DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-449/S-006

Gilead Sciences, Inc
Attn: Nikki McMillan
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. McMillan:

Please refer to your supplemental new drug application dated December 21, 2005, received December 22, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HEPSERA (adefovir dipivoxil) 10 mg Tablets.

We acknowledge receipt of your submissions dated March 2, 2006, April 24, 2006, August 15, 2006, September 6, 2006, September 29, 2006, October 13, 2006, October 16, 2006, and October 17, 2006.

This supplemental new drug application provides for the use of HEPSERA (adefovir dipivoxil) 10 mg Tablets for the treatment of chronic hepatitis B virus infection and the labeling has been updated to include information about continuous treatment up to 240 weeks.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert) dated October 17, 2006.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-449/S-006**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric subjects unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages birth to 2 years of age and 2 to 17 years of age until December 31, 2015 and January 1, 2008, respectively.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments (PMCs). Please note that while this wording translates into postmarketing commitments, they are deferred and do not change the requirements of your Written Request.

The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Deferred pediatric study under PREA for the treatment of chronic hepatitis B infection in pediatric subjects from 2 to 17 years of age. Conduct a pediatric safety and efficacy study of adefovir dipivoxil with efficacy based on the results of a variety of virologic, biochemical, serologic, and composite endpoints over at least 48 weeks of dosing and safety monitored over 48 weeks.
   Protocol submission: *Previously submitted*
   Final report submissions: *January 1, 2008*

2. Deferred pediatric study under PREA for the treatment of chronic hepatitis B viral infection in pediatric subjects from birth to 2 years of age. This study will determine the pharmacokinetic profile, safety, and activity of adefovir dipivoxil in pediatric subjects from birth to 2 years of age.
   Protocol submission: *January 1, 2008 (Pending completion of PMC #1)*
   Final report submissions: *December 31, 2015.*

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**."

We remind you of your postmarketing study commitments from the NDA approval letter dated September 20, 2002.

Also, we remind you of your postmarketing study commitments as agreed to in your submission of October 18, 2006. These are listed below:

1. Please determine the susceptibility in cell culture to adefovir of HBV encoding rtL80V/I, rtV84M, rtS85A, rtV214A, rtQ215S, rtI233V, rtP237H, and rtN238T/D substitutions. Include as positive controls HBV encoding rtA181V, rtA181T, rtN236T, and rtA194T (TDF susceptibility; in an rtL180M/rtM204V background) substitutions.

   Protocol Submission: *January 31, 2007*
   Study Start: *March 31, 2008*
   Final Report Submission: *September 30, 2008*

2. Please determine the effect of nucleoside analog reverse transcriptase inhibitors (NRTIs) used for HIV-1 treatment on the anti-HBV activity of adefovir in cell culture.

   Protocol Submission: *January 31, 2007*
   Study Start: *March 31, 2008*
   Final Report Submission: *September 30, 2008*

3. Please determine the effect of adefovir on the anti-HIV-1 activity of NRTIs used for the treatment of HIV-1 infection.

   Protocol Submission: *Ongoing*
   Study Start: *Ongoing*

Final Report Submission: *December 31, 2006*

4. Please determine the effect of changing the lower limit of quantitation of the HBV DNA assay from 400 copies/mL to 1,000 copies/mL on the efficacy calculations at Weeks 48, 96, 144, 196, and 240.

Protocol Submission: *January 31, 2007*
Study Start: *September 30, 2007*
Final Report Submission: *September 30, 2008*

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of subjects entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
White Oak, Building 22, Mail Stop 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Marsha Holloman, Regulatory Health Project Manager, at (301) 796-0731.

Sincerely,

{See appended electronic signature page}

Debra B. Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Revised Package Insert and Patient Package Insert

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

/s/

Debra Birnkrant
10/18/2006 04:38:39 PM
NDA 21-449