CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022577Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review - Addendum

Date	January 18, 2012
From	Linda L. Lewis, M.D. Medical Officer Team Leader DAVP/OAP/CDER/FDA
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 22577/000 NDA 21-356/SE-038
Applicant	Gilead Sciences, Inc. Foster City, CA
Date of Submission	July 18, 2011
PDUFA Goal Date	January 18, 2012
Proprietary Name / Established (USAN) names	Viread Tenofovir disoproxil fumarate
Dosage forms / Strength	Tablets: 150, 200, 250, and 300 mg Oral powder: 40 mg/g powder
Proposed Indication(s)	Treatment of HIV-1 infection in pediatric patients 2 to less than 12 years of age
Recommended:	***Approval,*** *with labeling revisions as specified in the Package Insert included in the approval letter*

1. Introduction

Tenofovir disoproxil fumarate (TDF, Viread) is an oral pro-drug of tenofovir, a synthetic nucleotide that inhibits both HIV-1 reverse transcriptase and hepatitis B virus (HBV) polymerase. The current submissions provide the 48 week clinical study report and datasets for Study 0352, seek an indication for treatment of HIV-1 in the 2 to less than 12 years age group, and propose labeling describing the PK, safety, and efficacy results of the study. In addition to the clinical data, the submission to NDA 22577 provides CMC data for a new oral powder formulation and a bioequivalence study (Study 0312) demonstrating the similarity in exposure between the oral powder and the approved 300 mg tablets. The supplement to NDA 21356 provides CMC data on new reduced-strength tablets of 150 mg, 200 mg, and 250 mg similar in composition to the approved 300 mg tablets. Both formulations (oral powder and tablets of multiple strengths) are included in a single product label and dosing recommendations appropriate are provided for the two formulations across the pediatric age range greater than 2 years of age.

The purpose of this CDTL addendum is to describe the resolution of CMC issues raised during the primary review of NDA 22577 and the inspections of facilities manufacturing Viread oral powder. Please refer to the original CDTL Review dated January 4, 2012 for a summary of all other aspects of the NDA reviews.

2. CMC/Device

As noted in the full CDTL Review, these submissions contain new CMC information regarding Viread oral powder and reduced-strength tablets. For a full description of the CMC issues related to the oral powder please refer to the CMC Review performed by Dr. Rao Kambhampati dated December 23, 2011. The oral powder, containing 40 mg of TDF per gram of the powder, represents a new, age-appropriate formulation for patients unable to swallow tablets. Oral powder is produced by (b) (4)

The Office of Compliance notified the Review Team of a potentially significant issue identified at the site manufacturing the bulk oral powder (Aptalis, previously known as Eurand). The investigator observed (b) (4)

The Applicant submitted the additional CMC data on January 6, 2012, to clarify the issue of (b) (4) raised during the facilities inspections. These data were reviewed by Dr. Kambhampati, who submitted a second Quality/CMC Review for the powder formulation (dated January 17, 2012). In his review, Dr. Kambhampati concludes that Gilead and Aptalis, the DMF holder, provided data demonstrating (b) (4) He noted that the final blend was uniformly mixed and the strength of the powder was within an acceptable percentage of the labeled strength before and after simulated shipping and during storage. Additionally, Aptalis agreed to continue to monitor blend uniformity during commercial manufacture. However, some concern remains that segregation of granules by size might occur during the bottle-fill process or when the bottles are shipped, stored, and used for dosing by a caregiver. This concern led to the two post-marketing commitments (PMC) described below.

Other deficiencies were mentioned in the Form 483 issued to the Aptalis site and were being further reviewed by the Office of Compliance staff at the time of the original CDTL Review. In addition, a Gilead Sciences site in Ireland (where packaging of bulk

powder into bottles is performed) was inspected and deficiencies were identified and cited in a 483. Responses to these deficiencies were also under review at the time of the original CDTL Review. Since that time, the Office of Compliance determined that the sites provided adequate responses to address the deficiencies cited in the 483s and the sites have been given "acceptable" designations.

For a more complete discussion of the CMC issues and their resolution, please refer to the CMC Review submitted by Dr. Rapti Madurawe, the CMC Branch Chief.

3. Labeling

At the request of both the CMC reviewers and the reviewers in the Division of Medication Error Prevention and Analysis (DMEPA), the Applicant has provided revisions to their proposed container and carton labeling for Viread oral powder. As requested, the Applicant added the following statement to both the bottle label and carton label:

> *"Each level dosing scoop provides approximately 1 g of the oral powder which contains 40 mg of tenofovir disoproxil fumarate, which is equivalent to 33 mg of tenofovir disoproxil."*

Because it was considered more informative to patients/caregivers and prescribers, DMEPA recommended that the strength statement on the bottle and carton labels be written as "*40 mg/scoop*" rather than (b) (4)

4. Final Recommendations/Risk Benefit Assessment

With the resolution of the previously noted CMC and site inspection issues, I recommend approval of TDF (Viread) for the treatment of HIV-1-infected pediatric patients 2 to < 12 years of age and approval of Viread oral powder and reduced strength tablets. The CMC reviewers confirm that the formulation used in the pediatric clinical trial was the same formulation planned for commercial use and the PK, safety and efficacy data submitted reflect the manufacturing process described in the CMC reviews and the sites inspected. The good results from the pediatric clinical trial suggest that the issues raised by the manufacturing facilities inspections do not prompt clinical concern and the likelihood of significant improper dosing as a result of non-uniform blending of powder is very small.

However, I agree with the CMC review team's recommendation to request two additional studies of the manufacturing process to verify that uniformity of dose is maintained during commercial packaging and patient use. In order to provide enhanced oversight, the Applicant has agreed to the following CMC post-marketing commitments:

PMC # 1865-1
During the filling of one commercial full-scale Viread oral powder lot, execute a stratified sampling plan to determine the potency of the powder blend and verify that

potency variation does not occur due to segregation. Include individual measurements of strength from at least one single scoop sample per container for containers spanning the full packaging run. Include both individual values and statistical analysis of the data in the study report.
The timetable you submitted on January 17, 2012, states that you will conduct this study according to the following schedule:

Study/Trial Completion: 12/18/2012
Final Report Submission: 01/18/2013

PMC # 1865-2
Submit data from a simulated in-use study of strength per scoop where a bottle is exhaustively sampled one scoop at a time. Use a bottle subjected to appropriate simulated shipping conditions so that it is representative of a bottle obtained by a patient. Include data from each scoop sampled and appropriate statistical analysis in the study report.
The timetable you submitted on January 17, 2012, states that you will conduct this study according to the following schedule:

Study/Trial Completion: 12/18/2012
Final Report Submission: 01/18/2013

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LINDA L LEWIS
01/18/2012