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RESEARCH**

APPLICATION NUMBER:

208464Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	Nov 7, 2016
From	Jeffrey Murray, M.D., M.P.H.
Subject	Division Director Summary Review
NDA/BLA #	208464
Supplement #	
Applicant	Gilead Sciences, Inc.
Date of Submission	Jan. 11, 2016
PDUFA Goal Date	Nov. 11, 2016
Proprietary Name / Non-Proprietary Name	Vemlidy tenofovir alafenamide (TAF)
Dosage Form(s) / Strength(s)	25 mg tablet
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with chronic hepatitis B virus infection
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s) (if applicable)	Treatment of adults with chronic hepatitis B virus infection with compensated liver disease

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Tanvir Bell, M.D.
Statistical Review	Frazer Smith, Ph.D.
Pharmacology Toxicology Review	Claudia Wrzesinski, DVM, Ph.D.
OPQ Review	Ying Wang, Ph.D. Yong Wang, Ph.D. Frank Wackes Ph.D. Jing Lee, Ph.D. Stephen Miller, Ph.D.
Microbiology Review	Sung Rhee, Ph.D.
Clinical Pharmacology Review	Mario Sampson, Pharm.D.
OSI	Tony El-Hage
CDTL Review	Russ Fleischer, PA-C. MPH

OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader

1. Benefit-Risk Assessment

The benefit-risk of tenofovir alafenamide (TAF), 25 mg, for the treatment of adults with chronic HBV (CHB) infection with compensated liver disease is favorable. The approval is based on two randomized controlled trials comparing TAF to tenofovir disoproxil fumarate (or TDF with the tradename of Viread) in the treatment of adults with CHB. In addition, safety is supported by a substantial data base that includes trials used to support the approval of TAF-containing drug products for the treatment of HIV.

I concur with the risk-benefit summaries and reviews prepared by Tanvir Bell, clinical reviewer, and Russ Fleischer, Cross Discipline Team Leader (CDTL). Interested readers should refer to these reviews for details regarding trial designs and analyses of efficacy and safety. This memorandum only provides a high level summary and addresses a few notable review issues because the efficacy and safety of TAF for the treatment of CHB was unambiguous and noncontroversial. In brief, based on the data available in this NDA, TAF was shown to be noninferior to TDF (a drug previously approved for CHB) in both hepatitis Be antigen positive (HBeAg+) and hepatitis B e antigen negative (HBeAg-) disease. Overall, the safety and tolerability of TAF and TDF appear to be comparable with potential safety advantages of TAF compared to TDF with respect to bone and renal toxicity as described in sections below. Potential safety signals to watch for with longer term assessments of TAF include uveitis and pancreatitis or amylase/lipase increases.

2. Background

In the U.S. an estimated 700,000 to 1.4 million persons have CHB, a potentially serious and life-threatening disease that can lead to cirrhosis, end-stage liver disease, and hepatocellular carcinoma over years of infection. Patients with immune active disease are at risk of complications; HBeAg+ patients and some patients who are HBeAg- have active liver disease and are candidates for treatment. The most widely used treatments for CHB in the U.S. are the nucleo(t)side analogues such as TDF and entecavir, which are effective at durably suppressing virus and decreasing liver inflammation but do not provide a “virologic cure” and produce a low rate of HB surface antigen (HBsAg) seroconversion.

TAF and TDF are both pro-drugs of the active metabolite tenofovir diphosphate. Viread (TDF) has been previously approved for the treatment of CHB and HIV. Three approved HIV antiretroviral drug fixed doses combinations (FDCs) contain TAF: Genvoya (TAF, emtricitabine, elvitegravir, cobicistat), Odefsy (TAF, emtricitabine, rilpivirine), and Descovy (TAF, emtricitabine). Multiple other approved products include TDF and preceded the approvals of TAF formulations. The advantage of TAF compared to TDF is the ability of TAF to deliver tenofovir to intracellular sites of viral replication (where tenofovir is phosphorylated to tenofovir diphosphate) using lower doses and with lower systemic exposures of TFV. TAF with its lower associated plasma TFV exposures is expected to result in less renal and bone toxicity than TDF. In fact, when Genvoya was compared to Stribild (same four drug combination as Genvoya except for TDF in place of TAF), the products were equally efficacious and some markers of renal function and bone density were less adversely affected with Genvoya. Comparisons of bone and renal safety for TAF and TDF as evaluated for the treatment of chronic hepatitis B are described in section 8.

3. Product Quality

There are no product quality issues precluding approval of this application. For additional details on chemistry, manufacturing and product quality, please review to the review documents prepared by the OPQ review team referred to in the beginning of this review.

4. Nonclinical Pharmacology/Toxicology

There are no nonclinical pharmacology issues precluding approval of this application. In dogs, but not in other animals, a minimal to slight infiltration of mononuclear cells of the posterior uvea was seen in animals receiving the high dose with similar severity after three and nine months administration of TAF. Reversibility was seen after a three months recovery period. Because of this toxicologic finding in dogs, clinical signs and symptoms of uveitis were evaluated in the clinical drug development programs of TAF for both HIV and CHB

5. Clinical Pharmacology

The Clinical Pharmacology review team recommends approval of this NDA. As stated in Russ Fleischer's CDTL review, the clinical pharmacology team identified four issues that differed from the applicant's conclusions. These issues related to food effect, renal impairment, hepatic impairment, and a drug-drug interaction with carbamazepine. All of these issues have been resolved with the applicant. TAF will be recommended to be administered with food, not recommended for patients on dialysis and not recommended for patients with moderate or severe hepatic impairment. Additional safety and efficacy data are needed for patients with moderate or severe hepatic impairment; the Division concluded that PK extrapolation was not sufficient given that the target of the drug is the liver and exposure response relationships may be altered in patients with hepatic impairment.

6. Clinical Microbiology

There are no clinical virology issues precluding approval of this application. In her review, Dr. Rhee states that the applicant conducted genotypic resistance analyses in the two phase 3 trials in patients meeting criteria for virologic breakthrough¹ through Week 48 and in patients who had HBV DNA greater than or equal to 69 IU/mL at early discontinuation at or after Week 24. Treatment-emergent amino acid substitutions in the HBV reverse transcriptase domain occurred in 5/20 patients evaluated. All of these substitutions occurred at polymorphic positions and did not occur with sufficient frequency that would define a specific resistance pathway. Clinical conclusions were that virologic rebound may have represented incomplete adherence or minor blips in HBV DNA and not true virologic failure like what is often seen in HIV-infected patients who experience viral rebound associated with genotypic resistance and reduced susceptibility.

7. Clinical/Statistical-Efficacy

The applicant conducted two randomized-controlled phase III noninferiority trials comparing TAF to TDF (2:1 randomization), one in HBeAg- patients (Trial 108) and one in HBeAg+ patients (Trial 110). Both trials used a noninferiority margin of 10% (clinical-M2) and had

¹Defined as 2 consecutive visits with HBV DNA greater than or equal to 69 IU/mL (400 copies/mL) after having been less than 69 IU/mL, or 1.0-log₁₀ or greater increase in HBV DNA from nadir

similar designs but different baseline viral load stratification factors. The primary efficacy endpoint was HBV < 29 IU/mL as shown in the tables below. In both studies 108 (HBeAg-) and 110 (HBeAg+) TAF was statistically noninferior to TDF. Response rates were higher for HBeAg- patients as is expected due to lower baseline HBV DNA levels. TDF showed a small numerical advantage over TAF in HBeAg+ disease.

Trial 108: HBeAg- CHB. Proportion with HBV DNA < 29 IU/mL at 48 weeks.

	TAF	TDF	Risk Difference* TAF-TDF (95% CI)
Overall Number (%) Responders HBV DNA < 29 IU/mL	268/285 (94.0%)	130/140 (92.9%)	+1.7% (-3.5% to +7.1%) p=0.51
Baseline HBV DNA strata			
<7 log ₁₀ HBV DNA	221/230 (96%)	106/116 (92%)	+3.8% (-1% to 11%) p=0.13
>7 log ₁₀ HBV DNA	47/55 (85%)	23/24 (96%)	-10% (-23% to +9%) p=0.23

*Adjusted by baseline strata

Trial 110: HBeAg+ CHB

	TAF	TDF	Risk Difference* TAF-TDF (95% CI)
Overall Number (%) Responders HBV DNA < 29 IU/mL	371/581 (63.9%)	195/292 (66.8%)	-3.5% (-9.7% to +2.6%) p=0.26
Baseline HBV DNA strata			
< 7 log ₁₀ IU/mL	132/150 (88%)	60/77 (78%)	+10 (+0.1% to +22%) p=0.049
7 to < 8 log ₁₀ IU/mL	122/159 (77%)	66/73 (86%)	-10% (-20% to +2%) p=0.09
≥ 8 log ₁₀ IU/mL	117/272 (43%)	72/142 (51%)	-8% (-18% to +2%) p=0.14

*Adjusted by baseline strata

The clinical and statistical reviews address stratification factor subgroup analyses that suggest a lower response rate in patients with higher baseline HBV-DNA (> 7 log₁₀) in subjects receiving TAF compared to TDF. The lower response of TAF vs. TDF with higher baseline viral load was observed in two trials; however, the reverse effect was seen for lower baseline viral loads so it is not clear whether this is a real phenomenon or a chance finding related to subgroup analyses. In my opinion, small differences in virologic response rates are not of clinical concern for the following reasons:

- HBV DNA suppression below assay limits occurs over a prolonged period of time and is a function of baseline viral load. Viral rebound was infrequent and viral resistance was not documented in the phase 3 trials.
- Most subjects who were not suppressed by week 48 were HBeAg+ and had low HBV DNA levels close to the assay limits. These subjects are expected to fully suppress (HBV DNA < 29 IU/mL) over longer periods of time. Therefore, small differences in the proportion of responders are probably time-limited.
- In older studies of CHB drugs that included liver biopsy data, complete suppression of HBV-DNA was not needed to see improvements in liver inflammation and small differences in HBV-DNA between treatment arms weren't associated with differences in inflammation as measured by transaminases or biopsy. Therefore, HBV DNA appears to be a very sensitive pharmacodynamic marker for assessing virologic activity, but without significant virologic rebound and development of resistance, there is likely to be little clinical consequence from small differences in HBV-DNA measurements over a limited amount of time.
- The subgroup analyses showing differences between response rates by baseline HBV DNA for TAF vs. TDF lacks biological plausibility. Specifically it is difficult to think of an explanation for TDF having a better response than TAF for higher baseline viral load levels but a worse response than TAF for lower baseline viral load levels. If this observation was related to improved drug exposures in liver tissues, it seems logical that an improved response would have been observed across all baseline viral load levels or a least the response would have been equivalent between TDF and TAF at lower baseline viral load levels.

8. Safety

The safety and tolerability of TAF was similar to TDF. The most common treatment adverse events included abdominal pain, headache, fatigue and nausea in subjects treated with TAF and most events were mild or moderate and not dose limiting. Only 2% of subjects in both treatment groups (15/866 receiving TAF and 8/432 receiving TDF) discontinued study medication due to an adverse event through the first 48 weeks of the trials.

With respect to bone toxicity, TAF appears to have substantially less of an adverse effect on bone mineral density (BMD) than TDF. BMD declines of 5% or greater at the lumbar spine were experienced by 6% of TAF subjects and 20% of TDF subjects. BMD declines of 7% or greater at the femoral neck were experienced by 3.2% of TAF subjects and 5.7% of TDF subjects. The long-term clinical relevance of these changes is not clear for TDF or TAF, but TAF would be predicted to pose less of a risk for fragility fractures than TDF. Based on this information, the Division agreed that TAF effects on BMD could be displayed in the Adverse Events section of labeling rather than the Warnings section.

Renal laboratory abnormalities were observed in a similar proportion of subjects treated with TAF and TDF. No proximal tubular dysfunction occurred in either treatment arms. Until additional renal safety information becomes available, renal warnings will be maintained in labeling until longer term data is reviewed. A concern is that renal toxicity could still occur with TAF with longer term follow-up.

Of note, a potential signal for pancreatitis was identified. As stated in Dr. Bell's review, a small number of subjects had amylase elevations with clinical symptoms (i.e., nausea, back pain, abdominal pain) possibly associated with pancreatitis, and one subject had recurrent AEs associated with elevated amylase after rechallenge with TAF. At this point, it is not clear whether TAF is causally associated with pancreatitis. Long term data from trials 108 and 110 and postmarketing surveillance will be helpful in further evaluating this signal.

Posterior uveitis was observed in a dog study. The applicant instituted increased screening for eye disorders and a fundoscopic sub study. There was one SAE of retinal detachment in a TAF recipient and one of uveitis in a TDF subject; neither were determined to be related to study drug and both subjects remained on their assigned treatment. The occurrence of uveitis events will be monitored in postmarketing surveillance.

9. Advisory Committee Meeting

An advisory committee was not convened for this NDA. This application is an FDC of previously approved drugs with established efficacy and safety profiles.

10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement in patients from birth to less than 2 years of age because necessary studies are impossible or highly impracticable. This is because the number of patients in this age group is too small. Pediatric trials with TAF in children ages 2 years and up are deferred and are postmarketing requirements as outlined in the approval letter. These include two trials: 1) A pediatric trial to assess the pharmacokinetics, safety/tolerability, and antiviral activity of TAF in HBV infected subjects 12 to less than 18 years of age, followed by a rollover to a long-term, open-label, extension to assess longer-term pediatric safety and antiviral activity, 2) A pediatric trial to assess the pharmacokinetics, safety/tolerability, and antiviral activity of TAF in HBV infected subjects 2 to less than 12 years of age, followed by a rollover to a long-term, open-label, extension to assess longer-term pediatric safety and antiviral activity.

11. Other Relevant Regulatory Issues

There are no outstanding regulatory issues.

12. Labeling

One label issue of mention is the display of information related to potential bone toxicity and decreases in BMD. The Division concurred with the Applicant that a Warning was not warranted for bone toxicity at this time and that the data of BMD changes could instead be displayed in the Adverse Reactions Section. Longer term studies of TDF in the treatment of

CHB have not identified a risk of fractures and the BMD changes of TAF appears to be substantially less than that of TDF. At this time significant bone toxicity over time is a potential concern for TAF but not sufficient to warrant specific warnings or precautions at this time.

13. Postmarketing

There are no Postmarketing Risk Evaluation and Mitigation Strategies associated with this application and the postmarketing requirements are:

In addition to postmarketing requirements related to PREA as listed in section 10, there are several postmarketing requirements for virologic studies including resistance analyses. These are listed in the approval letter.

In addition as a postmarketing commitment, Gilead has agreed to submit the long-term (through 144 weeks) efficacy, safety and antiviral activity data for Studies GSUS-320-0108 and GS-US-320-0110 that supported the approval of the current application.

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/s/

JEFFREY S MURRAY
11/10/2016