February 1, 2022

VIA ELECTRONIC SUBMISSION: ncdrequest@cms.hhs.gov
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Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services
7500 Security Boulevard
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RE: Formal Request for National Coverage Determination for Provider-Administered Pre-Exposure Prophylaxis (PrEP) for HIV Prevention

Dear Director Syrek Jensen and Deputy Director Chin:

ViiV Healthcare (ViiV) hereby submits a complete, formal request for a National Coverage Determination (NCD) for Provider-Administered PrEP for HIV Prevention. This request is based on the clinical evidence and other information supporting FDA approval of APRETUDE (cabotegravir extended-release injectable suspension), the first FDA-approved provider-administered option for PrEP for HIV prevention.

HIV continues to be a global public health crisis, with an estimated 38 million people living with HIV around the world and 1.5 million new cases in 2020.[1] In the United States, an estimated 1.1 million people are living with HIV and there are approximately 37,000 new HIV diagnoses each year.[2] Provider-administered PrEP is an effective tool to reduce new cases of HIV which, in addition to successful HIV antiretroviral treatment, will help efforts to end the HIV epidemic. However, only 18% of the approximately 1.2 million people who could benefit from PrEP in the United States are currently taking it.[3] Despite the availability of daily oral PrEP for

[1] HIV.gov Global HIV/AIDS Overview.
[2] Centers for Disease Control and Prevention, HIV Surveillance Report, Diagnoses of HIV Infection in the United States and Dependent Areas 2019: vol. 32.
[3] HIV National Strategic Plan 2021-2025.

over a decade,[4] its effectiveness can be limited by inconsistent adherence as well as structural and cultural barriers that lead to underutilization in key populations, perpetuating health disparities. In the United States, 42% of new HIV diagnoses in 2019 occurred among Black individuals, and 28% occurred among Hispanic/Latinx individuals.[5]

ViiV, a global specialist HIV company established in 2009, is the only company 100 percent dedicated to combating, preventing, and ultimately curing HIV. ViiV specializes in the development of therapies for HIV infection and is devoted exclusively to advancing science into HIV treatment, prevention and care. From its inception, ViiV has had a singular focus to improve the health and quality of life of people affected by this disease and has worked to address significant gaps and unmet needs in HIV care. ViiV is proud of the scientific advances in the treatment and prevention of this disease, which have helped to transform HIV from a terminal illness to a manageable chronic condition. In collaboration with the HIV community, ViiV remains committed to developing meaningful HIV treatment and prevention advances, improving access to its HIV medicines, and supporting the HIV community to facilitate enhanced care, prevention and treatment. ViiV is privileged to be responsible for the development of APRETUDE, the first FDA-approved provider-administered option for PrEP for HIV prevention.

1. Medicare Benefit Category

Provider-administered PrEP is a Medicare Part B product that falls within the "additional preventive services" Medicare benefit category and is, therefore, eligible for an NCD. Pursuant to Section 1861(ddd) of the Social Security Act, the Secretary of Health and Human Services is authorized to provide Medicare coverage for "additional preventive services" if certain statutory requirements are met.[6] Specifically, the Secretary must determine that the services are:

- Reasonable and necessary for the prevention or early detection of an illness or disability;
- Recommended with a grade of A or B by the United States Preventive Services Task Force (USPSTF); and
- Appropriate for individuals entitled to benefits under Part A or enrolled under Part B.

Provider-administered PrEP satisfies each of the above requirements. First, as set forth in more detail below, the scientific evidence supporting APRETUDE's clinical indications demonstrates that provider-administered PrEP is reasonable and necessary for HIV prevention.

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[4] Until APRETUDE was approved by FDA, only oral PrEP therapies (once-daily tablets) were available. These include TRUVADA (tenofovir disoproxil fumarate 300 mg in combination with emtricitabine 200 mg) and DESCOVY (tenofovir alafenamide 25 mg in combination with emtricitabine 200 mg). Multi-source generic TRUVADA is also available.

[5] Centers for Disease Control and Prevention, HIV Surveillance Report, Diagnoses of HIV Infection in the United States and Dependent Areas 2019: vol. 32.

[6] *See also* 42 C.F.R. § 410.64.

Second, the current USPSTF recommendation for Preexposure Prophylaxis for the Prevention of HIV Infection (issued in June 2019) is a Grade A recommendation for PrEP as a preventive service indication. This recommendation referenced evidence supporting the products available for PrEP at the time, which included only oral products (i.e., combined tenofovir disoproxil fumarate and emtricitabine or, as an alternative, oral tenofovir disoproxil fumarate monotherapy). The USPSTF Grade A recommendation is for PrEP as a preventive service without specific reference to the drug regimen utilized.[7]

In November 2021, given the recent availability of clinical evidence regarding newer PrEP regimens (i.e., oral tenofovir alafenamide-emtricitabine, injectable cabotegravir and the dapivirine vaginal ring), the USPSTF initiated a process to further refine the Grade A recommendation for PrEP to include these newer regimens.[8] The USPSTF will assess the comparative benefits and harms of these newer regimens versus tenofovir disoproxil fumarate-emtricitabine, as well as comparing PrEP generally to placebo or no PrEP for a number of different considerations. That process is ongoing and may take 12-24 months to complete.

CMS should not wait until the USPSTF refinement process concludes to initiate a National Coverage Analysis for provider-administered PrEP. Any delay will result in Medicare beneficiaries not having access to this clinically superior option for HIV prevention, notwithstanding the FDA approval of APRETUDE and its availability on the market to individuals with other health insurance coverage.[9] Moreover, the Centers for Disease Control and Prevention (CDC) specifically recommends PrEP with intramuscular cabotegravir injections for HIV prevention in adults reporting sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition (IA Recommendation).[10] The International Antiviral Society-USA Panel also recommends long-acting injectable cabotegravir for cisgender men and transgender women who have sex with men (AIa Recommendation).[11] As explained in more detail below, the clinical evidence supporting FDA approval of APRETUDE demonstrates that APRETUDE is superior to daily oral PrEP options for certain at-risk populations.

Provider-administered PrEP is a critical tool in advancing health equity among individuals at risk of exposure to HIV, as well as furthering President Biden's commitment to

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[7] USPSTF Recommendation for Prevention of HIV Infection: Preexposure Prophylaxis (June 2019), Recommendation Summary ("The USPSTF recommends that clinicians offer preexposure prophylaxis (PrEP) with effective antiretroviral therapy to persons who are at high risk of HIV acquisition."). This approach is similar to that taken by CMS when issuing NCDs that encompass coverage for a procedure or service based on the clinical evidence that exists at the time for particular products that are used in that procedure or service. The procedure or service is subject to the coverage determination as a general matter, and newer products that become available are also subject to the coverage determination unless CMS reevaluates its coverage determination to further refine its earlier assessment in light of additional evidence.

[8] Update in Progress for USPSTF Recommendation for Prevention of HIV Infection: Preexposure Prophylaxis.

[9] *See, e.g.*, California Insurance Commissioner Bulletin 2021-10 (December 29, 2021) (requiring all non-grandfathered group and individual health insurance policies to cover provider-administered PrEP without cost sharing, prior authorization or step therapy).

[10] U.S. Public Health Service, Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2021 Update, A Clinical Practice Guideline.

[11] Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults, 2020 Recommendations of the International Antiviral Society-USA Panel (JAMA 2020;324(16):1651-1669).

end the HIV/AIDS epidemic by 2030.[12] Waiting for the USPSTF to incorporate information about newer PrEP regimens into its Grade A recommendation before initiating a National Coverage Analysis for provider-administered PrEP will unnecessarily delay these important efforts. Given that the USPSTF's current Grade A recommendation, by its terms, broadly applies to all PrEP therapies (even if it was based on clinical evidence supporting daily oral tenofovir disoproxil fumarate-emtricitabine), it is appropriate to apply the USPSTF's current Grade A recommendation for PrEP to APRETUDE.

Finally, provider-administered PrEP is appropriate for individuals enrolled under Medicare Part B. Data show that the Medicare program covers approximately 10% of individuals who could benefit from PrEP, including primarily younger individuals who are eligible for Medicare based on disability.[13] Indeed, patients under age 65 account for approximately 65% of total monthly Medicare claims for PrEP.[14]

2. Description of Provider-Administered PrEP for HIV Prevention

APRETUDE (cabotegravir extended-release injectable suspension) is an HIV-1 integrase strand transfer inhibitor (INSTI) for use in at-risk adults and adolescents weighing at least 35 kilograms (77 pounds) for PrEP to reduce the risk of sexually acquired HIV-1 infection.

APRETUDE is administered as two initiation injections one month apart, and then every two months thereafter for as long as HIV prevention is indicated and desired. Dosing consists of one gluteal intramuscular injection of cabotegravir long-acting (600 mg/3 mL) that must be administered by a health care professional. Patients can either initiate their PrEP medication directly with APRETUDE or take daily, oral cabotegravir (30 mg tablet) (VOCABRIA) as an optional "lead-in" for four weeks to assess tolerability before receiving APRETUDE.

Screening for HIV using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection must occur prior to initiating administration of APRETUDE (or oral cabotegravir lead-in) and with each subsequent injection.

APRETUDE is supplied in a kit containing one 600 mg/3 mL (200 mg/mL) vial of cabotegravir extended-release injectable suspension, 1 syringe, 1 syringe adapter, and 1 needle for intramuscular injection (23 gauge, 1 ½ inch) (NDC 49702-264-23).[15]

3. Clinical Evidence Supporting Reasonable and Necessary Determination

The pivotal studies upon which FDA approval of APRETUDE was based strongly support a determination that APRETUDE is reasonable and necessary for the prevention of HIV infection in Medicare beneficiaries.

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[12] By 2025, the HIV National Strategic Plan has set a key target to increase PrEP coverage to 50% from a 2017 baseline of 12.6%.
[13] Data derived from ViiV Healthcare's proprietary IQVIA PrEP Lives Dataset 2020 refresh (reflective of medical and pharmacy benefits).
[14] IQVIA APLD Weekly Patient Regimen (includes DESCOVY, TRUVADA and generic TRUVADA claims for PrEP identified patients).
[15] APRETUDE Prescribing Information.

FDA's approval of APRETUDE was based on two large multinational, randomized, double-blind, active controlled clinical trials—HPTN 083[16] and HPTN 084[17]—comparing cabotegravir extended-release injectable suspension to once-daily oral tenofovir disoproxil fumarate in combination with emtricitabine (TRUVADA).

HPTN 083 was conducted in 43 sites across 7 countries and included 4,566 cisgender men and transgender women who have sex with men at risk for HIV infection. The trial compared the rate of incident HIV infections among trial participants taking APRETUDE injections every two months compared to daily oral TRUVADA. The trial demonstrated that participants who took APRETUDE had **69% less risk of becoming infected with HIV** when compared to participants who took TRUVADA.

In HPTN 084, 3,224 cisgender women at risk of acquiring HIV based in 20 sites in 7 countries in sub-Saharan Africa received either APRETUDE or TRUVADA. The trial compared the rate of incident HIV infections in participants who took APRETUDE injections every two months to those who took daily oral TRUVADA. Participants who took APRETUDE had **90% less risk of getting infected with HIV** when compared to participants who took TRUVADA.

It should be noted that both HPTN 083 and HPTN 084 studies were reviewed periodically by independent data and safety monitoring boards (DSMBs). At their first pre-planned reviews, the DSMBs for each study concluded that the results for each study met predetermined criteria for stopping the blinded phase of the studies early due to established efficacy of APRETUDE.

Results from the clinical trials suggest that there may be adherence benefits to APRETUDE. In HPTN 083, the proportion of subjects maintaining ≥ 4 days/week adherence to oral TRUVADA declined from 82% to 67% over the study time period, whereas 91.5% of the cabotegravir injectable arm were adherent to their injection visit schedule over the course of the study. In HPTN 084, daily oral dosing adherence to TRUVADA dropped from 66% to 34% between weeks 4 and 57 while injection visit adherence remained steady at approximately 90% throughout.

In HPTN 083, participants in the U.S. were inclusive of the Black/African American and Latinx communities of men and transgender women who have sex with men, who are disproportionately affected by the HIV epidemic and comprise the greatest percentage of new HIV diagnoses. In HPTN 084, all participants were cisgender women from sub-Saharan Africa, as women in this region bear a disproportionate burden of the global HIV epidemic and may be twice as likely to acquire HIV as their male counterparts.

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[16] HIV Prevention Trials Network (HPTN) 083: A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), for Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men.

[17] HIV Prevention Trials Network (HPTN) 084: A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women.

4. Status of FDA Regulatory Review

APRETUDE was approved by the FDA on December 20, 2021, after having been granted Priority Review and Breakthrough Therapy designation.[18]

5. Request for Medicare Coverage

ViiV hereby requests that CMS issue an NCD that extends Medicare coverage to provider-administered PrEP for HIV prevention if the following coverage criteria are met:

- The Medicare beneficiary weighs at least 35 kg;
- The Medicare beneficiary is confirmed HIV-negative immediately prior to initiating use and with each injection; and
- The Medicare beneficiary is at risk of acquisition of HIV-1 infection.

Frequency of utilization is consistent with the FDA-approved label for APRETUDE, that is, two initiation injections (1 month apart for 2 consecutive months) followed by continuation injections once every 2 months for as long as reduction of risk is indicated and desired.

* * *

Thank you for your consideration of this request. ViiV looks forward to working with you to ensure that Medicare beneficiaries at risk of HIV infection have access to the first FDA-approved provider-administered option for PrEP. Ensuring access to provider-administered PrEP is a critical component of HIV prevention, in particular, for vulnerable and minority populations that exhibit disparate need, use and adherence to daily oral options for PrEP. Medicare coverage for provider-administered PrEP for HIV prevention will further the health equity priorities of the Biden Administration and CMS.

We urge CMS to initiate a National Coverage Analysis for provider-administered PrEP as soon as possible.

Sincerely,

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[18] APRETUDE Prescribing Information.