and 41 weeks, respectively. In PURPOSE 2, the median duration of exposure to both YEZTUGO and TRUVADA was 39 weeks.

The most common adverse reactions (all Grades) reported in at least 5% of participants receiving YEZTUGO in either PURPOSE 1 or PURPOSE 2 were injection site reactions, headache, and nausea. In PURPOSE 1, <1% of participants in the groups receiving YEZTUGO, DESCOVY or TRUVADA, discontinued due to adverse events (all causality). In PURPOSE 2, 1% of participants in the group receiving YEZTUGO and <1% of participants receiving TRUVADA discontinued due to adverse events (all causality). Table 6 presents the frequency of adverse reactions (all Grades) in at least 2% of participants receiving YEZTUGO in either PURPOSE 1 or PURPOSE 2.

11

QUESTION 2

Improper administration (ex. intradermal injection) of LEN has been associated with serious ISRs, including necrosis and ulcer

TRUE

TRUE. Ensure YEZTUGO is only administered subcutaneously

Please refer to sections 5.4 and 2.6 of the USPI for further information

ISR, injection-site reaction

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6. Adverse Reactions

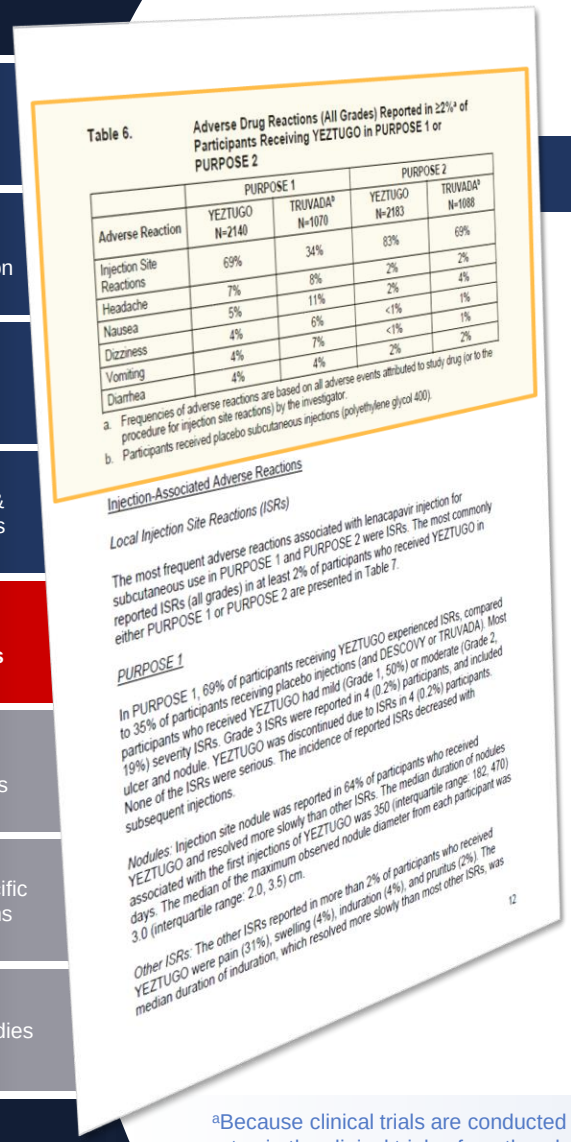

Table 6. Adverse Drug Reactions (All Grades) Reported in ≥2%[a] of Participants Receiving YEZTUGO in PURPOSE 1 or PURPOSE 2

Adverse Reaction	PURPOSE 1		PURPOSE 2	
	YEZTUGO N=2140	TRUVADA[b] N=1070	YEZTUGO N=2183	TRUVADA[b] N=1088
Injection Site Reactions	69%	34%	83%	69%
Headache	7%	8%	2%	2%
Nausea	5%	11%	2%	4%
Dizziness	4%	6%	<1%	1%
Vomiting	4%	7%	<1%	1%
Diarrhea	4%	4%	2%	2%

a. Frequencies of adverse reactions are based on all adverse events attributed to study drug (or to the procedure for injection site reactions) by the investigator.
b. Participants received placebo subcutaneous injections (polyethylene glycol 400).

Injection-Associated Adverse Reactions

Local Injection Site Reactions (ISRs)

The most frequent adverse reactions associated with lenacapavir injection for subcutaneous use in PURPOSE 1 and PURPOSE 2 were ISRs. The most commonly reported ISRs (all grades) in at least 2% of participants who received YEZTUGO in either PURPOSE 1 or PURPOSE 2 are presented in Table 7.

PURPOSE 1

In PURPOSE 1, 69% of participants receiving YEZTUGO experienced ISRs, compared to 35% of participants receiving placebo injections (and DESCOVY or TRUVADA). Most participants who received YEZTUGO had mild (Grade 1, 50%) or moderate (Grade 2, 19%) severity ISRs. Grade 3 ISRs were reported in 4 (0.2%) participants, and included ulcer and nodule. YEZTUGO was discontinued due to ISRs in 4 (0.2%) participants. None of the ISRs were serious. The incidence of reported ISRs decreased with subsequent injections.

Nodules: Injection site nodule was reported in 64% of participants who received YEZTUGO and resolved more slowly than other ISRs. The median duration of nodules associated with the first injections of YEZTUGO was 350 (interquartile range: 182, 470) days. The median of the maximum observed nodule diameter from each participant was 3.0 (interquartile range: 2.0, 3.5) cm.

Other ISRs: The other ISRs reported in more than 2% of participants who received YEZTUGO were pain (31%), swelling (4%), induration (4%), and pruritus (2%). The median duration of induration, which resolved more slowly than most other ISRs, was

12

6.1 Clinical Trials Experience[a]

The most common adverse reactions (all Grades) reported in ≥5% of participants receiving YEZTUGO in either PURPOSE 1 or PURPOSE 2 were **ISRs**, **headache and nausea**.

Table 6. Adverse Reactions (All Grades) Reported in ≥2%[b] of Participants Receiving YEZTUGO in PURPOSE 1 and PURPOSE 2

Adverse Reaction	PURPOSE 1		PURPOSE 2	
	YEZTUGO N=2140	TRUVADA[c] N=1070	YEZTUGO N=2183	TRUVADA[c] N=1088
ISRs	69%	34%	83%	69%
Headache	7%	8%	2%	2%
Nausea	5%	11%	2%	4%
Dizziness	4%	6%	<1%	1%
Vomiting	4%	7%	<1%	1%
Diarrhea	4%	4%	2%	2%

[a]Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice; [b]Frequencies of adverse reactions are based on all AEs attributed to study drug (or to the procedure for ISRs) by the investigator; [c]Participants received placebo SC injections (polyethylene glycol 400);

ISR, injection-site reaction

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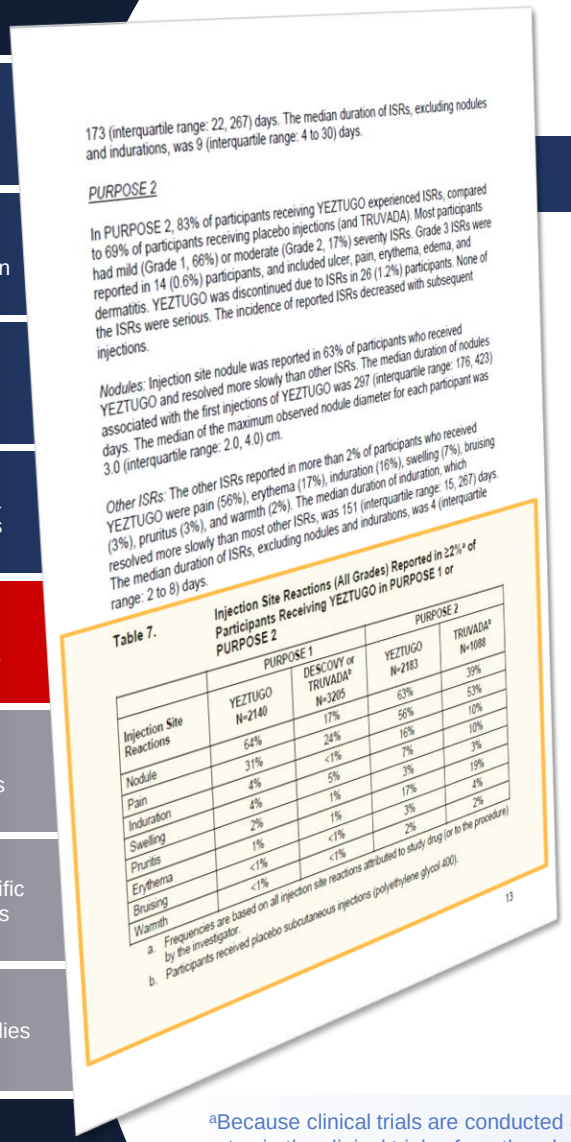
6. Adverse Reactions



173 (interquartile range: 22, 267) days. The median duration of ISRs, excluding nodules and indurations, was 9 (interquartile range: 4 to 30) days.

PURPOSE 2

In PURPOSE 2, 83% of participants receiving YEZTUGO experienced ISRs, compared to 69% of participants receiving placebo injections (and TRUVADA). Most participants had mild (Grade 1, 66%) or moderate (Grade 2, 17%) severity ISRs. Grade 3 ISRs were reported in 14 (0.6%) participants, and included ulcer, pain, erythema, edema, and dermatitis. YEZTUGO was discontinued due to ISRs in 26 (1.2%) participants. None of the ISRs were serious. The incidence of reported ISRs decreased with subsequent injections.

Nodules: Injection site nodule was reported in 63% of participants who received YEZTUGO and resolved more slowly than other ISRs. The median duration of nodules associated with the first injections of YEZTUGO was 297 (interquartile range: 176, 423) days. The median of the maximum observed nodule diameter for each participant was 3.0 (interquartile range: 2.0, 4.0) cm.

Other ISRs: The other ISRs reported in more than 2% of participants who received YEZTUGO were pain (56%), erythema (17%), induration (16%), swelling (7%), bruising (3%), pruritus (3%), and warmth (2%). The median duration of induration, which resolved more slowly than most other ISRs, was 151 (interquartile range: 15, 267) days. The median duration of ISRs, excluding nodules and indurations, was 4 (interquartile range: 2 to 8) days.

Table 7. Injection Site Reactions (All Grades) Reported in ≥2%[a] of Participants Receiving YEZTUGO in PURPOSE 1 or PURPOSE 2

	PURPOSE 1		PURPOSE 2	
Injection Site Reactions	YEZTUGO N=2140	DESCOVY or TRUVADA[b] N=3205	YEZTUGO N=2183	TRUVADA[b] N=1088
Nodule	64%	17%	63%	39%
Pain	31%	<1%	56%	53%
Induration	4%	5%	16%	10%
Swelling	4%	1%	7%	3%
Pruritus	2%	1%	3%	19%
Erythema	1%	<1%	17%	4%
Bruising	<1%	<1%	3%	2%
Warmth	<1%		2%	

a. Frequencies are based on all injection site reactions attributed to study drug (or to the procedure) by the investigator.
b. Participants received placebo subcutaneous injections (polyethylene glycol 400).

13

6.1 Clinical Trials Experience[a] (continued)

Table 7. ISRs (All Grades) Reported in ≥2%[b] of Participants Receiving YEZTUGO in PURPOSE 1 or PURPOSE 2

	PURPOSE 1		PURPOSE 2	
ISRs	YEZTUGO N=2140	DESCOVY or TRUVADA[c] N=3205	YEZTUGO N=2183	TRUVADA[c] N=1088
Nodule	64%	17%	63%	39%
Pain	31%	24%	56%	53%
Induration	4%	<1%	16%	10%
Swelling	4%	5%	7%	10%
Pruritus	2%	1%	3%	3%
Erythema	1%	1%	17%	19%
Bruising	<1%	<1%	3%	4%
Warmth	<1%	<1%	2%	2%

PURPOSE 1:

- Grade 3 ISRs were reported in 4 (0.2%) participants
- Included ulcer and nodule

PURPOSE 2:

- Grade 3 ISRs were reported in 14 (0.6%) participants
- Included ulcer, pain, erythema, edema and dermatitis

[a]Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice; [b]Frequencies are based on all ISRs attributed to study drug (or to the procedure) by the investigator; [c]Participants received placebo SC injections (polyethylene glycol 400)

ISR, injection-site reaction

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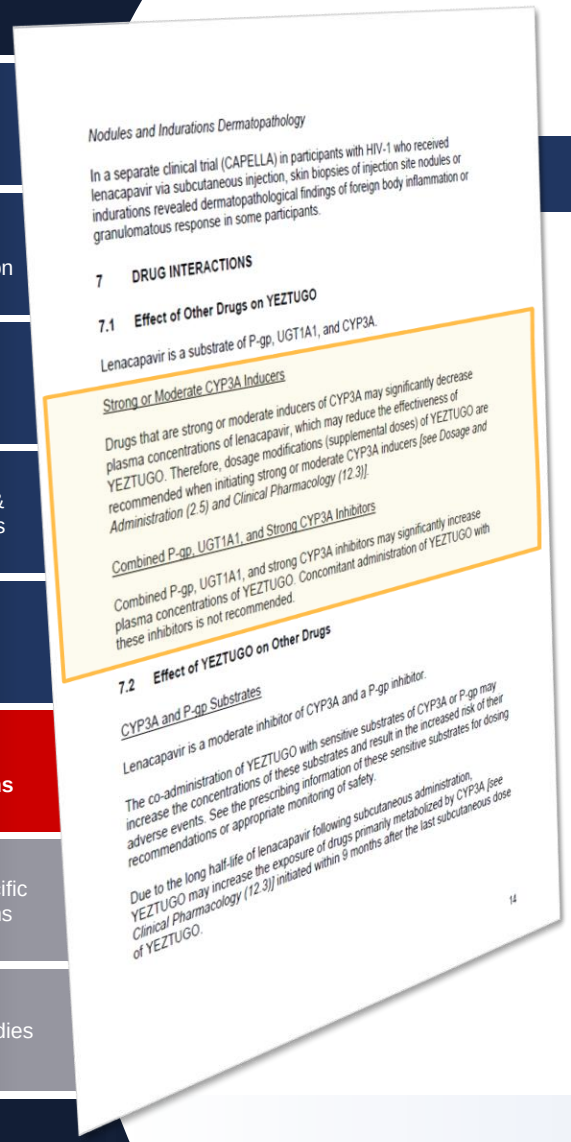
7. Drug Interactions



Nodules and Indurations Dermatopathology

In a separate clinical trial (CAPELLA) in participants with HIV-1 who received lenacapavir via subcutaneous injection, skin biopsies of injection site nodules or indurations revealed dermatopathological findings of foreign body inflammation or granulomatous response in some participants.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on YEZTUGO

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

Strong or Moderate CYP3A Inducers

Drugs that are strong or moderate inducers of CYP3A may significantly decrease plasma concentrations of lenacapavir, which may reduce the effectiveness of YEZTUGO. Therefore, dosage modifications (supplemental doses) of YEZTUGO are recommended when initiating strong or moderate CYP3A inducers *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

Combined P-gp, UGT1A1, and Strong CYP3A Inhibitors

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

7.2 Effect of YEZTUGO on Other Drugs

CYP3A and P-gp Substrates

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

The co-administration 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 following subcutaneous administration, YEZTUGO may increase the exposure of drugs primarily metabolized by CYP3A *[see Clinical Pharmacology (12.3)]* initiated within 9 months after the last subcutaneous dose of YEZTUGO.

14

7.1 Effect of Other Drugs on YEZTUGO

LEN is a substrate of P-gp, UGT1A1 and CYP3A.

Strong or Moderate CYP3A Inducers

Drugs that are strong or moderate inducers of CYP3A may significantly decrease plasma concentrations of LEN, which may reduce the effectiveness of YEZTUGO. Therefore, dosage modifications (supplemental doses) of YEZTUGO are recommended when initiating strong or moderate CYP3A inducers.

[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]

Combined P-gp, UGT1A1 and Strong CYP3A Inhibitors

These drugs may significantly increase plasma concentrations of YEZTUGO. Concomitant administration **is not recommended**.

CYP3A, cytochrome (P450) 3A; P-gp, P-glycoprotein; UGT1A1, UDP-glucuronosyltransferase family 1 member A1

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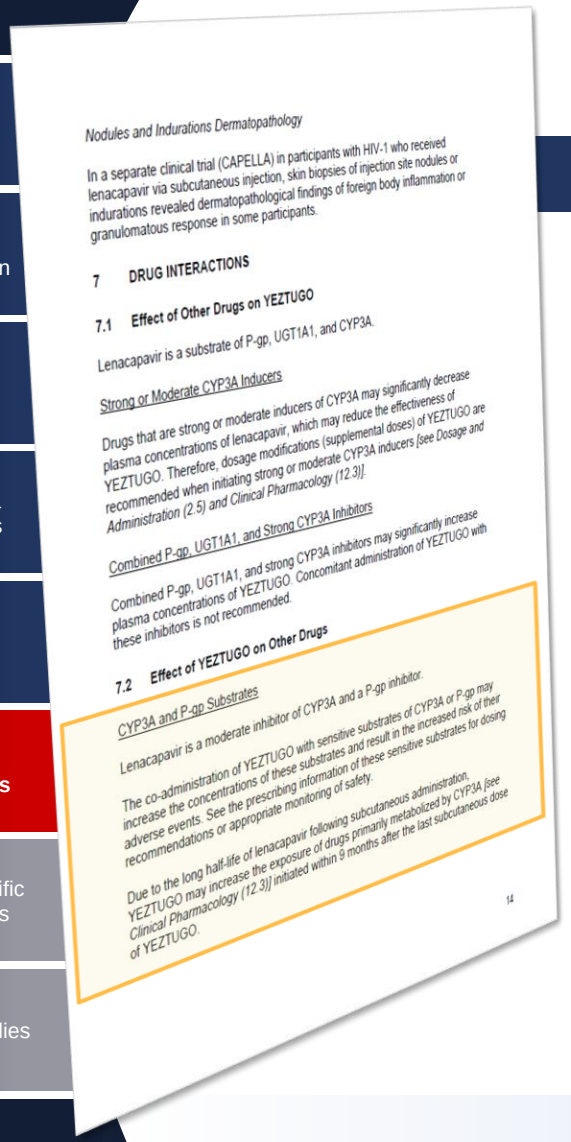
7. Drug Interactions



Nodules and Indurations Dermatopathology

In a separate clinical trial (CAPELLA) in participants with HIV-1 who received lenacapavir via subcutaneous injection, skin biopsies of injection site nodules or indurations revealed dermatopathological findings of foreign body inflammation or granulomatous response in some participants.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on YEZTUGO

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

Strong or Moderate CYP3A Inducers

Drugs that are strong or moderate inducers of CYP3A may significantly decrease plasma concentrations of lenacapavir, which may reduce the effectiveness of YEZTUGO. Therefore, dosage modifications (supplemental doses) of YEZTUGO are recommended when initiating strong or moderate CYP3A inducers *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

Combined P-gp, UGT1A1, and Strong CYP3A Inhibitors

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

7.2 Effect of YEZTUGO on Other Drugs

CYP3A and P-gp Substrates

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

The co-administration 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 following subcutaneous administration, YEZTUGO may increase the exposure of drugs primarily metabolized by CYP3A *[see Clinical Pharmacology (12.3)]* initiated within 9 months after the last subcutaneous dose of YEZTUGO.

14

7.2 Effect of YEZTUGO on Other Drugs

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

The co-administration 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 AEs. See the prescribing information of these sensitive substrates for dosing recommendations or appropriate monitoring of safety.

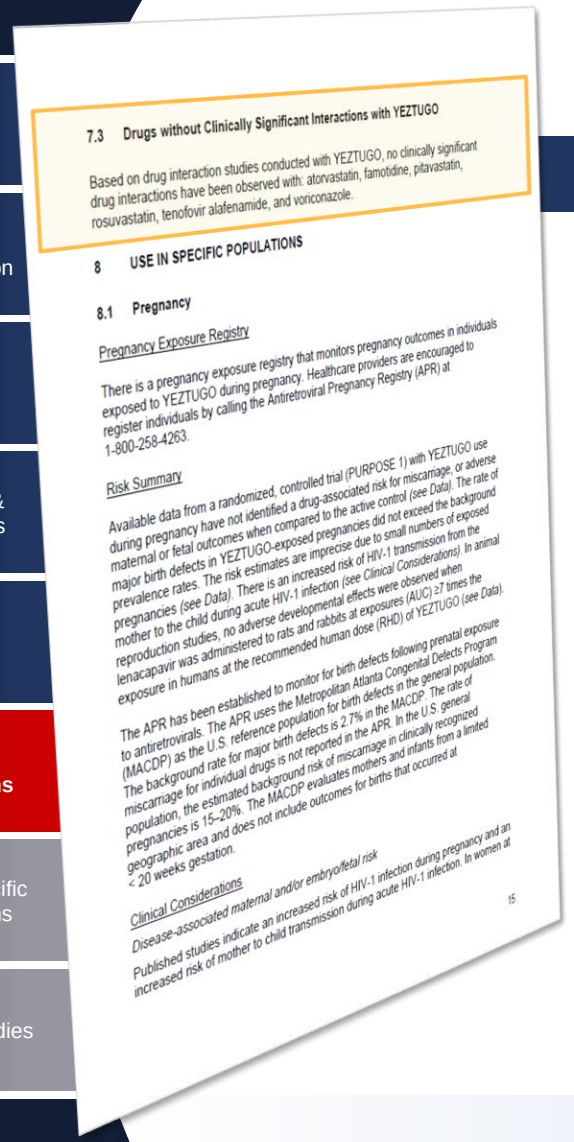
Due to the long half-life of LEN following SC administration, YEZTUGO may increase the exposure of drugs primarily metabolized by CYP3A initiated within 9 months after the last SC dose of YEZTUGO. [see Clinical Pharmacology (12.3)]

CYP3A, cytochrome (P450) 3A; P-gp, P-glycoprotein

Approved for Use on 18 Aug 2025

SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

7. Drug Interactions



7.3 Drugs without Clinically Significant Interactions with YEZTUGO

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to YEZTUGO during pregnancy. Healthcare providers are encouraged to register individuals by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Available data from a randomized, controlled trial (PURPOSE 1) 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 (see Data). The rate of major birth defects in YEZTUGO-exposed pregnancies did not exceed the background prevalence rates. The risk estimates are imprecise due to small numbers of exposed pregnancies (see Data). There is an increased risk of HIV-1 transmission from the mother to the child during acute HIV-1 infection (see Clinical Considerations). In animal reproduction studies, no adverse developmental effects were observed when lenacapavir was administered to rats and rabbits at exposures (AUC) ≥7 times the exposure in humans at the recommended human dose (RHD) of YEZTUGO (see Data).

The APR has been established to monitor for birth defects following prenatal exposure to antiretrovirals. The APR uses the Metropolitan Atlanta Congenital Defects Program (MACDP) as the U.S. reference population for birth defects in the general population. The background rate for major birth defects is 2.7% in the MACDP. The rate of miscarriage for individual drugs is not reported in the APR. In the U.S. general population, the estimated background risk of miscarriage in clinically recognized pregnancies is 15–20%. The MACDP evaluates mothers and infants from a limited geographic area and does not include outcomes for births that occurred at < 20 weeks gestation.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Published studies indicate an increased risk of HIV-1 infection during pregnancy and an increased risk of mother to child transmission during acute HIV-1 infection. In women at

15

7.3 Drugs Without Clinically Significant Interactions With YEZTUGO

Based on drug interaction studies conducted with YEZTUGO, no clinically significant drug interactions have been observed, nor are expected, with:

- Atorvastatin
- Famotidine
- Pitavastatin
- Rosuvastatin
- Tenofovir alafenamide
- Voriconazole

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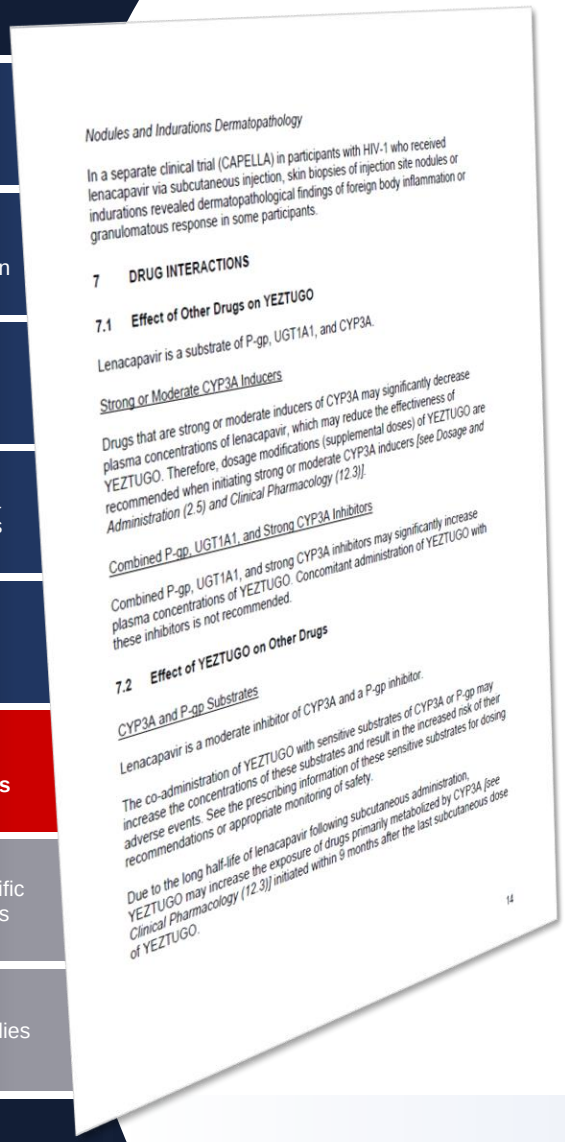
SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

7. Drug Interactions



Nodules and Indurations Dermatopathology

In a separate clinical trial (CAPELLA) in participants with HIV-1 who received lenacapavir via subcutaneous injection, skin biopsies of injection site nodules or indurations revealed dermatopathological findings of foreign body inflammation or granulomatous response in some participants.

7 DRUG INTERACTIONS

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

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CYP3A and P-gp Substrates

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The co-administration 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 following subcutaneous administration, YEZTUGO may increase the exposure of drugs primarily metabolized by CYP3A *[see Clinical Pharmacology (12.3)]* initiated within 9 months after the last subcutaneous dose of YEZTUGO.

14

QUESTION 1

YEZTUGO is a moderate inhibitor of CYP3A and a P-gp inhibitor

TRUE OR FALSE

CYP3A, cytochrome (P450) 3A; P-gp, P-glycoprotein

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SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

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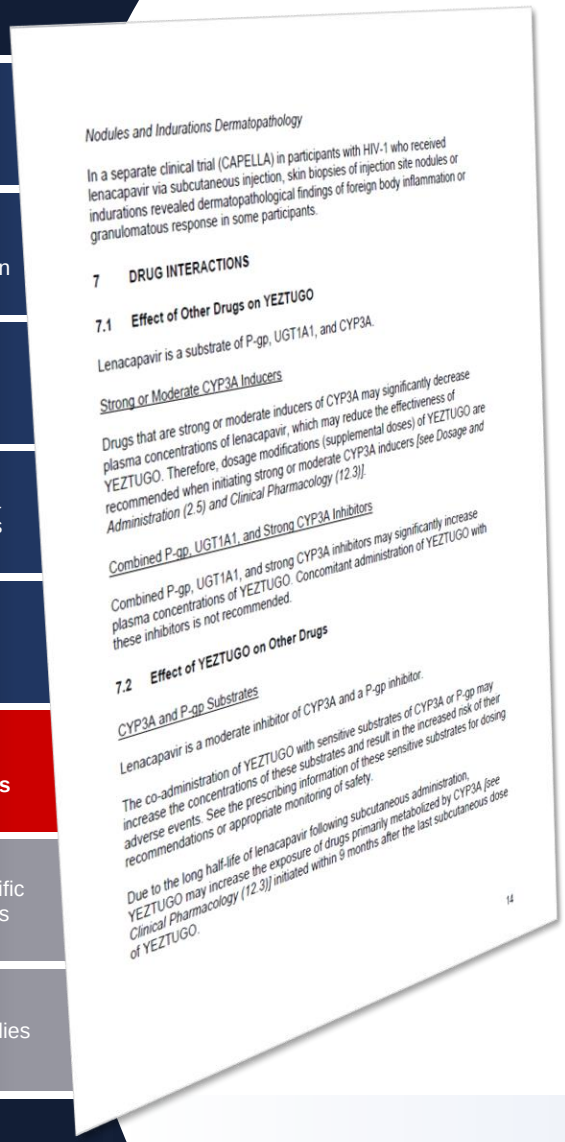

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Due to the long half-life of lenacapavir following subcutaneous administration, YEZTUGO may increase the exposure of drugs primarily metabolized by CYP3A *[see Clinical Pharmacology (12.3)]* initiated within 9 months after the last subcutaneous dose of YEZTUGO.

14

QUESTION 1

YEZTUGO is a moderate inhibitor of CYP3A and a P-gp inhibitor

TRUE

TRUE. *Please refer to section 7.2 of the USPI for further information*

CYP3A, cytochrome (P450) 3A; P-gp, P-glycoprotein

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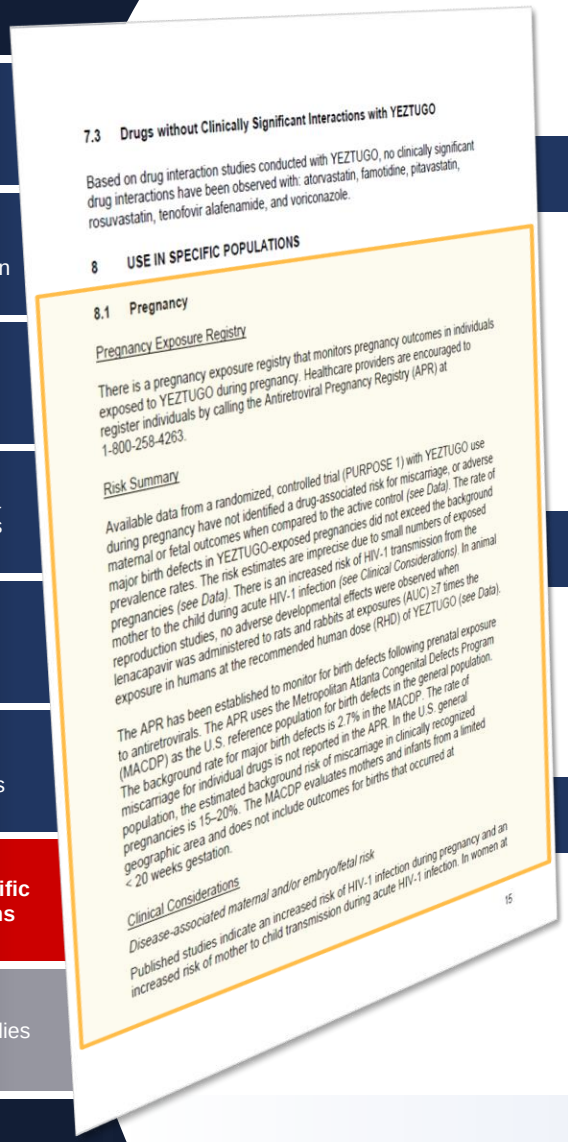
SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

8. Use in Specific Populations

Indications & Usage
Dosage & Administration
Contra-indications
Warnings & Precautions
Adverse Reactions
Drug Interactions
Use in Specific Populations
Clinical Studies



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Risk Summary

Available data from a randomized, controlled trial (PURPOSE 1) 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 (see Data). The rate of major birth defects in YEZTUGO-exposed pregnancies did not exceed the background prevalence rates. The risk estimates are imprecise due to small numbers of exposed pregnancies (see Data). There is an increased risk of HIV-1 infection (see Clinical Considerations) in the mother to the child during acute HIV-1 infection. In animal reproduction studies, no adverse developmental effects were observed when lenacapavir was administered to rats and rabbits at exposures (AUC) ≥7 times the exposure in humans at the recommended human dose (RHD) of YEZTUGO (see Data).

The APR has been established to monitor for birth defects following prenatal exposure to antiretrovirals. The APR uses the Metropolitan Atlanta Congenital Defects Program (MACDP) as the U.S. reference population for birth defects in the general population. The background rate for major birth defects is 2.7% in the MACDP. The rate of miscarriage for individual drugs is not reported in the APR. In the U.S. general population, the estimated background risk of miscarriage in clinically recognized pregnancies is 15–20%. The MACDP evaluates mothers and infants from a limited geographic area and does not include outcomes for births that occurred at < 20 weeks gestation.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Published studies indicate an increased risk of HIV-1 infection during pregnancy and an increased risk of mother to child transmission during acute HIV-1 infection. In women at

15

8.1 Pregnancy

Data from PURPOSE 1 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.[a] There is an increased risk of HIV-1 transmission from the mother to the child during acute HIV-1 infection. [see Clinical Considerations]

8.2 Lactation

LEN is present in human milk and was detected at very low levels in infants who were breastfed by individuals who became pregnant while receiving YEZTUGO. No adverse effects of LEN in breastfed infants have been observed.

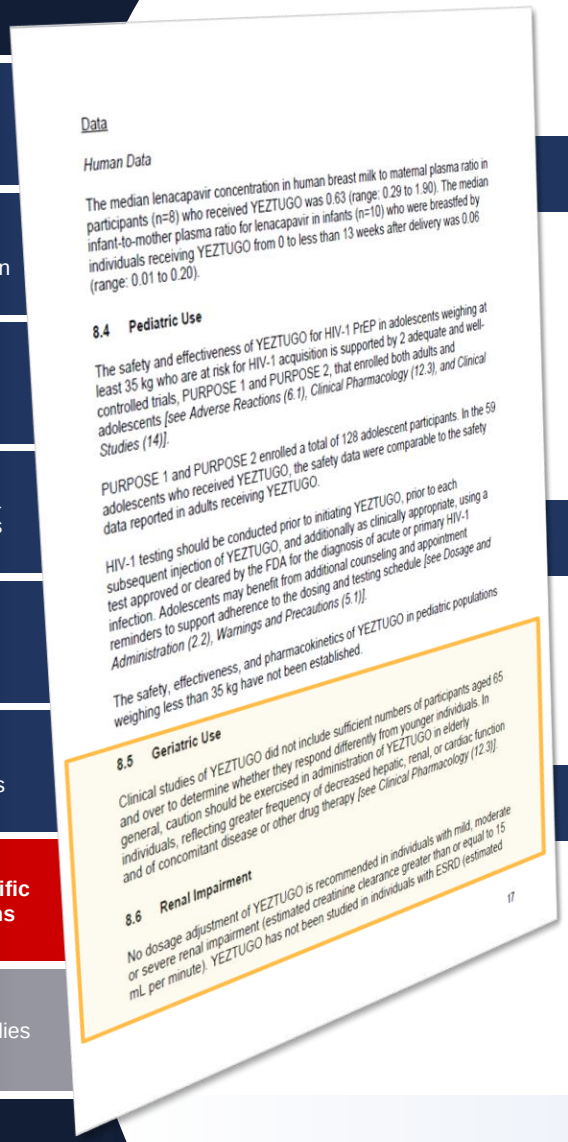
8.4 Pediatric Use

The safety and effectiveness of YEZTUGO for HIV-1 PrEP in adolescents weighing ≥35 kg who are at risk for HIV-1 acquisition is supported by 2 adequate and well-controlled trials, PURPOSE 1 and PURPOSE 2, that enrolled both adults and adolescents.
[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14)]

[a]The risk estimates are imprecise due to small numbers of exposed pregnancies

BACK NEXT

8. Use in Specific Populations



Data

Human Data

The median lenacapavir concentration in human breast milk to maternal plasma ratio in participants (n=8) who received YEZTUGO was 0.63 (range: 0.29 to 1.90). The median infant-to-mother plasma ratio for lenacapavir in infants (n=10) who were breastfed by individuals receiving YEZTUGO from 0 to less than 13 weeks after delivery was 0.06 (range: 0.01 to 0.20).

8.4 Pediatric Use

The safety and effectiveness of YEZTUGO for HIV-1 PrEP in adolescents weighing at least 35 kg who are at risk for HIV-1 acquisition is supported by 2 adequate and well-controlled trials, PURPOSE 1 and PURPOSE 2, that enrolled both adults and adolescents *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

PURPOSE 1 and PURPOSE 2 enrolled a total of 128 adolescent participants. In the 59 adolescents who received YEZTUGO, the safety data were comparable to the safety data reported in adults receiving YEZTUGO.

HIV-1 testing should be conducted prior to initiating 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. Adolescents may benefit from additional counseling and appointment reminders to support adherence to the dosing and testing schedule *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.

The safety, effectiveness, and pharmacokinetics of YEZTUGO in pediatric populations weighing less than 35 kg have not been established.

8.5 Geriatric Use

Clinical studies of YEZTUGO did not include sufficient numbers of participants aged 65 and over to determine whether they respond differently from younger individuals. In general, caution should be exercised in administration of YEZTUGO in elderly individuals, reflecting greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No dosage adjustment of YEZTUGO is recommended in individuals with mild, moderate or severe renal impairment (estimated creatinine clearance greater than or equal to 15 mL per minute). YEZTUGO has not been studied in individuals with ESRD (estimated

17

8.5 Geriatric Use

Clinical studies of YEZTUGO did not include sufficient numbers of participants aged ≥65 years to determine whether they respond differently from younger individuals. Exercise caution when administering YEZTUGO in elderly individuals due to greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. [see Clinical Pharmacology (12.3)]

8.6 Renal Impairment

No dosage adjustment of YEZTUGO is recommended in individuals with mild, moderate or severe renal impairment (eCrCl ≥15 mL/min). YEZTUGO has not been studied in individuals with ESRD (eCrCl <15 mL/min). [see Clinical Pharmacology (12.3)]

8.7 Hepatic Impairment

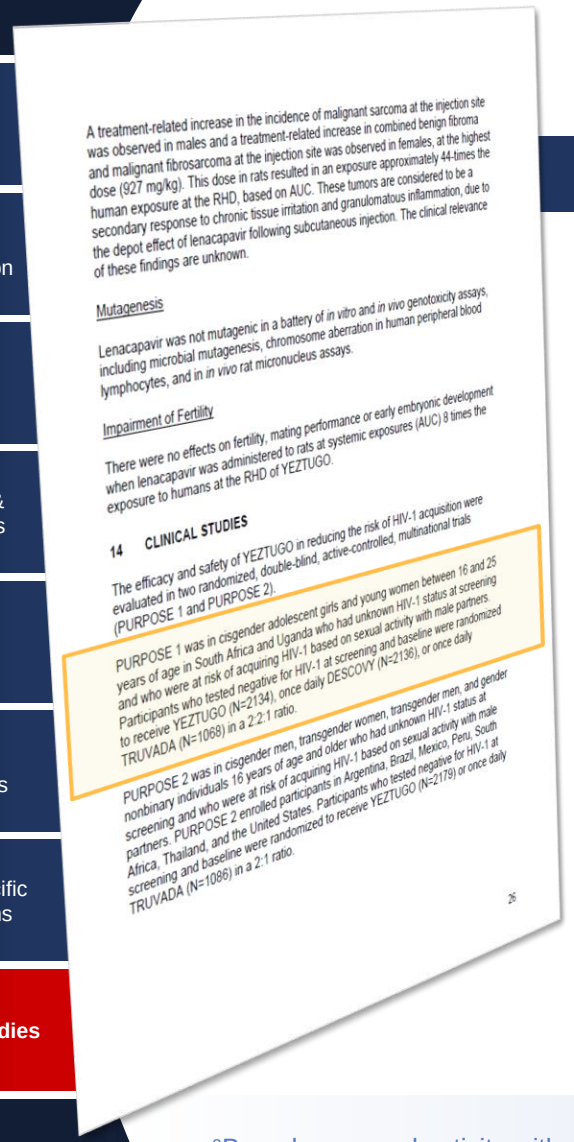
No dosage adjustment of YEZTUGO is recommended in individuals with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. YEZTUGO has not been studied in individuals with severe hepatic impairment (Child-Pugh Class C). [see Clinical Pharmacology (12.3)]

eCrCl, estimated creatinine clearance; ESRD, end-stage renal disease

Approved for Use on 18 Aug 2025

SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

14. Clinical Studies



A treatment-related increase in the incidence of malignant sarcoma at the injection site was observed in males and a treatment-related increase in combined benign fibroma and malignant fibrosarcoma at the injection site was observed in females, at the highest dose (927 mg/kg). This dose in rats resulted in an exposure approximately 44-times the human exposure at the RHD, based on AUC. These tumors are considered to be a secondary response to chronic tissue irritation and granulomatous inflammation, due to the depot effect of lenacapavir following subcutaneous injection. The clinical relevance of these findings are unknown.

Mutagenesis

Lenacapavir was not mutagenic in a battery of *in vitro* and *in vivo* genotoxicity assays, including microbial mutagenesis, chromosome aberration in human peripheral blood lymphocytes, and in *in vivo* rat micronucleus assays.

Impairment of Fertility

There were no effects on fertility, mating performance or early embryonic development when lenacapavir was administered to rats at systemic exposures (AUC) 8 times the exposure to humans at the RHD of YEZTUGO.

14 CLINICAL STUDIES

The efficacy and safety of YEZTUGO in reducing the risk of HIV-1 acquisition were 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 YEZTUGO (N=2134), once daily DESCOVY (N=2136), or once daily TRUVADA (N=1068) in a 2:2:1 ratio.

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 YEZTUGO (N=2179) or once daily TRUVADA (N=1086) in a 2:1 ratio.

26

14 ▸ Clinical Studies: PURPOSE 1

Study Design

- PURPOSE 1 was in cisgender adolescent girls and young women aged 16–25 years in South Africa and Uganda who had unknown HIV-1 status at screening and were at risk of acquiring HIV-1[a]
- Participants who tested negative for HIV-1 were randomized to receive YEZTUGO (N=2134), once-daily DESCOVY (N=2136), or once-daily TRUVADA (N=1068) in a 2:2:1 ratio
- **The use of DESCOVY (F/TAF) for the prevention of HIV in cisgender women is not approved. The safety and efficacy of this use have not been established**

Baseline Characteristics

Median participant age:
21 years
(range: 16–26)

99.9% of participants were Black

Baseline characteristics in the randomized participants were similar to those in the screened population

Outcomes/Results at Primary Analysis

- HIV incidence per 100/PY was compared between participants receiving YEZTUGO and TRUVADA
- YEZTUGO demonstrated superiority over TRUVADA, with a 100% reduction in the risk of incident HIV-1 infection (**Table 13**; see next slide)
- YEZTUGO also demonstrated superiority in the risk of incident HIV-1 infection over bHIV

[a]Based on sexual activity with male partners
bHIV, background HIV incidence; F/TAF, emtricitabine/tenofovir alafenamide; PY, person-years

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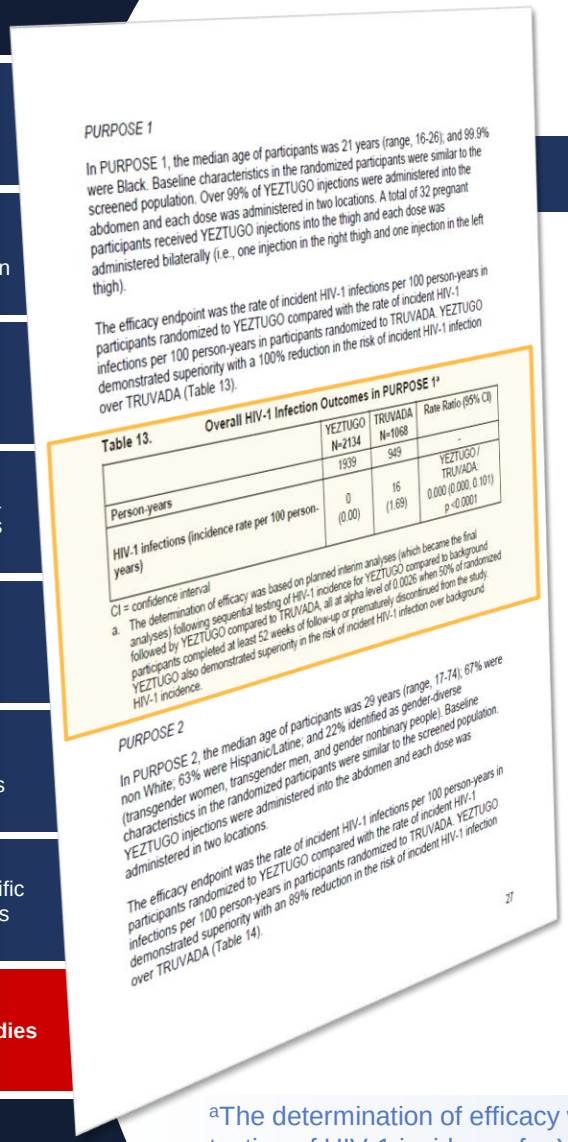
14. Clinical Studies



PURPOSE 1

In PURPOSE 1, the median age of participants was 21 years (range, 16-26); and 99.9% were Black. Baseline characteristics in the randomized participants were similar to the screened population. Over 99% of YEZTUGO injections were administered into the abdomen and each dose was administered in two locations. A total of 32 pregnant participants received 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 YEZTUGO compared with the rate of incident HIV-1 infections per 100 person-years in participants randomized to TRUVADA. YEZTUGO demonstrated superiority with a 100% reduction in the risk of incident HIV-1 infection over TRUVADA (Table 13).

Table 13. Overall HIV-1 Infection Outcomes in PURPOSE 1[a]

	YEZTUGO N=2134	TRUVADA N=1068	Rate Ratio (95% CI)
Person-years	1939	949	-
HIV-1 infections (incidence rate per 100 person-years)	0 (0.00)	16 (1.69)	YEZTUGO / TRUVADA: 0.000 (0.000, 0.101) p <0.0001

CI = confidence interval

a. 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

In PURPOSE 2, the median age of participants was 29 years (range, 17-74); 67% were non White; 63% were Hispanic/Latine; and 22% identified as gender-diverse (transgender women, transgender men, and gender nonbinary people). Baseline characteristics in the randomized participants were similar to the screened population. 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. YEZTUGO demonstrated superiority with an 89% reduction in the risk of incident HIV-1 infection over TRUVADA (Table 14).

27

14 ▸ Clinical Studies: PURPOSE 1 (continued)

Table 13. Overall HIV-1 Incidence Outcomes in PURPOSE 1[a]

	YEZTUGO N=2134	TRUVADA N=1068	Rate Ratio (95% CI)
Person-years	1939	949	–
HIV-1 infections (incidence rate per 100 person-years)	0 (0.00)	16 (1.69)	YEZTUGO / TRUVADA: 0.000 (0.000, 0.101) *P*<0.0001

There were **2 incident infections**[b] among participants in the YEZTUGO arm of the PURPOSE 1 trial. Both occurred **after** the time of the primary analysis:

- 1 occurred in a participant after LEN exposures fell below the target concentration following discontinuation of YEZTUGO, and virus from this participant had no LEN resistance-associated capsid substitutions
- 1 occurred in a participant with viral loads that were too low for genotyping

[a]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; [b]Infections that occurred after starting YEZTUGO for HIV-1 PrEP.

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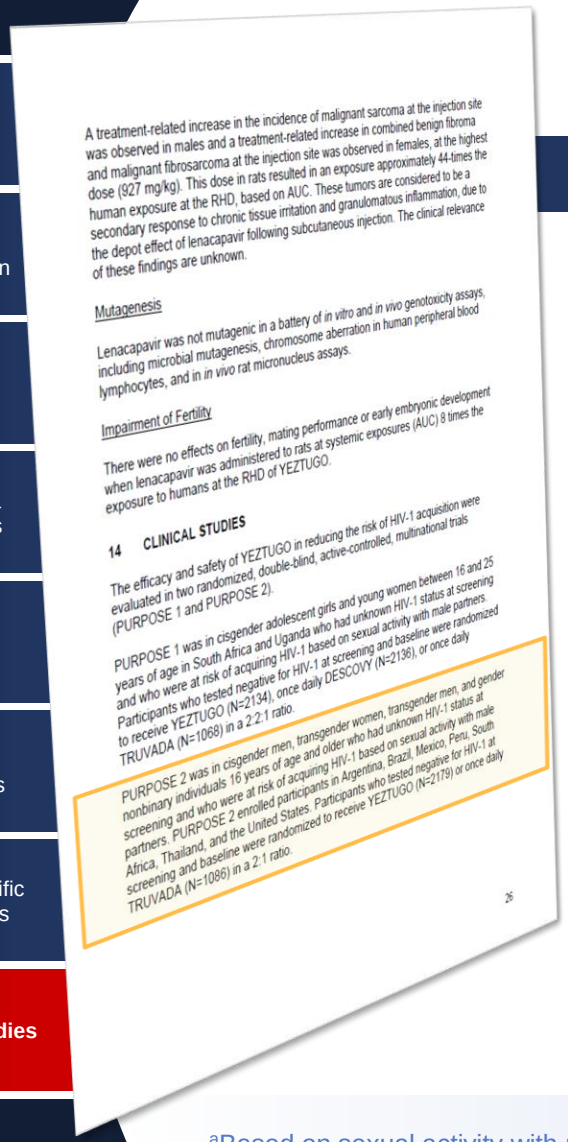
SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

14. Clinical Studies



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26

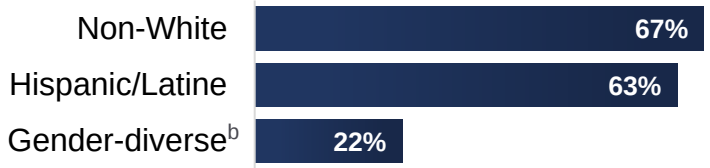
14 ▸ Clinical Studies: PURPOSE 2

Study Design

- PURPOSE 2 was in cisgender men, transgender women, transgender men and gender-nonbinary individuals aged ≥16 years with unknown HIV-1 status at screening and at risk of acquiring HIV-1[a]
- PURPOSE 2 enrolled participants in Argentina, Brazil, Mexico, Peru, South Africa, Thailand and the US
- Participants who tested negative for HIV-1 were randomized to receive YEZTUGO (N=2179) or once-daily TRUVADA (N=1086) in a 2:1 ratio

Baseline Characteristics

Median participant age:
29 years
(range: 17–74)



Baseline characteristics in the randomized participants were similar to those in the screened population

Outcomes/Results at Primary Analysis

- HIV incidence per 100/PY was compared between participants receiving YEZTUGO and TRUVADA
- YEZTUGO demonstrated superiority over TRUVADA, with an 89% reduction in the risk of incident HIV-1 infection (**Table 14**; see next slide)
- YEZTUGO also demonstrated superiority in the risk of incident HIV-1 infection over bHIV

[a]Based on sexual activity with male partners; [b]Transgender women, transgender men and gender-nonbinary people
bHIV, background HIV incidence; PY, person-years

Approved for Use on 18 Aug 2025

SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

14. Clinical Studies

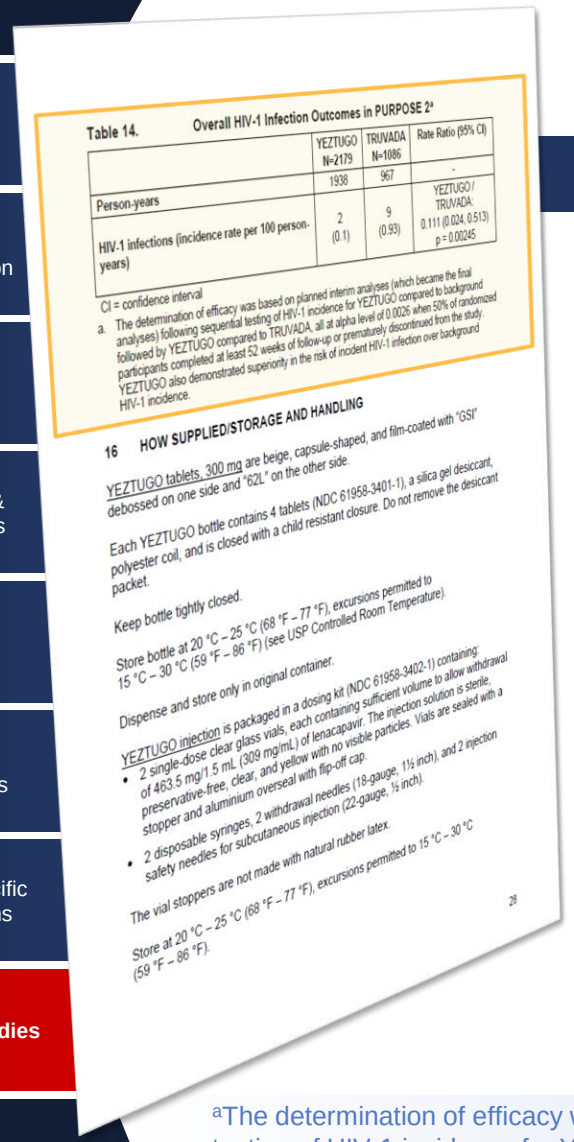


Table 14. Overall HIV-1 Infection Outcomes in PURPOSE 2[a]

	YEZTUGO N=2179	TRUVADA N=1086	Rate Ratio (95% CI)
Person-years	1938	967	-
HIV-1 infections (incidence rate per 100 person-years)	2 (0.1)	9 (0.93)	YEZTUGO / TRUVADA: 0.111 (0.024, 0.513) p = 0.00245

CI = confidence interval

a. 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

YEZTUGO tablets, 300 mg are beige, capsule-shaped, and film-coated with "GSI" debossed on one side and "62L" on the other side.

Each YEZTUGO 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.

Keep bottle tightly closed.

Store bottle at 20 °C – 25 °C (68 °F – 77 °F), excursions permitted to 15 °C – 30 °C (59 °F – 86 °F) (see USP Controlled Room Temperature).

Dispense and store only in original container.

YEZTUGO injection is packaged in a dosing kit (NDC 61958-3402-1) containing:

- 2 single-dose clear glass vials, each containing sufficient volume to allow withdrawal of 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir. The injection solution is sterile, preservative-free, clear, and yellow with no visible particles. Vials are sealed with a stopper and aluminium overseal with flip-off cap.
- 2 disposable syringes, 2 withdrawal needles (18-gauge, 1½ inch), and 2 injection safety needles for subcutaneous injection (22-gauge, ½ inch).

The vial stoppers are not made with natural rubber latex.

Store at 20 °C – 25 °C (68 °F – 77 °F), excursions permitted to 15 °C – 30 °C (59 °F – 86 °F).

28

14 ▸ Clinical Studies: PURPOSE 2 (continued)

Table 14. Overall HIV-1 Incidence Outcomes in PURPOSE 2[a]

	YEZTUGO N=2179	TRUVADA N=1086	Rate Ratio (95% CI)
Person-years	1938	967	-
HIV-1 infections (incidence rate per 100 person-years)	2 (0.1)	9 (0.93)	YEZTUGO / TRUVADA: 0.111 (0.024, 0.513) *P*=0.00245

There were **3 incident infections**[b] among participants in the YEZTUGO arm of the PURPOSE 2 trial:

- 1 occurred **after** the time of primary analysis
- LEN resistance-associated substitutions were detected in viruses from all 3 participants: 2 with N74D, and 1 with Q67H/K70R

[a]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; [b]Infections that occurred after starting YEZTUGO for HIV-1 PrEP.

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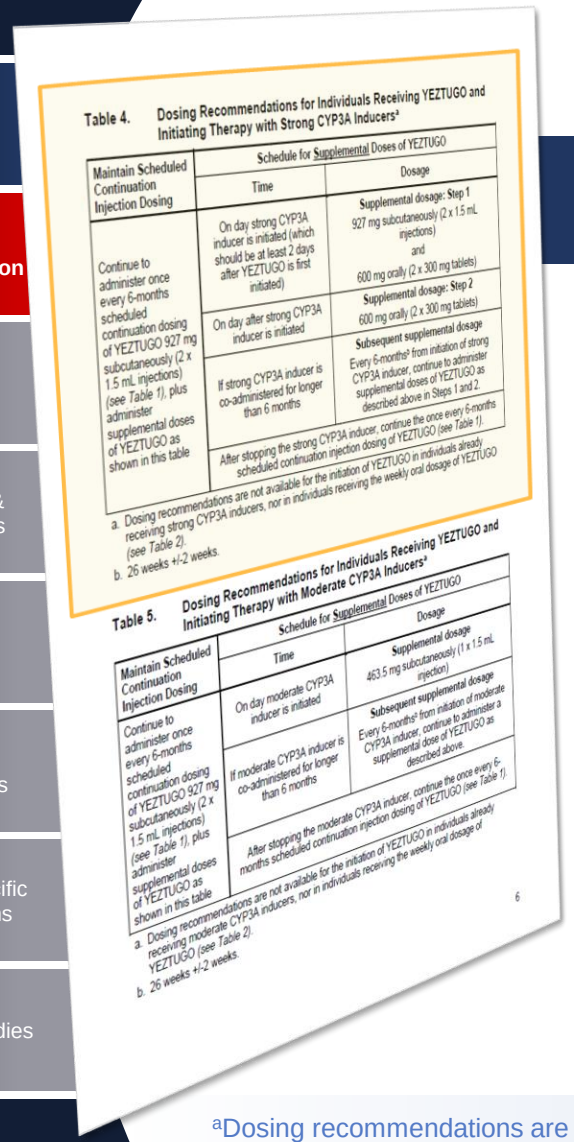
SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

Appendix

2. Dosage and Administration



2.5 Dosage Modifications for Co-administration with Strong or Moderate CYP3A Inducers

Table 4. Dosing Recommendations for Individuals Receiving YEZTUGO and Initiating Therapy with Strong CYP3A Inducers[a]

Maintain Scheduled Continuation Injection Dosing	Schedule for Supplemental Doses of YEZTUGO	
	Time	**Dosage**
Continue to administer once Q6M scheduled continuation dosing of YEZTUGO (see **Table 1**), plus administer supplemental doses of YEZTUGO as shown here:	On day strong CYP3A inducer is initiated (≥2 days after YEZTUGO is first initiated)	**Supplemental dosage: Step 1** 927 mg subcutaneously (2 × 1.5 mL injections) and 600 mg orally (2 × 300 mg tablets)
	On day after strong CYP3A inducer is initiated	**Supplemental dosage: Step 2** 600 mg orally (2 × 300 mg tablets)
	If strong CYP3A inducer is co-administered for >6 months	**Subsequent supplemental dosage** Q6M[b] from initiation of strong CYP3A inducer, continue to administer supplemental doses of YEZTUGO as described above in Steps 1 and 2
	After stopping the strong CYP3A inducer, continue the Q6M scheduled continuation injection dosing of YEZTUGO (see **Table 1**)	

[a]Dosing recommendations are not available for the initiation of YEZTUGO in individuals already receiving moderate CYP3A inducers, nor in individuals receiving the weekly oral dosage of YEZTUGO (see **Table 2**); [b]26 weeks ±2 weeks

CYP3A, cytochrome (P450) 3A; Q6M, every 6 months

Approved for Use on 18 Aug 2025

SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

2. Dosage and Administration

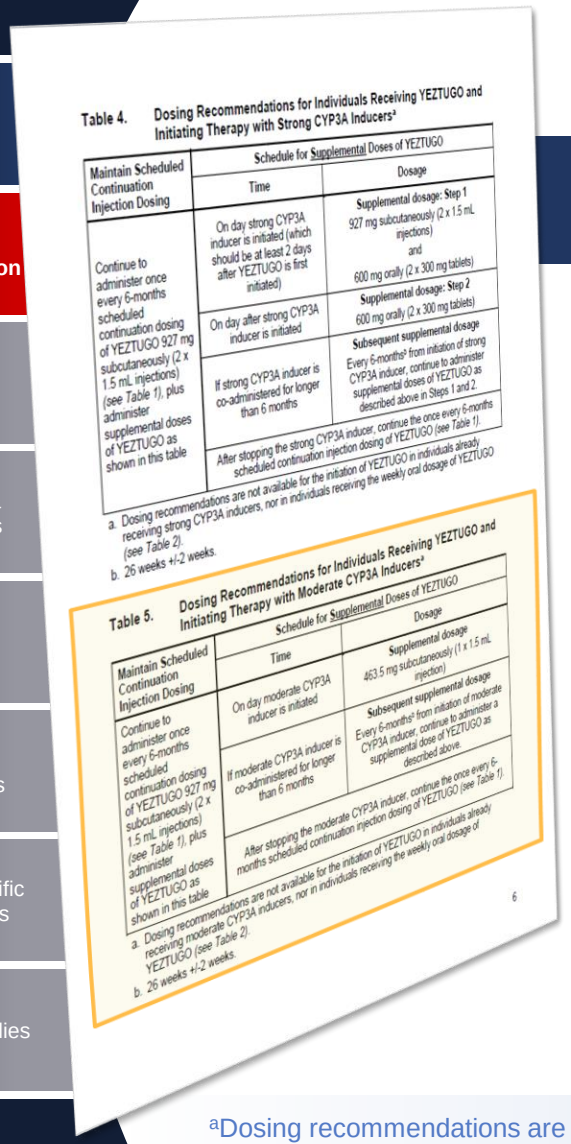


Table 4. Dosing Recommendations for Individuals Receiving YEZTUGO and Initiating Therapy with Strong CYP3A Inducers[a]

Maintain Scheduled Continuation Injection Dosing	Schedule for Supplemental Doses of YEZTUGO	
	Time	Dosage
Continue to administer once every 6-months scheduled continuation dosing of YEZTUGO 927 mg subcutaneously (2 x 1.5 mL injections) (see Table 1), plus administer supplemental doses of YEZTUGO as shown in this table	On day strong CYP3A inducer is initiated (which should be at least 2 days after YEZTUGO is first initiated)	Supplemental dosage: Step 1 927 mg subcutaneously (2 x 1.5 mL injections) and 600 mg orally (2 x 300 mg tablets)
	On day after strong CYP3A inducer is initiated	Supplemental dosage: Step 2 600 mg orally (2 x 300 mg tablets)
	If strong CYP3A inducer is co-administered for longer than 6 months	Subsequent supplemental dosage Every 6-months[b] from initiation of strong CYP3A inducer, continue to administer supplemental doses of YEZTUGO as described above in Steps 1 and 2
After stopping the strong CYP3A inducer, continue the once every 6-months scheduled continuation injection dosing of YEZTUGO (see Table 1).		

a. Dosing recommendations are not available for the initiation of YEZTUGO in individuals already receiving strong CYP3A inducers, nor in individuals receiving the weekly oral dosage of YEZTUGO (see Table 2).
b. 26 weeks +/-2 weeks.

Table 5. Dosing Recommendations for Individuals Receiving YEZTUGO and Initiating Therapy with Moderate CYP3A Inducers[a]

Maintain Scheduled Continuation Injection Dosing	Schedule for Supplemental Doses of YEZTUGO	
	Time	Dosage
Continue to administer once every 6-months scheduled continuation dosing of YEZTUGO 927 mg subcutaneously (2 x 1.5 mL injections) (see Table 1), plus administer supplemental doses of YEZTUGO as shown in this table	On day moderate CYP3A inducer is initiated	Supplemental dosage 463.5 mg subcutaneously (1 x 1.5 mL injection)
	If moderate CYP3A inducer is co-administered for longer than 6 months	Subsequent supplemental dosage Every 6-months[b] from initiation of moderate CYP3A inducer, continue to administer a supplemental dose of YEZTUGO as described above.
After stopping the moderate CYP3A inducer, continue the once every 6-months scheduled continuation injection dosing of YEZTUGO (see Table 1).		

a. Dosing recommendations are not available for the initiation of YEZTUGO in individuals already receiving moderate CYP3A inducers, nor in individuals receiving the weekly oral dosage of YEZTUGO (see Table 2).
b. 26 weeks +/-2 weeks.

6

2.5 ▸ Dosage Modifications for Co-administration with Strong or Moderate CYP3A Inducers

Table 5. Dosing Recommendations for Individuals Receiving YEZTUGO and Initiating Therapy with Moderate CYP3A Inducers[a]

Maintain Scheduled Continuation Injection Dosing	Schedule for Supplemental Doses of YEZTUGO	
	Time	**Dosage**
Continue to administer once Q6M scheduled continuation dosing of YEZTUGO (see **Table 1**), plus administer supplemental doses of YEZTUGO as shown here:	On day moderate CYP3A inducer is initiated	**Supplemental dosage** 463.5 mg subcutaneously (1 × 1.5 mL injection**)**
	If moderate CYP3A inducer is co-administered for >6 months	**Subsequent supplemental dosage** Q6M[b] from initiation of moderate CYP3A inducer, continue to administer a supplemental dose of YEZTUGO as described above
	After stopping the moderate CYP3A inducer, continue the Q6M scheduled continuation injection dosing of YEZTUGO (see **Table 1**)	

[a]Dosing recommendations are not available for the initiation of YEZTUGO in individuals already receiving moderate CYP3A inducers, nor in individuals receiving the weekly oral dosage of YEZTUGO (see **Table 2**); [b]26 weeks ±2 weeks

CYP3A, cytochrome (P450) 3A; Q6M, every 6 months

Approved for Use on 18 Aug 2025

SLD-LEN-NA-US-00012 MRC Approved 18-Aug-2025 External Use and Distribution Proactive Use

YEZTUGO® (lenacapavir) for HIV-1 PrEP

Navigating the US Prescribing Information

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