Written Testimony: Arizona Health Care Cost Containment System (AHCCS), *Apretude*

This document is a written testimony intended to summarize the key points below required for the Arizona Health Care Cost Containment System (AHCCS) review of *Apretude* (cabotegravir extended-release injectable suspension [CAB LA]) for intramuscular (IM) use.

Indication

Apretude is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection.(PI,2.2.1) 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.

Boxed Warnings (see attached Prescribing Information, Section 5, for further information)

Individuals must be tested for HIV-1 infection prior to initiating *Apretude* or oral cabotegravir, and with each subsequent injection of *Apretude*, using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection.(PI, 2.1.1)

Dosing

Prior to initiating *Apretude*, an oral lead-in therapy may be used for about one month to assess the tolerability of *Apretude*.(PI, 2.4.1) *Apretude* is for IM gluteal injection only. Initiate *Apretude* with a single 600 mg (3 mL) injection given 1 month apart for 2 consecutive months on the last day of an oral lead-in if used or within 3 days and continue with the injections every 2 months thereafter.

Contraindications

Apretude is contraindicated in patients: unknown or positive HIV-1 status; with previous hypersensitivity reaction (HSR) to CAB; coadministration with drugs where significant decreases in CAB plasma concentrations may occur.(PI, 6.6.1)

Warnings and Precautions (see attached Prescribing Information, Section 5, for further information)(PI,6.7.1)

- Use *Apretude* as part of comprehensive management strategy to reduce the risk of HIV-1 acquisition.
- Potential risk of developing resistance to *Apretude* if an individual acquires HIV-1 either before or while taking *Apretude* or following discontinuation of *Apretude*. Reassess risk of HIV-1.
- Residual concentrations of CAB may remain in the systemic circulation of individuals up to 12 months or longer.
- HSRs have been reported with other INSTIs. Discontinue *Apretude* immediately if signs or symptoms of HSRs develop.
- Hepatotoxicity has been reported in patients receiving CAB. Clinical and laboratory monitoring should be considered.
- Depressive disorders have been reported with *Apretude*. Prompt evaluation is recommended.

Efficacy Data

- The efficacy of *Apretude* to reduce the risk of acquiring HIV-1 infection is supported by data from two Phase 3 randomized, multinational, double-blinded, double-dummy trials: HPTN 083 [NCT02720094] and HPTN 084 [NCT03164564].(PI,26.7.1)
- Patients were randomized to receive daily oral CAB 30 mg + daily oral TDF/FTC placebo for up to 5 weeks, followed by CAB LA 600 mg IM every 4 weeks x2 doses followed by CAB LA 600 mg every 8 weeks thereafter + daily oral TDF/FTC placebo OR daily oral TDF/FTC 300 mg/200 mg and oral CAB placebo for 5 week, followed by daily oral TDF/FTC 300 mg/200 mg + CAB LA placebo IM every 4 weeks x2 doses then every 8 weeks thereafter.(PI,27.2.1)
- HPTN 083, a non-inferiority study, evaluated CAB LA vs. daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for PrEP in HIV-1 uninfected cisgender men and transgender women who have sex with men.(PI, 27.3.1)(Landovitz,2.4.1) The primary endpoint was the rate of incident HIV-1 infections.
- CAB LA was statistically superior to TDF/FTC at preventing HIV acquisition (HR=0.34, 95% CI 0.18-0.62, P<0.001).(PI,27.5.3)(Landovitz,6.1.1) There were a total of 52 incident HIV infections with 13 incident infections in the CAB LA arm vs 29 incident infections in the TDF/FTC arm. Further testing revealed 1 of the infections in the CAB LA arm to be prevalent then yielding a 69% reduction in the risk of HIV-1 incident infection relative to TDF/FTC (HR=0.31, 95% CI 0.16-0.58, P=0.0003).
- Based on a random subset of 390 patients receiving TDF/FTC, tenofovir concentrations were detectable (>0.31 ng/mL) in 86% of patients and indicative of daily TDF (>40 ng/mL) in 74.2% of patients.(Landovitz,5.4.1) Adherence was 91.5% of person-years as defined as injections having been received with a delay of <2 weeks.
- Overall, 81.4% of patients who received CAB LA experienced at least 1 injection site reaction (ISR) during the course of the study.(Landovitz,7.4.1) The most common ISR reported was pain (60.8%); the events began a median of 1 day (IQR, 0 to 2) after injection and lasted a median of 3 days (IQR, 2 to 6).
- HPTN 084, a superiority study, evaluated CAB LA vs. daily oral TDF/FTC for PrEP in HIV-1 uninfected cisgender women. The primary endpoint was the rate of incident HIV-1 infections.(PI,29.1.1)
- CAB LA was statistically superior to TDF/FTC at preventing HIV acquisition (HR=0.12, 95% CI 0.05-0.31).(PI,29.3.3)(Delany-Moretlwe,1781.1.1) There were a total of 40 incident HIV infections with 4 incident infections in the CAB LA arm and 36 in the TDF/FTC arm. Further testing revealed 1 of the infections in the CAB LA arm to be prevalent then yielding a 90% reduction in the risk of HIV-1 incident infection relative to TDF/FTC (HR=0.10, 95% 0.04-0.27; P<0.0001).
- Based on a random subset of 405 patients receiving TDF/FTC, tenofovir concentrations were detectable (>0.31 ng/mL) in 55.9% of patients and indicative of receipt of daily TDF (>40 ng/mL) in 42.1% of the plasma samples tested.(Delany-Moretlwe,1785.2.1) Adherence to CAB LA was 93.1%.
- ISRs were reported in 38% of patients in the CAB LA arm compared to 10.8% in the TDF/FTC arm.(Delany-Moretlwe,1785.6.1) The most common ISR symptom was pain and most injection site reactions were reported at the first injection and diminished over time.

Treatment Guidelines

- *Apretude* is recommended for HIV prevention in adults reporting sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition in the CDC (IA rating) guidelines.(CDC,2.4.1)
- *Apretude* is recommended as PrEP for cisgender men and transgender women who have sex with men in the IAS-USA (AIa rating) guidelines.(Saag,1662.Box4)

This information is provided as professional service in response to your unsolicited request. ViiV Healthcare requests that the recipient of this information only share the contents with the Pharmacy and Therapeutics Committee members for the purposes of making evidence-based decisions regarding formulary inclusion.

References: **1.**ViiV Healthcare Local Label; **2.** Landovitz R, et al. N Engl J Med. 2021;385(7):595-609; **3.** Delany-Moretlwe S, et al. Lancet 2022; 399(10337):1779-1789. **4.** US Public Health Service. CDC. Available at: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. Accessed August 3, 2022. **5.** Saag MS, et al. *JAMA*. 2020;324(16):1651-1669.