DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-003/SE1-002
NDA 21-004/SE1-002

GlaxoSmithKline
Attention: Mary E. Martinson
Product Director
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC
27709

16 AUG 2001

Dear Ms. Martinson:

Please refer to your supplemental new drug applications dated February 27, 2001, received February 28, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Epivir-HBV® (lamivudine) 100mg tablets and 5 mg/mL oral solution.

We acknowledge receipt of your submissions dated:

May 7, 2001	June 27, 2001	July 25, 2001	August 9, 2001
June 7, 2001	July 6, 2001	July 31, 2001	August 10, 2001
June 13, 2001	July 11, 2001	August 3, 2001	August 15. 2001
June 22, 2001	July 17, 2001	August 7, 2001	

These supplemental new drug applications provide for the use of Epivir-HBV® in the treatment of hepatitis B in pediatric patients ages 2-17 years.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 9, 2001, patient package insert submitted August 9, 2001).

Please submit the copies of final printed labeling (FPL) electronically to each application 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 heavyweight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 21-003/SE1-002, 21-004/SE1-002." In addition, please provide a clean text MS Word version of the label as a desk copy. Approval of these submissions by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated August 15, 2001, with the revisions to these commitments agreed upon during your August 15, 2001, teleconference with Dr. Birnkrant and the review team. These commitments are listed below.

1. Propose and execute a plan for continued follow-up for children treated for chronic hepatitis B in studies NUC30903 and NUC30926 (through a cumulative 5-year period).

   - Amendment to protocol NUC30926 to be submitted to IND 40,916 within 6 months
   - Report by end of 2003 on available data (through a cumulative 3.5 year period)
   - Final report by end of 2006 on available data (through a cumulative 5 year period)

2. Perform exploratory analyses of data from two adult studies (NUCB3018 and NUCA/B3017) and pediatric studies (NUC30903 and NUC30926) to try to identify baseline demographic and disease-related variables that may represent risk factors for emergence of YMDD variants of hepatitis B virus during lamivudine therapy, as well as risk factors for re-emergence of HBV DNA (without identifiable YMDD mutations) during lamivudine therapy. Assess other mutations in this non-YMDD subgroup that may be associated with resistance, as well as other accompanying mutations in patients with YMDD mutant HBV DNA.

   - Final report by end of 2003

3. Re-examine data from pediatric study NUCB2020 and from two adult Phase II studies (NUCB2002 and NUCA2003) to explore any evidence for a relationship between individual lamivudine exposure (within dose groups, as well as across dose groups) and short-term antiviral activity. Compare these analyses with exploratory analyses of data from 12-month studies (adult studies NUCB3009, NUCA3010, NUCB3010, and NUCB3011; and pediatric study NUC30903) for any evidence of a relationship between short-term antiviral activity and one-year efficacy measures (including emergence of YMDD variants).

   - Final report by end of 2003

4. Provide a listing of information of treatment responses and pharmacokinetic variables for adolescent patients within the final reports provided by the end of 2003 for commitments 1 and 3 above.

5. Conduct vira1 genetic analyses on samples from pediatric patients in studies NUC30903/30926 with reported negative HBV surface antigen or e antigen (especially those with anomalous results on these assays relative to other virologic/serologic/biochemical measurements), to ascertain any mutations that might prevent expression of these antigens and the potential relationship to clinical and laboratory outcomes.

   - Final report by the end of 2003

6. Provide additional data in pediatric patients in study NUC30926 to assess the relative risks and benefits of stopping or continuing treatment after emergence of resistance-associated mutations.

   - Amendment to Protocol NUC30926 to be submitted to IND 40,916 within 6 months
   - Final report by end of 2003

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to these NDAs. 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 these NDAs. 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."**

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). We note that you have fulfilled the pediatric study requirement for ages 2-17 years. The need for therapeutic intervention in the age group 0-2 years, and therefore the need for clinical studies in this age group, is not clear at this time. Therefore, we are deferring submission of any additional pediatric studies for ages 0-2 years until December 31, 2006. In the interim we would be glad to review any plans or data you may have that are relevant to the youngest age group.

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

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

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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 call Christine Lincoln RN, MS, MBA, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

Debra Birnkrant, M.D.
Acting Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research