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State of Alaska Department of Health and Social Services, Division of Health Care Services
Submission Request Form for Pharmaceutical Manufacturers

E-mail as an attachment to patelu@magellanhealth.com and EAEdwards@magellanhealth.com; include in subject line Manufacturer Submission

OR Fax this request to: 1-888-656-6822 ATTN: Umang Patel, PharmD and Elaine Edwards, RPh

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Members of the Pharmacy and Therapeutics (P&T) Committee have requested that all clinical information, questions, or comments about the Preferred Drug List (PDL) be sent directly to Magellan Medicaid Administration. Manufacturers and other interested parties have been requested not to contact the members directly. Written comments on the PDL from all interested parties should be submitted to Erin Narus, PharmD, R.Ph. at the State of Alaska.

Note: Manufacturers submitting comments are requested to do so through their Product Manager using this form. This form constitutes a request for ***NEW*** information pertaining to peer-reviewed literature including off-label peer-reviewed studies.

Contact Information

MANUFACTURER NAME: Gilead Sciences, Inc.

DATE: 04 – 03 – 2018

PRODUCT MANAGER'S NAME: Coleen Fong, PharmD

TITLE: Associate Director, Medical Sciences

ADDRESS: 333 Lakeside Dr.

CITY: Foster City

STATE: CA

ZIP CODE: 94404

PHONE NUMBER: 916 – 215 – 4048

FAX NUMBER:

PRODUCT: Tenofovir Alafenamide (TAF) 25 mg (Vemlidy) tablet

Clinical Rationale Request for Consideration (If additional space is required, use Clinical Rationale Continuation Page).

In two international trials, patients with chronic hepatitis b virus (HBV) infection, were randomized 2:1 to receive 25 mg tenofovir alafenamide (TAF) or 300 mg tenofovir disoproxil fumarate (TDF) in a double-blinded fashion. Study 108 enrolled only patients with HBeAg+ HBV infection and Study 110 enrolled only patients with HBeAg- HBV infection. Both are ongoing, phase 3 clinical trials in predominantly nucleos(t)ide-naive chronic hepatitis B (CHB) patients. This submission provides efficacy and safety data up to 96 weeks from these two ongoing phase 3 clinical trials.

The primary endpoint were the proportion of patients with HBV DNA <29 IU/ml, proportions of patients with HBsAg loss and seroconversion to anti-HBs, and, in the HBeAg+ patients, proportions of patients HBeAg loss and seroconversion to anti-HBe. Other prespecified efficacy endpoints include proportion of patients with ALT normalization (defined as ALT above the ULN at baseline but within the normal range at week 96) and the incidence of drug-resistant mutations. Safety endpoints included percentage change in hip BMD, percentage change in spine BMD, and changes in renal function, as measured by serum creatinine and estimaged glomerular filtration rate (eGFR) determined by the Cockcroft-Gault method.

A total of 1298 adult mono-infected CHB patients with compensated liver function were randomized and also received treatment (Study 108 HBeAg-; n=425 and Study 110 HBeAg+; n=873). At week 96, in both studies, viral suppression rates were similar between TAF- and TDF-treated patients (HBV < 29 IU/ml Study 108 90% TAF vs 91% TDF; p=0.84 and Study 110 73% TAF vs 75% TDF; p=0.47). Patients treated with TAF demonstrated significantly higher rates of ALT normalization based on both AASLD and central laboratory criteria (ALT normalization AASLD criteria Study 108 50% TAF vs 40% TDF; p=0.035 and Study 110 52% TAF vs 42% TDF; p=0.003; ALT normalization Central Laboratory Study 108 81% TAF vs 71% TDF; p=0.038 and Study 110 75% TAF vs 68% TDF; p=0.017). The rate of HBeAg loss among HBeAg+ patients receiving TAF was 22%, which was not statistically different from the rate of 18% among those receiving TDF. The rate of HBeAg seroconversion was also numerically higher among those receiving TAF (18%) than among those receiving TDF (12%), but the difference did not achieve statistical significance. In both groups, the rate of HBsAg loss at week 96 was 1%. HBsAg seroconversion was experienced by 1% receiving TAF and no patients receiving TDF

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Of the 1298 patients who were randomized and treated in both studies, 1242 entered year two of the study. Of these, 132 (11%) met the criteria for resistance testing at week 96 (87 patients receiving TAF and 45 receiving TDF). Through Week 96, there was no resistance detected in either treatment group.

The pooled safety analysis population included 866 patients receiving TAF and 432 receiving TDF. Overall, TAF was safe and well tolerated with treatment-emergent adverse events (AE) similar to TDF. Serious AEs occurred in 7% of subjects in both the TAF and TDF arms, with none being reported as study drug-related. Medication discontinuations due to AEs were 2% in the TAF arm and 1% in the TDF arm of Studies 108 and 110. Patients receiving TAF experienced significantly smaller mean increases in serum creatinine (SCr) and median decreases in eGFR compared to those treated with TDF [SCr, mean change (mg/dl) TAF 0.003 vs TDF 0.019; p=0.001; eGFR, median change (ml/min) TAF -1.2 vs TDF -4.8; p<0.001]. In both HBeAg- and HBeAg+ patients, there were significantly less mean percent declines in BMD with TAF compared to TDF in both spine and hip (Hip BMD TAF -0.33 vs TDF -2.51; p<0.001; Spine BMD TAF -0.75 vs TDF -2.57; p<0.001).

A subset of subjects, after completing 96 weeks of double-blind TAF (n=361) or TDF (n=181), entered the open-label phase of TAF treatment and will continue through week 384. Week 144 results (48 weeks post switch) represent those patients who switched from TDF to TAF at Week 96. The overall baseine demographics between the TAF and TDF groups were similar except for the proportion of subjects who were greater than or equal to 50 years of age (TAF 21% vs TDF 33%). At week 144, 48 weeks after switching from TDF to TAF, viral suppression was maintained (TDF to TAF, Week 144 HBV DNA <29 IU/ml 89% vs TDF, Week 96, HBV DNA 29 IU/ml 88%). After switching from TDF to TAF, a statistically significant increase was seen in the percentage of patients showing ALT normalization by both AASLD and central laboratory criteria (TDF to TAF, Week 144 65% vs TDF, Week 96 47%; p<0.001 per AASLD criteria and TDF to TAF, Week 144 89% vs TDF, Week 96 78%; p<0.001 per central laboratory). In patients who switched from TDF to TAF at Week 96, eGFR median change from baseline improved significantly (TDF to TAF, Week 144 -1.2 vs TDF, Week 96 -4.8; p<0.001). Hip and spine BMD also showed significant improvement at Week 144 in patients who switched from TDF to TAF at Week 96 (Hip BMD, mean change from baseline TDF to TAF, Week 144 -1.6 vs TDF, Week 96 -2.7; p<0.001 and spine BMD, mean change from baseline TDF to TAF, Week 144 -1.2 vs TDF, Week 96 -3.1; p<0.001).

Study 1249 is a phase 3 study evaluating the efficacy and safety of elvitegravir/cobicistat/emtricitabine/TAF (Genvoya) in HIV virologically suppressed patients (n=72) with CHB co-infection. The primary endpoint is the proportion of patients with HBV DNA <29 IU/ml and HIV-1 RNA < 50 copies/ml (FDA snapshot) at week 24. Switching to Genvoya maintained and achieved a high rate of HBV viral suppression (HBV DNA < 29 IU/ml 86%), as well as HIV suppression (HIV-1 RNA < 50 copies/ml 94%).

The Update on Prevention, Diagnosis, and Treatment of CHB AASLD guidelines were recently updated and recommended TAF as a list of preferred HBV therapies, along with entecavir, TDF, and peginterferon.

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Published Citations (If additional space is required, use Published Citations Continuation Page).

Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs tenofovir disoproxil fumarate for hepatitis B virus infection. [Article in Press]. Journal of Hepatology 2018.

Pan CQ, Brunetto MR, Hui AJ, et al. Improved Bone and Renal Safety at 1 Year After Switching From Tenofovir Disoproxil Fumuarate to Tenofovir Alafenamide: Results From 2 Phase 3 Studies in HBeAg-Positive and HBeAg-Negative Patients With Chronic Hepatits B [Poster 904]. Paper presented at: The Liver Meeting 2017- The 68th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD);20-24 October, 2017;Washington, D.C.

Gallant J, Brunetta J, Crofoot G, et al. Efficacy and safety of Switching to a Single-Tablet Regimen of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) in HIV-1/Hepatitis B Coinfected Adults [Accepted Manuscript]. J Acquir Immune Defic Syndr. 2016. http://www.ncbi.nlm.nih.gov/pubmed/27171740

Terrault NA, Lok ASF, McMahon BJ, et al. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. Hepatology 2018;67(4):1560-1599

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ACTION TO BE TAKEN:

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