Drug Coverage Policy

Effective Date.....08/01/2024
Coverage Policy Number.....IP0435
Policy Title.....Apretude

Human Immunodeficiency Virus – Apretude

- Apretude (cabotegravir intramuscular injection – ViiV)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

Overview
Apretude, a human immunodeficiency virus-1 (HIV-1) integrase strand transfer inhibitor (INSTI), is indicated for **pre-exposure prophylaxis (PrEP)** in at-risk adults and adolescents weighing ≥ 35 kg to reduce the risk of sexually acquired HIV-1 infection.[1] Individuals must have a negative HIV-1 test prior to initiating Apretude (with or without an oral lead-in with Vocabria® [cabotegravir tablets]) for HIV-1 PrEP. All individuals should be screened for HIV-1 infection prior to each injection of Apretude.

Dosing
Apretude is administered by intramuscular (IM) gluteal injections and must be given by a healthcare provider. Vocabria *may* be administered for approximately 1 month prior to Apretude

(Table 1) or the patient may proceed directly to Apretude without an oral lead-in (Table 2). If an oral lead-in is used, Apretude should be administered on the last day of oral lead-in or within 3 days thereafter (Table 1). Note: Vocabria is only (and will only ever be) available from the manufacturer.

Initial dosing: The recommended initiation dose of Apretude is two, single 600 mg IM injections, given 1 month apart for 2 consecutive months (Months 1 and 2 if no oral lead-in is used [Months 2 and 3 if oral lead-in is used]).[1] After the initiation injection doses, the recommended continuation dose of Apretude is a single 600 mg IM injection every 2 months (Q2M) [starting at Month 4 if no oral-lead in is used or Month 5 if oral lead-in is used]. Apretude may be given up to 7 days before or after the date of the scheduled injection.

Table 1. Recommended Dosing Schedule (with Oral Lead-in) for PrEP.[1]

Oral Lead-in (at Least 28 Days)	IM (Gluteal) Initiation Injection (Month 2 and Month 3)	IM (Gluteal) Continuation Injection (Month 5 and Q2M Onwards)
Vocabria 30 mg QD for 28 days	Apretude 600 mg (3 mL)[a]	Apretude 600 mg (3 mL)[b]

PrEP – Pre-exposure prophylaxis; IM – Intramuscular; Q2M – Every 2 months; QD – Once daily; [a] Should be administered on the last day of oral lead-in or within 3 days thereafter; [b] Individuals may be given Apretude up to 7 days before or after the date the individual is scheduled to receive the injections.

Table 2. Recommended Dosing Schedule (Direct to Injection) for PrEP.[1]

IM (Gluteal) Initiation Injection (Month 1 and Month 2)	IM (Gluteal) Continuation Injection (Month 4 and Q2M Onwards)
Apretude 600 mg (3 mL)[a]	Apretude 600 mg (3 mL)[a]

PrEP – Pre-exposure prophylaxis; IM – Intramuscular; Q2M – Every 2 months; [a] Individuals may be given Apretude up to 7 days before or after the date the individual is scheduled to receive the injections.

Adherence to the injection dosing schedule is strongly recommended. Individuals who miss a scheduled injection visit should be clinically reassessed to ensure resumption of Apretude remains appropriate.

Planned Missed Injections: If an individual plans to miss a scheduled (Q2M) continuation injection visit by > 7 days, take Vocabria 30 mg once daily (QD) for a duration of up to 2 months to replace one missed scheduled (Q2M) injection. The first dose of Vocabria should be taken approximately 2 months after the last injection dose of Apretude. Restart Apretude on the day Vocabria dosing completes or within 3 days (Table 3). For Vocabria durations > 2 months, an alternative oral regimen is recommended.

Unplanned Missed Injections: If a scheduled injection visit is missed or delayed by > 7 days and oral dosing has not been taken in the interim, clinically reassess the individual to determine if resumption of Apretude remains appropriate (if the injection schedule will be continued, see Table 3).

Table 3. Apretude Dosing Recommendations After Missed Injections.[1]

Time Since Last Injection	Recommendation
Initiation Injection – If the second injection is missed and time since first injection is:	
≤ 2 months	Administer Apretude (600 mg) as soon as possible, then continue to follow the Q2M injection dosing schedule.

> 2 months	Restart Apretude (600 mg) with one injection, followed by a second injection (600 mg) 1 month later. Then continue to follow the Q2M injection dosing schedule thereafter (starting at Month 4).
Maintenance Injection – If third or subsequent injection is missed and time since prior injection is:	
≤ 3 months	Administer Apretude as soon as possible, then continue with the Q2M injection dosing schedule.
> 3 months	Restart Apretude (600 mg) with one injection, followed by a second injection (600 mg) 1 month later. Then continue to follow the Q2M injection dosing schedule thereafter (starting at Month 4).

Q2M – Every 2 months.

Dose modifications for Apretude are needed when administered with rifabutin. When rifabutin is started before or concomitantly with the first initiation injection of Apretude, the recommended dosing of Apretude is one 600 mg injection, followed 2 weeks later by a second 600 mg initiation injection and monthly thereafter while on rifabutin. When rifabutin is started at the time of the second initiation injection or later, the recommended dosing schedule of Apretude is 600 mg monthly while on rifabutin. After stopping rifabutin, the recommended dosing schedule of Apretude is 600 mg Q2M.

Guidelines

Apretude has been incorporated into the US Public Health Service PrEP for the Prevention of HIV Infection in the US Clinical Practice Guidelines (December 2021).[2] The update was published just prior to the FDA approval of Apretude.[2] A guideline available from the International Antiviral Society-USA (IAS-USA) [December 2022] provides similar guidance to the US Public Health Services guidelines.[3] The World Health Organization (WHO) published a guideline on Apretude for PrEP in 2022 to serve as a supplement to their other oral PrEP recommendations.[4] These guidelines are intended for a broader, world-wide audience, but generally echo the US Public Health Service PrEP and IAS-USA guideline recommendations. Table 4 provides a summary of the recommendations for daily oral PrEP and Apretude (every 2 months).

Table 4. US Public Health Service PrEP Recommendations (December 2021).[2]

	Recommendation for PrEP	Evidence Rating
Apretude[a]	For adults and adolescents who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition.	IA
FTC/TDF	For adult and adolescent (≥ 35 kg) **men and women**: • **Sexually active individuals** who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition; OR • **IDU** and report injection practices that place them at substantial ongoing risk of HIV exposure and acquisition.	1A

Table 4 (continued). US Public Health Service PrEP Recommendations (December 2021).[2]

	Recommendation for PrEP	Evidence Rating
Descovy	For adult and adolescent (≥ 35 kg) **cis-gender men**[*] and **transgender women**[†]**:** • **Sexually active individuals** who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition. Descovy PrEP has **not been studied in cis-gender women**[‡] and is **not recommended** for HIV prevention for women or other individuals at risk through receptive vaginal sex (IA).	IA (cis-gender men) IIB (transgender women)

PrEP – Pre-exposure prophylaxis; [a] Conditioned on FDA-approval at the time of guideline publication; HIV – Human immunodeficiency virus; FTC/TDF – Emtricitabine/tenofovir disoproxil fumarate; IDU – Injection drug user(s); [*] Individuals assigned male sex at birth whose gender identity is male; [†] Individuals assigned male sex at birth whose gender identity is female; [‡] Individuals assigned female sex at birth whose gender identity is female.

The US Public Health Service Guidelines also make the following points related to monitoring for PrEP.[2] Prior to prescribing PrEP, acute and chronic HIV infection must be excluded by symptom history and HIV testing must be performed immediately before any PrEP regimen is started (IA). Clinicians should document a negative HIV test result within the week before initiating (or reinitiating) PrEP medications, ideally with an antigen/antibody test conducted by a laboratory. The required HIV test prior to initiation of PrEP can be accomplished in one of two ways: 1) drawing blood and sending the specimen to a laboratory for an antigen/antibody test or 2) performing a rapid, point-of-care, FDA-approved, fingerstick antigen/antibody blood test. For PrEP, rapid tests that use oral fluid should not be used to screen for HIV infection because they are less sensitive for the detection of acute or recent infection than blood tests. HIV infection should be assessed every 2 months for patients receiving Apretude so that individuals with incident infection do not continue taking PrEP. When PrEP is prescribed, clinicians should provide access to support for medication adherence and continuation in follow-up PrEP care (IIA) and additional proven effective risk-reduction services to enable the use of PrEP in combination with other effective prevention methods to reduce risk for sexual acquisition of sexually transmitted infections or blood borne bacterial and viral infections though intravenous drug use (IIIA).

Guidelines from the IAS-USA state that for Apretude, HIV testing at initiation and at all visits should ideally include an HIV RNA tests with a lower limit of quantification of ≤ 50 copies/mL AND a laboratory-based antigen-antibody test.[3] If RNA testing is not available, Apretude can still be considered using antigen/antibody screening only. Results of such testing do not need to be available to provide injections.

The WHO guidelines for Apretude in PrEP enforce that HIV testing prior to offering Apretude is required and should be continued prior to each injection with Apretude.[4] Only individuals who are HIV-negative should be initiated on PrEP. HIV testing can be conducted using quality-assured serology assays (i.e., rapid diagnostic tests and enzyme immunoassays).

Medical Necessity Criteria

Apretude is considered medically necessary when the following are met:

FDA-Approved Indication

1. **Pre-exposure Prophylaxis (PrEP) of Human Immunodeficiency Virus (HIV)-1 Infection.** Approve for 2 months if the patient meets the following (A, B, C, and D):
   - **A)** Patient is ≥ 35 kg; AND
   - **B)** Patient meets both of the following conditions (i and ii):
     - **i.** The medication will be administered only if the patient has a negative HIV-1 test result ≤ 1 week prior to the dose of Apretude; AND
     - **ii.** The medication will be administered only if the patient has no signs or symptoms of acute HIV infection, according to the prescriber: AND
   - **C)** The medication is prescribed as part of a comprehensive HIV-1 prevention strategy (i.e., adherence to administration schedule and safer sex practices, including condoms); AND
   - **D)** The medication is prescribed by or in consultation with a physician who specializes in the management of HIV infection.

   Dosing. Approve the following dosing regimens (A or B):
   - **A)** Approve 600 mg intramuscularly for one dose, followed by 600 mg for a second dose 1 month later, then approve 600 mg intramuscularly once every 2 months thereafter.
   - **B)** If Apretude will be given concomitantly with rifabutin, approve Apretude 600 mg intramuscularly for one dose, followed by 600 mg for a second dose 2 weeks later, then approve 600 mg intramuscularly once-monthly thereafter.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Treatment of Human Immunodeficiency Virus (HIV).** Apretude is not indicated for the treatment of HIV. It is inadequate therapy for established HIV infection and use in persons with early HIV infection may encourage resistance of one or more of the PrEP medications.[2]

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0739	Injection, cabotegravir, 1 mg

References

1. Apretude® injectable suspension [prescribing information]. Research Triangle Park, NC: ViiV; December 2023.
2. Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. Available at: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. Published December 2021. Accessed on: January16, 2024.
3. Ghandi RT, Bedimo R, and Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults. 2022 recommendations of the International Antiretroviral Society-USA Panel. *JAMA*. 2023;329(1):63-84.
4. Guidelines on long-acting injectable cabotegravir for HIV prevention. Geneva: World Health Organization; 2022. License: CC BY-NC-SA 3.0 IGO. Available at: https://www.who.int/publications/i/item/9789240054097. Accessed on January 16, 2024.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Pre-exposure Prophylaxis (PrEP) of Human Immunodeficiency Virus (HIV)-1 Infection:** **Decreased** the approval duration from 12 months to two months. **Added** a requirement for the patient to have had a negative HIV-1 test no more than 1 week prior to the dose of Apretude. **Added** a requirement for the patient to have no signs or symptoms of acute HIV infection. **Added** a specialist prescribing requirement. **Added** dosing information.	08/01/2024

The policy effective date is in force until updated or retired.