DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-449

Gilead Sciences, Inc.
Attention: Martine Kraus, PhD
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Kraus:

Please refer to your new drug application (NDA) dated March 20, 2002, received March 21, 2002, 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:

April 15, 2002	June 27, 2002	September 6, 2002
April 16, 2002	July 8, 2002	September 11, 2002
April 29, 2002	July 19, 2002	September 12, 2002
May 2, 2002	August 2, 2002	September 16, 2002
May 22, 2002	August 3, 2002	September 17, 2002
May 29, 2002	August 19, 2002	September 18, 2002
June 3, 2002	August 20, 2002	September 19, 2002
June 7, 2002	August 23, 2002	September 20, 2002
June 12, 2002	August 29, 2002	

This new drug application provides for the use of HEPSERA™ for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) or histologically active disease.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed-upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the agreed-upon labeling (text for the package insert, text for the patient package insert, and immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). 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. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "**FPL for approved NDA 21-449**." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments as agreed to in your submission dated September 19, 2002. These commitments are listed below:

1. Obtain long-term (up to 5-year) follow-up information on adefovir dipivoxil 10 mg patients rolled over from the pivotal clinical trials 437 and 438 and from the observational study 481 to address the following issues:
   - maintenance of virologic suppression; and,
   - durability of HBeAg and HBsAg seroconversion and the rate of new events.
   - risk of drug-related adverse effects, particularly nephrotoxicity; and
   - risk for development of HBV resistance to adefovir.

   Protocol Submissions: Studies ongoing
   Final Report Submissions: by Q3 2006

2. Conduct study 526 to determine safety, efficacy and optimal dosing (based on creatinine clearance) in renally impaired patients with chronic hepatitis B. Include complete pharmacokinetic assessments (plasma concentration-time profiles) at treatment initiation (Day 0) and following chronic dosing.

   Protocol Submission: by Q4 2002
   Final Report Submission: by Q4 2004

3. Submit studies 488 and 489 in order to provide additional pharmacokinetic data in non-Caucasian subjects and further evaluate the efficacy and safety of adefovir dipivoxil in ethnic groups that were underrepresented in the pivotal trials.

   Protocol Submission: Both studies completed
   Final Report Submissions: Studies 488 and 489 by Q4 2002
   Final report summarizing the safety and efficacy of adefovir dipivoxil 10 mg by ethnicity from the phase 2-4 program submitted by Q3 2006

4. Continue to perform genotypic and phenotypic analyses of HBV DNA from patients receiving long-term adefovir dipivoxil therapy. Provide data on the genotypic and phenotypic analyses of HBV DNA from adefovir dipivoxil - treated patients with chronic hepatitis B and with rebound in serum HBV DNA. Provide data on the genotypic and phenotypic analyses of HBV DNA and HIV-1 RT from adefovir dipivoxil - treated patients with chronic hepatitis B, lamivudine-resistant HBV, and HIV-1 co-infection.

   Protocol Submissions: Studies 437 and 438 ongoing
   Final Report Submissions: by Q3 2006

Protocol 460i Submission: Ongoing
Final Report Submission: by Q3 2004 (virology summary)

Protocol 496i Submission: Ongoing
Final Report Submission: by Q1 2006 (virology summary)

Protocol ACTG 5127 Submission: Ongoing
Final Report Submission: by Q4 2006 (virology summary)

5. Evaluate adefovir dipivoxil 10 mg monotherapy compared with combination therapy with lamivudine (Study 468) or pegylated interferon in treatment-naïve patients with chronic hepatitis B to determine whether there is any added benefit to combination therapy.

Protocol Submission: Study 468 ongoing
Final Report Submission: by Q4 2005

Protocol Submission: by Q2 2003 for new study to evaluate combination of adefovir dipivoxil 10 mg and pegylated interferon.
Final Report Submission: by Q4 2007

6. Characterize the specific renal transport pathways of adefovir in vivo (anionic vs. cationic transport). Once determined, evaluate the potential for drug interactions between adefovir and drugs that are renally eliminated and may be co-administered in patients with coexisting diseases.

Protocol Submission: by Q1 2003 for new study (TOX-103-002) characterizing the specific renal transport pathways of adefovir in pre-clinical animal models
Final Report Submission: by Q4 2003

7. Conduct drug interaction studies of adefovir dipivoxil with cyclosporine, tacrolimus, pegylated interferon, tenofovir disoproxil fumarate and didanosine.

- Study to evaluate potential for drug interactions between adefovir dipivoxil and cyclosporine and adefovir dipivoxil and tacrolimus.

Protocol Submission: by Q4 2002
Final Report Submission: by Q1 2004

- Study 940 evaluating potential for drug interactions between adefovir dipivoxil and tenofovir disoproxil fumarate.

Protocol Submission: by Q2 2003
Final Report Submission: by Q4 2003

- Conduct a study to evaluate potential for drug interactions between adefovir dipivoxil and didanosine.

  Protocol Submission: by Q4 2003
  Final Report Submission: by Q2 2004

- Conduct a study to evaluate potential for drug interactions between adefovir dipivoxil and pegylated interferon.

  Protocol Submission: by Q1 2003 (draft protocol and timeline for submission of study data)
  Final Report Submission: by Q3 2004

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 patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, 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 patients, unless this requirement is waived or deferred (63 *FR* 66632) (21 CFR 314.55.). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 21 CFR 601.27). We are deferring submission of your pediatric studies until June 30, 2006.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Antiviral Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Also, please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, MD, MPH
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosures: Final Proposed Labeling (PI, PPI, and bottle and carton labels)

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

/s/

Mark Goldberger

9/20/02 05:41:06 PM