CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-003/SE1-002

21-004/SE1-002

CORRESPONDENCE

June 27, 2001

GlaxoSmithKline

GlaxoSmithKline
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Five Moore Drive
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North Carolina 27709

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Debra Birnkrant, M.D., Acting Director
Division of Antiviral Drug Products
Attn: Document Control Room
Food and Drug Administration
Fourth Floor, HFD-530
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 21-003; EPIVIR-HBV® (lamivudine) Tablets
NDA 21-004; EPIVIR-HBV® (lamivudine) Oral Solution
Pediatric Exclusivity Determination Requested

Dear Dr. Birnkrant:

Reference is made to our approved lamivudine products, EPIVIR-HBV Tablets and Oral Solution for the treatment of chronic hepatitis B infection (NDAs 21-003 and 21-004, respectively). Reference is also made to S-002 to NDA's 21-003 and 21-004, dated February 27, 2001, which is currently under review.

The purpose of this submission is to formally request a determination of pediatric exclusivity on the basis of a pediatric study report previously submitted with S-002 that, we believe, satisfies the Written Request for a study of lamivudine in pediatric patients with chronic hepatitis B. It is our understanding the completion of this study qualifies GlaxoSmithKline for pediatric exclusivity pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act. A copy of the Written Request from the Office of Drug Evaluation IV, dated November 25, 1998, is attached.

On July 28, 1998, GlaxoWellcome submitted a Proposed Pediatric Study Request (IND [redacted] to the Division of Antiviral Drug Products in order to seek a Written Request for Pediatric Studies in accordance with Section 505A of the Federal Food, Drug and Cosmetic Act. On November 25, 1998, the Office of Drug Evaluation IV provided GlaxoWellcome with an official pediatric Written Request to NDA's 21-003 and 21-004. The Written Request stipulated that GlaxoWellcome must perform an adequate and well-controlled Phase III study to evaluate the efficacy of lamivudine and to obtain safety data for treatment up to one year in pediatric patients in the age range of 2 years to 17 years of age with evidence of chronic hepatitis B to provide information sufficient to qualify for additional exclusivity under Section 505A.

DESK COPY

The correspondence of November 25, 1998 from the Office of Drug Evaluation IV contained a list of specific issues to be addressed in the requested study conducted by GlaxoWellcome in support of pediatric exclusivity for lamivudine. Attachment 1 contains a table describing the specific information requested and also references the location in the final study report of supportive data for each request. The Written Request specified that GlaxoWellcome's response to this request must be provided to FDA by June 30, 2001.

Study Information

We are referencing data from one adequate and well-controlled study in pediatric patients ages from ages 2 to 17 years in support of this request for pediatric exclusivity. It is important to note, no new drug safety concerns were observed by the investigators in this study.

NUC30903: A Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of 52 Weeks Lamivudine Treatment at a Dose of 3mg/kg in Pediatric Subjects with Chronic Hepatitis B

In correspondence to IND [redacted] dated February 2, 1998 [redacted] we provided a draft protocol for this treatment study (NUC30903) in pediatric patients (ages ≥2 years to <18 years) with chronic hepatitis B. That letter included a statement of our regulatory intent to conduct a single, large, multinational study as a means for revising the product labeling with information regarding this pediatric patient population. After review and comment were provided by DAVDP, the final protocol was submitted to the IND on June 30, 1998 [redacted]

The study objectives include:

- to compare the efficacy of lamivudine versus placebo in children with chronic hepatitis B with regard to complete virologic response (loss of detectable HBeAg and HBV DNA from serum) and sustained normalization of serum alanine aminotransferase (ALT) levels at Week 52
- to compare the safety of lamivudine versus placebo in children with HBV infection.

As mentioned above, the final study report with 52 week results from study NUC30903 in 286 pediatric patients with chronic hepatitis B was included in S-002 to NDA's 21-003 and 21-004 dated February 27, 2001, which is currently under review in DAVDP. This double-blind, placebo-controlled, multicenter study showed that a significantly higher proportion of lamivudine-treated patients versus placebo-treated patients exhibited a Complete Virologic Response (defined as loss of detectable HBeAg from serum and

reduction of HBV DNA in serum to undetectable levels), and ALT normalization at Week 52. Importantly, the efficacy and safety results from this study in children were consistent with those from the placebo-controlled Phase III study in adults.

As stated above, Attachment 1 contains a table containing cross-reference information from the specific issues described in the Written Request to the final study report for NUC30903. Completion of this study and provision of the results to FDA satisfies the conditions of the Written Request issued on November 25, 1998.

Closing Information

As noted above, a copy of the Division's November 25, 1998 correspondence is attached to this cover letter as requested. Also, a copy of the cover letter of this submission is being sent simultaneously to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

This correspondence is being provided in duplicate to the NDAs referenced above. Four desk copies have been provided directly to Ms. Christine Lincoln for use by the review team. Please contact me at (919)-483-3763 for any matters regarding this application. Thank you.

Sincerely,

Mary E. Martinson

Mary E. Martinson
Product Director
Regulatory Affairs

cc: Christine Lincoln (HFD-530)

Attachment:
Forms FDA 356h
Attachment 1: Description of Information Requested

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

[redacted]
NDA 21-003
NDA 21-004

NOV 25 1998

GlaxoWellcome Inc.
Attention: David M. Cocchetto. Ph.D.
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. Cocchetto:

To obtain needed pediatric information on Epivir®-HBV™ (lamivudine) Tablets and Oral Solution for the treatment of chronic hepatitis B, the Food and Drug Administration (FDA) is hereby issuing to you an official Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act. FDA requests that you submit information from the following:

***Types of study*:**

An adequate and well-controlled phase III study to evaluate the efficacy of lamivudine as determined by effects on serologic parameters of chronic hepatitis B (HBeAg, HBV DNA, ALT), and to obtain safety information for treatment up to one year, in pediatric patients in the age range of 2 to 17 years of age with evidence of hepatitis B disease.

***Objective/rationale*:**

To assess the safety and efficacy of lamivudine in pediatric patients with chronic hepatitis B.

***Indication to be studied*:** Chronic hepatitis B.

***Study design*:**

Adequate and well-controlled safety and efficacy study in chronic hepatitis B.

***Age group in which study will be performed*:**

Should include children between the ages of 2 to 17.

***Number of patients to be studied or power of study to be achieved*:**

A number of subjects adequate to detect clinically meaningful differences between treatment arms.

***Entry criteria: (i.e., inclusion/exclusion criteria)*:**

Pediatric patients with chronic hepatitis B disease documented by presence of hepatitis B surface antigen, e antigen, and HBV DNA in serum, with ongoing hepatitis documented by transaminase levels and review of available liver biopsies, and without evidence of decompensated liver disease.

***Clinical endpoints, if appropriate*:**

Virologic efficacy as determined (for each patient) by the combination of loss of hepatitis B e antigen and loss of HBV DNA assay positivity (that is, reduction of HBV DNA to below the assay limit as measured by an adequately characterized assay) at week 52.

***Study evaluations*:**

Safety and efficacy data through week 52.

***Drug information*:**

- ***Dosage form*:** 5 mg/mL oral solution or 100 mg tablet
- ***Route of administration*:** oral
- ***Formulation*:** as appropriate for dosage form and age of patient

***Safety concerns*:** Potential for development of viral resistance; post-treatment hepatitis flares; pancreatitis

***Statistical information (statistical analyses of the data to be performed)*:**

Comparisons of primary endpoint between treatment groups using appropriate statistical methods including 95% confidence interval for relative treatment effect.

Labeling that may result from the study:

Information regarding dosing and safety in patients in the age range of 2 to 17 years with chronic hepatitis B.

***Format of report to be submitted*:**
The full study report providing the analyses outlined in this request with full analysis, assessment, and interpretation. Include other information as appropriate. A description of plans for obtaining ongoing follow-up information should be included.

Timeframe for submitting report of the study:

On or before June 30, 2001.

The report of this study should be submitted as a supplement to an approved NDA, or as an amendment to your pending application with the proposed labeling changes you believe would be warranted based on the data derived from this study. When submitting the report of this pediatric study, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORT - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact Terrie Crescenzi, R.Ph., Regulatory Management Officer, at (301) 827-2335.

Sincerely yours,

/S/

M. Dianne Murphy, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Attachment 1

Issue as described in Correspondence from the Agency on November 25, 1998	Study NUC30903
Type of study: An adequate and well-controlled phase III study to evaluate the efficacy of lamivudine as determined by effects on serologic parameters of chronic hepatitis B (HBeAg, HBV, DNA, ALT), and to obtain safety information for treatment up to one year, in pediatric patients in the age range of 2 to 17 years of age with evidence of hepatitis B disease.	Study NUC30903 was a randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of 52 weeks lamivudine treatment at a dose of 3mg/kg in pediatric subjects with chronic hepatitis B
Objective/rationale: To assess the safety and efficacy of lamivudine in pediatric patients with chronic hepatitis B.	• Safety was assessed as described in Sections 4.4, pages 35 to 38 of the report, the results are described in Section 8, pages 82 to 90. • Efficacy was assessed as described in Section 4.3, pages 33 to 35 of the clinical study report, the results are described in Section 7, pages 63 to 81.
Indication to be studied: Chronic hepatitis B.	Subjects with chronic hepatitis B were enrolled
Study design: Adequate and well-controlled safety and efficacy study in chronic hepatitis B.	The design of this randomized, double blind, placebo controlled study is described in Section 3 of the clinical study report, pages 24 to 32.
Age group in which study will be performed: Should include children between the ages of 2 to 17.	The study recruited children between the ages of 2 and 17, as described in the inclusion criteria, Section 3.2, pages 25 to 27, and as described in the results, Section 6.4 pages 55 and 56 of the clinical study report.

Number of patients to be studied or power of study to be achieved: A number of subjects adequate to detect clinically meaningful differences between treatment arms.	• Details of the sample size considerations are presented in Section 5.2, page 39 of the clinical study report. • The study population results, describing the numbers of subjects enrolled and the populations analyzed are presented in Section 6, pages 53 to 55 of the clinical study report.
Entry criteria: (i.e., inclusion/exclusion criteria): Pediatric patients with chronic hepatitis B disease documented by presence of hepatitis B surface antigen, e antigen, and HBV DNA in serum, with ongoing hepatitis documented by transaminase levels and review of available liver biopsies, and without evidence of decompensated liver disease.	• Details of the inclusion / exclusion criteria used for the screening and enrollment of subjects in the NUC30903 study are listed in Section 3.2, pages 25 to 29 of the clinical study report. • A description of the populations used for analyses is presented in Section 6.3, pages 54 to 55 of the study report. • Data on subjects who failed screening are presented in Listing 2 of the study report.
Clinical endpoints, if appropriate: Virologic efficacy as determined (for each patient) by the combination of loss of hepatitis B e antigen and loss of HBV DNA assay positivity (that is, reduction of HBV DNA to below the assay limit as measured by an adequately characterized assay) at week 52.	• The study objectives and endpoints are described in Section 2, pages 23 to 24 of the clinical study report. • The results for the primary efficacy endpoint of complete virologic response (CVR) are presented in Section 7.1, pages 63 to 67.
Study evaluations: Safety and efficacy data through week 52.	• The efficacy analyses are described in Section 5.6, pages 44 to 49 of the clinical study report. • The safety analyses are described in Section 5.7, pages 49 to 50 of the clinical study report. • Results for the secondary efficacy endpoints are presented in Section 7.2, 7.3, and 7.4, pages 69 to 81 of the study report. • Results for safety data are presented in Section 8, pages 82 to 90.
Drug information: • **Dosage form:** 5 mg/mL oral solution or 100 mg tablet • **Route of administration:** oral • **Formulation:** as appropriate for dosage form and age of patient	• Details of the study treatments, assignments blinding and compliance are presented in Section 3.3, pages 29 to 32 of the clinical study report. • Results for treatment compliance are presented in Section 6.6, page 62 of the clinical study report.

Safety concerns: Potential for development of viral resistance; post-treatment hepatitis flares; pancreatitis	• Viral genotyping measurements are described in Section 5.8 pages 50 to 52 of the study report, with results presented in Section 9, pages 91 to 106. • For subjects discontinuing from study NUC30903 early the protocol requires monthly follow-up visits for 3 months to capture safety data, including serum chemistry and hematology. [redacted] • Subjects with clinically apparent pancreatitis were specifically excluded from enrollment in the study until 6 months after the resolution of all signs and symptoms (Section 3.2.2, page 28, criteria 7). Serum amylase and lipase were monitored at all study visits (Section 4.4.2, page 37) and laboratory data are presented as changes over time, and as graded laboratory toxicities, (Section 8.7, pages 86 to 88).
Statistical information (statistical analyses of the data to be performed): Comparisons of primary endpoint between treatment groups using appropriate statistical methods including 95% confidence interval for relative treatment effect.	Details of the data analysis methods are presented in Section 5, pages 38 to 52 of the clinical study report.
Labeling that may result from the study: Information regarding dosing and safety in patients in the age range of 2 to 17 years with chronic hepatitis B.	Draft labeling regarding the dosing and safety in patients in the age range 2 to 17 years with chronic hepatitis B was submitted with S-002 to NDAs 21-003 and 21-004 on February 27, 2000.
Format of report to be submitted: The full study report providing the analyses outlined in this request with full analysis, assessment, and interpretation. Include other information as appropriate. A description of plans for obtaining ongoing follow-up information should be included.	The final study report for NUC30903 was submitted on February 27, 2000 as Supplement 002 to NDAs 21-003 and 21-004. [redacted]

Timeframe for submitting report of the study: On or before June 30, 2001.	