Long-Acting Injectable Antiretroviral Agents for HIV

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Instructions for Use

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Coverage Rationale

See Benefit Considerations

This policy refers to the following long-acting injectable antiretroviral products:

- Apretude (cabotegravir)
- Cabenuva (cabotegravir/rilpivirine)

Apretude (cabotegravir)

Apretude (cabotegravir) is proven to reduce the risk of sexually acquired HIV-1 infection in at-risk adults and adolescents weighing at least 35kg. Apretude is medically necessary when the following additional criteria are met:[5-6]

- For initial therapy, all of the following:
  - Used for HIV-1 pre-exposure prophylaxis (PrEP); and
  - Patient has a negative HIV-1 test; and
  - Provider confirms that the patient will be tested for HIV-1 infection with each subsequent injection; and
  - Patient is not an appropriate candidate for oral PrEP (e.g. difficulty with adherence to prior oral PrEP, significant renal disease); and
  - Provider attests that patient demonstrates treatment readiness by both of the following:
    - Patient understands the risks of missed doses of Apretude
    - Patient has the ability to adhere to the required every 2 months injection and testing appointments

    and
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Initial authorization is for no more than 12 months.
- For continuation therapy, all of the following:
  - Patient has previously received treatment with Apretude; and
  - Patient has a negative HIV-1 test; and
  - Provider confirms that the patient will be tested for HIV-1 infection with each subsequent injection; and
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Authorization is for no more than 12 months.

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Apretude is unproven and not medically necessary for the treatment of human immunodeficiency virus type-1 (HIV-1).

Cabenuva (cabotegravir/rilpivirine)

Cabenuva (cabotegravir/rilpivirine) is proven for the treatment of a human immunodeficiency virus type-1 (HIV-1) in patients who are virologically suppressed (HIV-1 RNA less than 50 copies per mL). Cabenuva is medically necessary when the following additional criteria are met:[1-3]

- For initial therapy, all of the following:
  - Diagnosis of HIV-1 infection; and
  - Patient has no prior virologic failures or baseline resistance to either cabotegravir or rilpivirine; and
  - Patient is currently on a stable antiretroviral regimen; and
  - Submission of medical records (e.g., chart notes, laboratory results) showing viral suppression (HIV-1 RNA less than 50 copies per mL) for at least 6 months prior to initiation of Cabenuva; and
  - Provider attests that patient demonstrates treatment readiness by both of the following:
    - Patient understands the risks of missed doses of Cabenuva
    - Patient has the ability to adhere to the required monthly or every 2 months injection appointments;

    and
  - Provider confirms that tolerability will be assessed using a 28-day oral lead-in of Vocabria (cabotegravir) and Edurant® (rilpivirine) tablets prior to the first injection of Cabenuva; and
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Initial authorization is for no more than 12 months.
- For continuation therapy, all of the following:
  - Patient has previously received treatment with Cabenuva; and
  - Provider confirms that the patient has achieved and maintained viral suppression (HIV-1 RNA less than 50 copies per mL) while on Cabenuva therapy; and
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Authorization is for no more than 12 months.

Cabenuva is unproven and not medically necessary for the treatment of human immunodeficiency virus type-1 (HIV-1) in patients who are not currently virally suppressed (HIV-1 RNA less than 50 copies per mL).

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage, but do not guarantee coverage of the service requested.

HCPCS Codes*	Required Clinical Information
Cabenuva	
J0741	For initial therapy requests, medical notes or laboratory results documenting viral suppression (HIV-1 RNA less than 50 copies per mL) for at least 6 months prior to initiation of Cabenuva.

*For code description, refer to the Applicable Codes section.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0739	Injection, cabotegravir, 1mg

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HCPCS Code	Description
J0741	Injection, cabotegravir and rilpivirine, 2 mg/3 mg

Diagnosis Code	Description
B20	Human immunodeficiency virus [HIV] disease
Z11.3	Encounter for screening for infections with a predominantly sexual mode of transmission
Z11.4	Encounter for screening for human immunodeficiency virus [HIV]
Z20	Contact with and (suspected) exposure to communicable diseases
Z20.2	Contact with and (suspected) exposure to infections with a predominantly sexual mode of transmission
Z20.6	Contact with and (suspected) exposure to human immunodeficiency virus (HIV)
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
Z72.5	High risk sexual behavior
Z72.51	High risk heterosexual behavior
Z72.52	High risk homosexual behavior
Z72.53	High risk bisexual behavior

Background

Apretude (cabotegravir) inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. Blocking this key function within the HIV replication cycle plays a role in both treatment and prevention.

Cabenuva (cabotegravir/rilpivirine) is a 2-drug co-packaged product of extended-release injectable suspension formulations of cabotegravir, a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI). Cabotegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Rilpivirine is a diarylpyrimidine NNRTI of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT).[1]

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

The efficacy of Apretude has been evaluated in two randomized, double-blind, controlled, multinational trials:[5,7]

- Trial 201738 (HPTN 083 [NCT02720094]), (n = 4,566): HPTN 083 was a non-inferiority study in cisgender men and transgender women who have sex with men who were randomized 1:1 and received either Apretude (n = 2,281) or Truvada (n = 2,285) as a blinded study up to Week 153. At baseline, the median age of participants was 26 years, 12% were transgender women, 72% were non-White, and 67% were younger than 30 years. The primary endpoint was the rate of incident HIV-1 infections among participants randomized to daily oral cabotegravir and intramuscular injections of Apretude every 2 months compared with daily oral Truvada (corrected for early stopping). The primary analysis demonstrated the superiority of Apretude compared with Truvada with a 66% reduction in the risk of acquiring HIV-1 infection, hazard ratio

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(95% CI) 0.34 (0.18, 0.62); further testing revealed 1 of the infections on Apretude to be prevalent then yielding a 69% reduction in the risk of HIV-1 incident infection relative to Truvada.
- Trial 201739 (HPTN 084 [NCT03164564]), (n = 3,224): HPTN 084 was a superiority study in cisgender women who were randomized 1:1 and received either Apretude (n = 1,614) or Truvada (n = 1,610) as blinded study medication up to Week 153. At baseline, the median age of participants was 25 years, > 99% were non-White, >99% were cisgender women, and 49% were < 25 years of age. The primary endpoint was the rate of incident HIV-1 infections among participants randomized to oral cabotegravir and injections of Apretude compared with oral Truvada (corrected for early stopping). The primary analysis demonstrated the superiority of Apretude compared with Truvada with an 88% reduction in the risk of acquiring incident HIV-1 infection, hazard ratio (95% CI) 0.12 (0.05, 0.31); further testing revealed 1 of the infections on Apretude to be prevalent then yielding a 90% reduction in the risk of HIV-1 incident infection relative to Truvada.

In December 2021, the Centers for Disease Control and Prevention published the US Public Health Service Pre-Exposure Prophylaxis for the Prevention of HIV Infection in the United States – 2021 Update – A Clinical Practice Guideline.[6] The updated included a new section about prescribing PrEP with intramuscular injections of cabotegravir in anticipation of likely FDA approval in early 2022. A recommendation was added that states PrEP with intramuscular cabotegravir injections (conditional on FDA approval) is recommended for HIV prevention in adults reporting sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition. Regarding prescribing cabotegravir PrEP injections, the following information is included: "Patients considering PrEP should be informed of all FDA approved options. Cabotegravir injections may be especially appropriate for patients with significant renal disease, those who have had difficulty with adherent use of oral PrEP and those who prefer injections every 2 months to an oral PrEP dosing schedule."

The efficacy of Cabenuva has been evaluated in three Phase 3 randomized, multicenter, active-controlled, parallel-arm, open-label, non-inferiority trials:[1-3]
- Trial 201584 (FLAIR, [NCT02938520]), (n = 629): HIV-1–infected, antiretroviral treatment (ART)- naive subjects received a dolutegravir INSTI-containing regimen for 20 weeks (either dolutegravir/abacavir/lamivudine or dolutegravir plus 2 other NRTIs if subjects were HLA-B*5701 positive). Subjects who were virologically suppressed (HIV-1 RNA less than 50 copies/mL, n = 566) were then randomized (1:1) to receive either a cabotegravir plus rilpivirine regimen or remain on the current antiretroviral regimen. Subjects randomized to receive cabotegravir plus rilpivirine initiated treatment with daily oral lead-in dosing with one 30-mg Vocabria (cabotegravir) tablet plus one 25-mg Edurant (rilpivirine) tablet for at least 4 weeks followed by monthly injections with Cabenuva for an additional 44 weeks.
- Trial 201585 (ATLAS, [NCT02951052]), (n = 616): HIV-1–infected, ART-experienced, virologically-suppressed (for at least 6 months; median prior treatment duration was 4.3 years) subjects (HIV-1 RNA less than 50 copies/mL) were randomized and received either a cabotegravir plus rilpivirine regimen or remained on their current antiretroviral regimen. Subjects randomized to receive cabotegravir plus rilpivirine initiated treatment with daily oral lead-in dosing with one 30-mg Vocabria (cabotegravir) tablet plus one 25-mg Edurant (rilpivirine) tablet for at least 4 weeks followed by monthly injections with Cabenuva for an additional 44 weeks.
- Trial 207966 (ATLAS-2M, [NCT03299049]), (n = 1,045): HIV-1–infected, ART-experienced, virologically suppressed subjects, including 504 subjects from the ATLAS trial (randomized to CAB plus RPV [n = 253] or CAR [n = 251]; prior exposure to cabotegravir plus rilpivirine [n = 391]), were randomized and received a cabotegravir plus rilpivirine regimen administered as injection doses of cabotegravir 400 mg plus rilpivirine 600 mg either monthly or cabotegravir 600 mg plus rilpivirine 900 mg every 2 months. Subjects without prior exposure to cabotegravir plus rilpivirine initiated treatment with daily oral lead-in dosing with one 30-mg VOCABRIA (cabotegravir) tablet plus one 25-mg Edurant (rilpivirine) tablet for at least 4 weeks followed by monthly or every-2-month injections with Cabenuva for an additional 44 weeks. The primary endpoint of ATLAS-2M was the proportion of subjects with a plasma HIV-1 RNA ≥50 copies/mL at Week 48. The primary endpoint was met with 2% of subjects in the every 2-month dosing arm having an HIV-RNA ≥ 50 copies/mL compared to 1% in the monthly dosing arm.

The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the trial prematurely. The primary endpoint of FLAIR and ATLAS was the proportion of subjects with plasma HIV-1 RNA greater than or equal to 50 copies/mL at Week 48. In both FLAIR and ATLAS 2% of subjects met the primary endpoint as compared to 2% and 1% in the comparator arms respectively. Subjects in both the FLAIR and ATLAS trials were virologically suppressed prior to Day 1 or at study entry, respectively, and no clinically relevant change from baseline in CD4+ cell counts was observed.[1]

In February 2021, the United States Department of Health and Human Services updated their guidelines for the use of antiretroviral agents in adults and adolescents with HIV with specific recommendations for use of Cabenuva. The guidelines

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panel made the following recommendation: “Cabenuva can be used as an optimization strategy for people with HIV currently on oral ART with documented viral suppression for at least 3 months (although optimal duration is not defined)”.[4] In the ATLAS trial, participants had viral suppression for at least 6 months on standard oral ART prior to randomization. A key consideration noted by the guidelines panel includes “experienced participants enrolled in completed clinical trials for Cabenuva were selected based on their history of good adherence and engagement in care, as documented by sustained viral suppression at baseline. Therefore, these therapies are currently recommended for participants who are similarly engaged in care.” The Panel does not recommend Cabenuva as initial therapy for people with HIV at this time.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Apretude (cabotegravir) is an HIV-1 integrase strand transfer inhibitor (INSTI) indicated in at-risk adults and adolescents weighing at least 35 kg for HIV-1 Pre-Exposure Prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test prior to initiating Apretude (with or without an oral lead-in with oral cabotegravir) for HIV-1 PrEP.[5]

Cabenuva, a 2-drug co-packaged product of cabotegravir, a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

References

1. Cabenuva [package insert]. Research Triangle Park, NC: ViiV Healthcare. February 2022.
2. Swindells S, et al. Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression (ATLAS). N Engl J Med. 2020 March 382:1112-1123.
3. Orkin C, et al. Long-Acting Cabotegravir and Rilpivirine after Oral Induction for HIV-1 Infection (FLAIR). N Engl J Med. 2020 March 382:1124-1135.
4. U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Updated January 20, 2022. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/guidelines-adult-adolescent-arv.pdf.
5. Accessed February 13, 2022.
6. Apretude [package insert]. Research Triangle Park, NC: ViiV Healthcare. December 2021.
7. 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. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf Published December 2021
8. Landovitz R.J., et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women (HPTN 083). N Engl J Med. 2021 August 385:595-608.

Policy History/Revision Information

Date	Summary of Changes
07/01/2022	**Coverage Rationale** • Removed reference link to the Medical Benefit Drug Policy titled *Review at Launch for New to Market Medications* for Apretude (cabotegravir); prior authorization requirements effective Jul. 1, 2022 **Applicable Codes** • Updated list of applicable HCPCS codes to reflect quarterly edits; replaced C9399 and J3490 with J0739

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Date	Summary of Changes
	Supporting Information • Archived previous policy version 2022D00103D

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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Nondiscrimination & Language Access Policy

Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, sex, sexual orientation, or gender identity. *We* do not exclude people or treat them differently because of race, color, national origin, age, disability, sex, sexual orientation, or gender identity.

We will:
Provide free aids and services to people with disabilities to communicate effectively with us, such as:
- Qualified sign language interpreters
- Written information in other formats (large print, audio, accessible electronic formats, other formats)

Provide free language services to people whose primary language is not English, such as:
- Qualified interpreters
- Information written in other languages

If *you* need these services, contact *us* at the phone number shown on the inside cover of this *contract*, *your* id card, or aspirushealthplan.com.

If *you* believe that *we* have failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, sex, sexual orientation, or gender identity, *you* can file a grievance with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1062
Minneapolis, MN 55440
Phone: 1.866.631.5404 (TTY: 711)
Fax: 763.847.4010
Email: customerservice@aspirushealthplan.com

You can file a grievance in person or by mail, fax, or email. If *you* need help filing a grievance, the Nondiscrimination Grievance Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1.866.631.5404 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً . اتصل بن اعلى رقم الهاتف 1.866.631.5404(رقم هاتف الصم والبك : 711)

French: ATTENTION : Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelezle 1.866.631.5404 (ATS : 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1.866.631.5404 (TTY: 711).

Hindi: _यान द_: य_द आप ि◌हंदी बोलते ह_ तो आपके ि◌लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_। 1.866.631.5404 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1.866.631.5404 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 1.866.631.5404 (TTY: 711)번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 1.866.631.5404 (TTY: 711).

Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода.Звоните 1.866.631.5404 (телетайп: 711).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 1.866.631.5404 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1.866.631.5404 (TTY: 711)

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Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1.866.631.5404 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1.866.631.5404 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັ້ງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1.866.631.5404 (TTY:711).

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