Written Testimony: AHCCCS – Updated Data, *Dovato*

This document is a written testimony intended to summarize the key points below required for the Arizona Health Care Cost Containment System (AHCCCS) review of *Dovato* (dolutegravir 50 mg/lamivudine 300 mg [DTG/3TC]).

Indication

Dovato, a two-drug combination of DTG and 3TC, is indicated as a complete regimen for the treatment of HIV-1 infection in adults with no antiretroviral treatment history or 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 no known substitutions associated with resistance to the individual components of *Dovato*.(PI, 2.3.1)

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

All patients with HIV-1 should be tested for the presence of hepatitis B virus (HBV) prior to or when initiating *Dovato*.(PI, 2.1.1) Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HIV-1 and HBV and have discontinued 3TC, a component of *Dovato*.

Updated Dosing and Administration

Prior to or when initiating *Dovato*, test patients for HBV infection. Pregnancy testing is recommended before initiation of *Dovato* in individuals of childbearing potential. The recommended dosage of *Dovato* in adults is one tablet taken orally once daily with or without food.(PI, 3.1.2) In patients taking *Dovato* and carbamazepine or rifampin, an additional tablet of *Tivicay* (DTG) 50 mg should be taken, separated by 12 hours from *Dovato*. Because *Dovato* is an FDC and dosage adjustments cannot be made to 3TC, *Dovato* is not recommended in patients with CrCl < 30 mL/min.

Updated Efficacy Data

- The efficacy of *Dovato* is supported by data from 2 randomized, double-blind, controlled trials (GEMINI-1 and GEMINI-2) in adults with no antiretroviral treatment history, and data from 2 randomized, open-label, controlled trials (TANGO and SALSA) in virologically suppressed adults.(PI. 27.2.1, Llibre, 5.5.1)

GEMINI 1&2 Results–Week 144

- Patients with screening plasma HIV-1 RNA of 1000 to ≤500,000 copies/mL were randomized 1:1 to receive DTG+3TC once daily or *Tivicay* 50 mg once daily + TDF/FTC.(PI, 27.3.2)
- In the Week 48 pooled analysis, virologic success was achieved in 91% of patients receiving DTG+3TC (N=716) and 93% receiving DTG+TDF/FTC (N=717); treatment difference: -1.7% (95% CI: -4.4%, 1.1%).(PI, 28, Table 11) Through 144 weeks, 82% and 84% of patients, respectively, maintained virologic suppression.(Cahn,41.7.4) None of the 12 patients receiving DTG+3TC or the 9 receiving DTG+TDF/FTC with confirmed virologic withdrawal (CVW) had treatment-emergent INSTI or NRTI substitutions through 144 weeks.(Cahn, 43.2.1) One DTG+3TC patient not meeting CVW criteria developed M184V at Week 132 and R263R/K at Week 144, conferring a 1.8-fold change in susceptibility to DTG; non-adherence to therapy was reported.
- Through Week 144, overall AE profiles were similar between treatment groups and consistent with results from Week 48 and 96.(Cahn,44.3.1) The most common AEs in the pooled safety population were diarrhea, nasopharyngitis, and headache.
- GEMINI Week 48 and Week 96 data have been previously reviewed by AHCCCS Committee on 10/18/21.

TANGO Results-Week 144

- Patients were randomized to receive DOVATO once daily or continue their tenofovir alafenamide-based regimen (TBR) for up to 200 weeks.(PI, 30.4.1) Randomization was stratified by baseline third-agent class. The primary efficacy endpoint was the proportion of patients with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) at Week 48 (Snapshot, ITT).
- In the primary analysis at Week 48, virologic non-response was <1% of patients receiving DTG/3TC (N=369) and <1% receiving TBR (N=372); treatment difference: -0.3% (95% CI: -1.2%, 0.7%).(PI, 31, Table 13) Through 144 weeks, 0.3% and 1.3% of patients, respectively, experienced virologic non-response.(Osiyemi,7.2.1) Zero patients receiving DTG/3TC and 3 patients (2 since Week 48) receiving TBR had CVW (no emergent resistance detected) through Week 144 and no resistance mutations were observed.(Osiyemi, 8.4.1)
- As observed at Week 48, cumulative incidence of drug-related AEs was higher in the DTG/3TC group than the TBR group at Week 96 (14% vs 3%, respectively) and Week 144 (15% vs 5%, respectively).(Osiyemi, 8.3.1) In the post-Week 48 analysis of AEs, rates of all AEs, drug-related AEs, serious AEs and AEs leading to discontinuation were similar between groups.
- The most common AEs were nasopharyngitis, upper respiratory tract infection, diarrhea, and back pain.
- TANGO Week 48 data has been previously reviewed by AHCCCS Committee on 10/18/21.

SALSA Results-Week 48

- Patients were randomized to switch to DOVATO once daily or continue their current antiretroviral regimen (CAR) for up to 52 weeks.(Llibre, 5.5.1) Randomization was stratified by baseline third-agent class. The primary efficacy endpoint was the proportion of patients with virologic failure (plasma HIV-1 RNA ≥50 copies/mL) at Week 48 (FDA snapshot algorithm, intent-to-treat-exposed population).
- In the primary analysis at Week 48, 1 patient (0.4%) in the DTG/3TC group (N=246) and 3 patients (1.2%) in the CAR group (N=247) had HIV-1 RNA ≥50 copies/mL, demonstrating non-inferiority; treatment difference: -0.8% (95% CI: -2.4%, 0.8%).(Llibre, 7.3.1) Zero patients met CVW criteria in either group and therefore, no resistance testing was performed.
- Drug-related AEs through Week 48 were more frequent in the DTG/3TC group (20%) than the CAR group (6%) but comparable post-Week 24 (5% vs 2%, respectively). (Llibre, 8.4.3) Drug-related AEs leading to withdrawal occurred in 4 patients in the DTG/3TC group and 1 patient in the CAR group.
- The most common AEs were weight increased, headache, and COVID-19. (Llibre, 8.4.2)

Treatment Guidelines

DHHS recommends the use of DTG + 3TC as an initial regimen for most people with HIV-1, except for individuals with pre-treatment HIV RNA >500,000, hepatitis B virus (HBV) coinfection, or who will initiate ART before results of HIV genotype testing for reverse transcriptase or HBV testing are available (AI rating).(DHHS, G-4, Table 6) The panel also provides recommendations to switch patients with suppressed viral loads to DTG + 3TC in patients who have no evidence of resistance to either drug and do not have HBV coinfection, unless the patient is also on an HBV active regimen (AI rating).(DHHS, I-31.3.1)

References: **1.** ViiV Healthcare Local Label. **2.** Cahn P, et al. *AIDS.* 2022;36:39-48. **3.** Osiyemi O, et al. *Clin Infect Dis.* 2022;ciac036. Online ahead of print. 4. Llibre J, et al. Clin Infect Dis. 2022;ciac130. Online ahead of print. **5.** DHHS Guidelines. Updated January 20, 2022. Accessed August 4, 2022.