CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-003/SE1-002

21-004/SE1-002

ADMINISTRATIVE DOCUMENTS

Patent Information

Pursuant to 21 C.F.R. § 314.53
for

Epivir-HBV® (lamivudine) Tablets
NDA 21-003

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	Epivir-HBV® Tablets
Active Ingredient:	lamivudine
Strength(s):	100 mg lamivudine
Dosage Form:	Tablet; oral
NDA Number:	21-003

Applicable Patent Numbers and Expiration Dates:

Patent No.	5,047,407
Expires:	February 8, 2009
Owner:	BioChem Pharma, Inc. Licensed to Glaxo Wellcome Inc.
Type:	Drug Product Composition/Formulation

Patent No.	5,532,246
Expires:	July 2, 2013
Owner:	BioChem Pharma Inc. Licensed to Glaxo Wellcome Inc.
Type:	Method of Use treatment of hepatitis B infection

Patent No.	5,905,082
Expires:	May 18, 2016
Owner:	Glaxo Group Ltd.
Type:	Drug product Composition/Formulation

The undersigned declares that U.S. Patent No. 5,047,407, covers the composition, formulation, and/or methods of use of Epivir-HBV® (lamivudine) Tablets. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

The undersigned declares that U.S. Patent No. 5,532,246 covers the composition, formulation, and/or methods of use of Epivir-HBV® (lamivudine) Tablets. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

The undersigned declares that U.S. Patent No. 5,905,082 covers the composition, formulation, and/or methods of use of Epivir-HBV® (lamivudine) Tablets. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

January 11, 2001
Date

Karen L. Prus, Ph.D.
Registered Patent Attorney
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Please address all communications to:

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EXCLUSIVITY SUMMARY for NDA # 21-003/21-004 SUPPL # SE1-002/002

Trade Name Epivir-HBV Generic Name lamivudine

Applicant Name GlaxoSmithKline HFD-530

Approval Date August17, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1-002/002

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /_X_/ NO /__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

The sponsor has requested three years of exclusivity

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_X_/ NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X_/ NO /___/

If yes, NDA # 21-003/21-004 has been approved for adults, this application provides for the treatment of chronic HBV in pediatric patients.

Drug Name Epivir-HBV

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/

Signature of Preparer

7-20-01

Date

Title: CSO

/S/

Signature of Office of Division Director

8/16/01

Date

cc:
Archival NDA
HFD-530/Division File
HFD-530/CSO/Lincoln
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

A/ # 21-003/21-004 Supplement # 002/002 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6 SE8

HFD-530 Trade and generic names/dosage form: EPIVIR-HBV®(lamivudine tablets and oral solution Action: (AP) AE NA

Applicant: GlaxoSmithKine Therapeutic Class Hepatitis B

Indication(s) previously approved: for the treatment of chronic HBV infection

Pediatric information in labeling of approved indication(s) is adequate X inadequate _

Proposed indication in this application to provide for the treatment of chronic HBV in pediatric patients

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? X Yes (Continue with questions) ___ No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
X Neonates (Birth-1month) X Infants (1month-2yrs) X Children (2-12yrs) X Adolescents (12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

X 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
- ___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- ___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- ___ c. The applicant has committed to doing such studies as will be required.
  - ___ (1) Studies are ongoing,
  - ___ (2) Protocols were submitted and approved.
  - ___ (3) Protocols were submitted and are under review.
  - ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
- ___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply**, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? X Yes ___No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from /S/ (e.g., medical review, medical officer, team leader).

/S/ 7-30-01

Signature of Preparer and Title Date

Archival NDA/PLA/PMA # 21-003/21-004
HFD-530 /Div File
NDA/PLA Action Package
HFD-104/Peds/T.Crescenzi

(revised 3/6/00)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, TERRIE CRESCENZI, HFD-104 (CRESCENZIT)

NDA 21-003
NDA 21-004

Epivir-HBV®
(lamivudine) Tablets and Oral Solution

Supplemental New Drug Application: Pediatrics

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

	11 NOV 2001
Charles E. Mueller Head, North American Clinical Compliance World Wide Compliance	Date

GROUP LEADER MEMORANDUM

NDA:	**21-003/SE1-002 and 21-004/SE1-002**
Drug and Indication:	**Epivir-HBV® for treatment of chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation in children 2 years of age and older**
Dose:	**3 mg/kg/day to a maximum of 100 mg/day, studied for one year**
Applicant:	**Glaxo SmithKline Inc.**
Submission Received:	**February 28, 2001**
Date of Memorandum:	**July 30, 2001**

I. Resume

In support of oral lamivudine for treatment of chronic hepatitis B in pediatric patients, the applicant has submitted safety and efficacy data from a randomized double-blind placebo-controlled study of treatment efficacy (NUC30903) that enrolled 288 children ages 2 to 17 years. Limited supporting data were submitted from a short-term pharmacokinetic and antiviral activity study (NUCB2020) that was previously submitted in the original NDA for Epivir-HBV

Lamivudine was originally approved as Epivir-HBV for treatment of chronic hepatitis B in 1998 based on placebo-controlled studies in adults, and has also been approved at a higher dose (as Epivir®) for use in combination therapy of HIV infection.

The principal pediatric efficacy study showed statistically significant results in the protocol-defined primary analysis of proportion of children with conversion to negative hepatitis B e antigen and HBV DNA below the assay limit of the investigational assay employed in the study, evaluated at week 52 with missing values considered as failures. Analyses of secondary endpoints including HBV DNA response and transaminase normalization showed robust treatment effects in favor of lamivudine treatment; endpoints driven by e antigen results showed smaller effects and more heterogeneity across subgroups but again generally favored the active treatment group. Emergence of viral resistance, and recrudescence of viral DNA and/or transaminase levels during or after treatment, were the principal safety issues and had similarly been identified as concerns during review of adult studies. Based upon consideration of the clinical trials in pediatric hepatitis B, in the context of information regarding other hepatitis

treatments and of previous studies leading to approval of lamivudine (as Epivir-HBV) for adults with chronic hepatitis B and (as Epivir) for adults and children with HIV infection, and discussion of pediatric study expectations with Pediatric Exclusivity Board members, this supplement was considered suitable for approval.

The principal safety and efficacy issues in the review of this supplement are well summarized by Dr. Melisse Baylor in the primary clinical review. This memorandum will focus on some of the principal issues related to these studies, their context from previous studies in children, and other concurrent events related to use of lamivudine that were considered in the review process.

II. Efficacy issues

For the principal pediatric efficacy study (NUC30903), the applicant used a primary endpoint of loss of hepatitis B e antigen and reduction of HBV DNA below the assay limit of the research assay employed in the study, assessed at week 52 with missing values treated as failures. The preliminary pharmacokinetic/activity study (NUCB2020) measured blood levels of lamivudine and assessed HBV DNA over a 4-week treatment period using a research assay, but did not use either a treatment duration or outcome measures that could be considered to demonstrate clinical benefit.

A. Magnitude of effect and comparison with other lamivudine studies

The primary analysis of the principal outcome measure showed 23% of lamivudine subjects and 13% of placebo subjects reaching the primary endpoint, with a p value of .037. Both the magnitude of treatment effect and the p value were sensitive to treatment of missing data as outlined in Dr. Baylor's and Dr. Hammerstrom's reviews. Therefore, secondary endpoints including HBV DNA response and ALT normalization were examined in detail; as also described in the primary clinical and statistical reviews, these secondary endpoints showed much stronger and more robust associations with treatment assignment. Analyses of e antigen loss as a secondary endpoint showed similar results to the primary endpoint, which was itself determined in large part by e antigen loss.

There has been debate in the past regarding the most appropriate endpoint for studies of chronic hepatitis B, reflecting the variable natural history of this disease and the limited information regarding predictors of long-term outcomes such as end-stage liver disease or hepatocellular carcinoma. The adult studies that were performed under [redacted] and contributed to approval of Epivir-HBV in 1998 had a principal outcome measure based on histology at the beginning and end of a year's course of treatment, with response defined as a reduction of at least 2 points in the Knodell histologic activity index. A composite serologic/virologic measure (loss of e antigen,

gain of e antibody, and reduction of HBV DNA below the assay limit, using a different research assay from that employed in the pediatric studies) was considered as a principal secondary or co-primary endpoint. Other measurements such as reduction in ALT to normal levels and reduction in HBV DNA below the assay limit (and loss or reversal of such responses) were also analyzed, and consistency among outcome measures was considered important, but it was considered that too little information was available about even medium-term implications of such ancillary measures for them to replace outcomes that either assessed intrahepatic activity directly or measured multiple components of immunologic and virologic activity that were thought to be related to longer-term outcomes on the basis of natural history surveys. In the analysis of the adult studies, histologic response in fact showed a larger and more consistent treatment effect across studies than the composite serologic/virologic principal secondary endpoint, but the general pattern of primary and secondary analyses all tended in the same direction.

For pediatric studies, it was considered that serial biopsies could not be done, especially for study of a drug that had already shown effects on both histologic and non-histologic measures in adults. Evaluation of multiple endpoints was considered important, and the selected primary endpoint was considered more stringent than some of the secondary measures that may have more spontaneous variability in the course of natural disease and for which assay measures may be variable and less well standardized. The effect observed was modest, but the magnitude of effect was not clearly out of proportion to that observed in adult studies, and the analyses of secondary endpoints were supportive.

B. Durability of response

Durability of response was identified as an unresolved issue in adult studies. In the pediatric study and its follow-on continuation, a substantial proportion of patients with initial suppression of HBV DNA below the assay limit had return of assay-detectable HBV DNA despite continued treatment, with or without detection of resistance-associated viral mutations. In addition, some patients who apparently converted to negative e antigen had subsequent positive e antigen values, either during treatment or after cessation of treatment. All of these signals of possible limited durability have been observed in adult studies, and the numbers of subjects and duration of follow-up do not suffice to determine whether the risk of loss of response differs between adults and children.

C. Effects of baseline characteristics

In analyses of the primary endpoint in the principal pediatric efficacy study, younger and smaller children appeared to have more treatment responses than older children. Potential interactions with treatment effect were also observed for a number of other characteristics including baseline ALT and HBV DNA levels, baseline histology, sex, geographic region, and race. However, these various baseline characteristics also were not uniformly distributed with respect to one another, and it was difficult to assess which might be most important to predicting response. Additional examination of secondary endpoints showed patterns of treatment response that were discernible across multiple demographic subgroups and multiple strata of baseline disease activity, as described in the primary clinical and statistical reviews. Furthermore, when emergence of resistance was also assessed (see below), it was not possible to select identifiers available at the beginning of treatment that would reliably select subjects who would or would not benefit: for example, although younger smaller children had a higher proportion of responders on e antigen driven endpoints, they also had a higher proportion of resistance-associated viral variants emerging during therapy. Because of the small numbers in the various subgroups determined by baseline characteristics, the small number of subjects achieving e-antigen-related endpoints overall, and the lack of support from other studies for any clear identification of groups particularly likely or highly unlikely to benefit from treatment within the population defined by study entry criteria, after extensive discussion it was not considered reasonable to provide guidelines that would exclude parts of this population from consideration for treatment.

D. Pharmacokinetic/activity data

The preliminary pharmacokinetic study performed in children (NUCB2020) also measured short-term changes in HBV DNA using a research assay different from that used in previous studies of lamivudine in hepatitis B. Results were used principally to define dose-exposure relationships and to provide limited preliminary safety data as reflected in the original Epivir-HBV label. Decreases in HBV DNA were seen across doses and age groups, but were smaller in magnitude in the adolescent group (which received the adult dose and had exposure assessments comparable to adult studies) than in the younger children receiving doses giving exposure comparable to adult studies. Because of the differences in HBV DNA assays, the lack of reliable information to allow conversion of results between different HBV DNA assays, and the lack of information relating specific results from the assay used in this study to longer-term clinical or other outcomes, results from this study were not considered useful in evaluation of clinically meaningful efficacy even in the short term. It did provide preliminary evidence of short-term antiviral activity that contributed to the rationale for an efficacy study in pediatric patients.

E. Context of other studies of hepatitis treatment in children

Children who acquire hepatitis B infection, especially those infected by vertical transmission in the perinatal period, are more likely to develop chronic hepatitis than persons who become infected with hepatitis B at older ages. Some studies have suggested that chronic hepatitis progresses slowly in most such children, and natural history data are unclear with respect to the likelihood of spontaneous clearance or major reduction in disease activity after establishment of chronicity. Some children clearly do develop complications such as cirrhosis or hepatocellular carcinoma, and others infected in childhood remain at risk for such complications later in life. In general, there has been insufficient information regarding the relative risks of adverse outcomes with or without treatment to establish convincing similarity of natural history and treatment responses between adult and pediatric hepatitis B for confident extrapolation of pediatric treatment responses from adult studies, and the need for more information has been widely acknowledged.

Large-scale programs of vaccination against hepatitis B have shown major potential for reducing morbidity from this infection in children as well as adults. However, given the existing reservoir of children who are already chronically infected and the incomplete success of vaccination programs, for the foreseeable future there will be a meaningful number of children at risk for complications of chronic hepatitis B and a concomitant interest in development of effective treatments.

Several interferon preparations have been used in investigational treatment of chronic hepatitis B in children and one, Intron-A®, is licensed for this purpose in the United States. The package insert describes one pediatric study comparing Intron-A to a no-treatment arm in a total of 149 children. Because of major differences in study design such as duration of treatment and timing of outcome assessments relative to treatment, no direct comparisons can be made between the Intron-A study and information included in this lamivudine supplement. The primary endpoint in the Intron-A study was loss of e antigen and undetectable HBV DNA 6 months after the end of a 16 to 24 week course of treatment, and this outcome was observed in 24% of interferon recipients and 10% of placebo recipients ($p=.05$); the package insert also notes that normal ALT was observed in 17% of interferon and 16% of placebo recipients 6 months after treatment. Larger treatment differences for both the primary endpoint and the ALT normalization outcome were reported for adult studies described in the package insert; histologic comparisons between interferon and control patients were described for one of the adult studies, as showing no significant difference. The limitations of interferon treatment include production of a treatment response in only a minority of recipients, the need for parenteral administration, and frequent side effects that limit acceptability for some users. As noted in Dr. Baylor's review, a substantial proportion of the subjects recruited for study NUC30903 had previous experience with interferon but had evidence of ongoing active disease sufficient for study eligibility.

III. Safety issues

A. Safety during initial treatment in pediatric studies

As noted in Dr. Baylor's review, studies NUCB2020 and NUC30903 raised no new safety concerns relative to those previously recognized with lamivudine. The safety database for this drug includes extensive experience in the treatment of adults and children with HIV (for whom dosing is higher than that studied for chronic hepatitis B), and more recent experience in adults with chronic hepatitis B, all of which have contributed to existing product labeling. The most prominent safety concern arising in this study is the risk of emergence of resistance-associated viral mutations, which have also been associated with increases in ALT and evidence of lesser treatment response on all measures relative to patients receiving lamivudine and not manifesting such viral mutations. This concern has similarly been noted in adult studies and will be discussed further below.

B. [redacted]

[redacted]

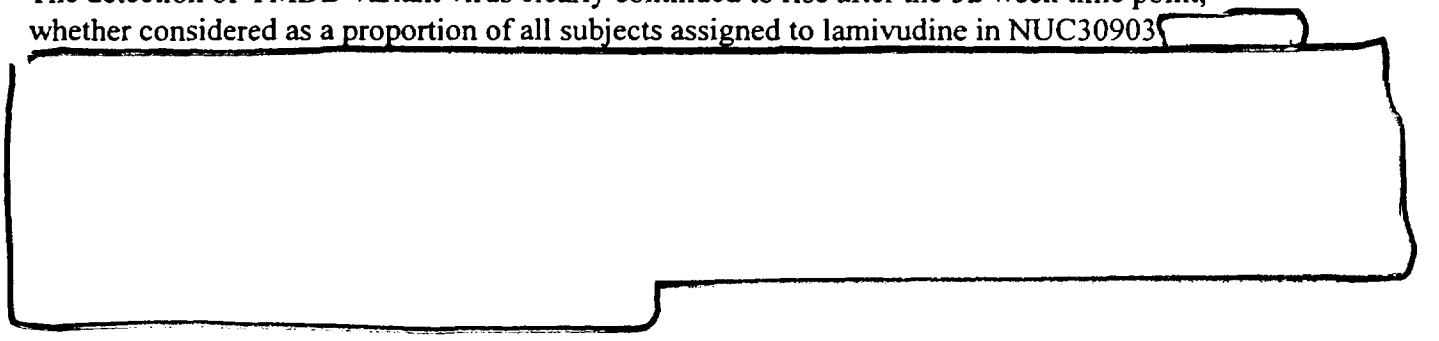
IV. [redacted]

[redacted]

A. Incidence of resistance-associated genotypic variants

YMDD variants were detected in 18% of week 52 samples assayed from lamivudine recipients in NUC30903. One additional lamivudine subject was later assumed to have probable variant virus (see discussion in Safety Update) as the most likely source of a YMDD variant labeled as originating from a placebo recipient: the two patients reportedly visited the same center on the same day, and their subsequent course together with the extreme rarity of such variants in past studies of lamivudine-unexposed patients raised the possibility of a sample mixup. An estimate of either 18% or 19% would be within the range observed after 52 weeks of treatment in the principal adult studies (16% to 32% across three studies).

The detection of YMDD variant virus clearly continued to rise after the 52 week time point, whether considered as a proportion of all subjects assigned to lamivudine in NUC30903



B. Association of resistance-associated mutants with other outcomes

As in the adult studies, subjects who developed YMDD variants had less likelihood of improvement than those who received lamivudine and did not have detectable viral variants, for every outcome examined. For outcomes involving loss of e antigen, subjects who developed YMDD variants fared no better than placebo recipients. The study design did not permit assessment of the relative value of continuing or stopping treatment after emergence of YMDD mutants. An argument might be made that it would be desirable to exclude those destined to develop such viral variants from treatment (although this subgroup might have transient improvement in ALT and HBV DNA levels relative to those receiving no treatment at all), but although variant emergence showed some associations with baseline characteristics, these patients could not be identified prospectively with enough confidence to allow definitive selection for treatment or no treatment.

V. Labeling discussions and Phase 4 commitments

Labeling discussions included issues such as the representation of principal and secondary outcomes and the updating of virologic information (based on adult data and literature review as well as the data from the principal pediatric study). Phase 4 commitments were drafted to address the following topics:

- longer-term follow-up of children treated with lamivudine for chronic hepatitis B, especially for major clinical outcomes such as endstage liver disease or transplant, hepatocellular carcinoma, and death.
- additional data on treatment responses and risk/benefit evaluation in adolescents.
- evaluation of the relationship between pharmacokinetics and treatment response.
- risk factors for emergence of YMDD variants, risk factors for re-emergence of HBV DNA during treatment without YMDD variants, and the mechanism of HBV DNA re-emergence not associated with YMDD variants.
- assessment of relative risks and benefits of stopping, continuing, or changing treatment after emergence of resistance-associated mutations.
- viral genetic analyses on samples from patients with reported negative HBV surface or e antigen, especially for anomalous results relative to other virologic/serologic/biochemical measurements.

VI. Summary

The principal pediatric efficacy study showed a modest difference between lamivudine and placebo recipients for the principal primary endpoint. Only a minority of lamivudine recipients reached this endpoint and the result varied on sensitivity analyses and in multiple subgroup analyses; however, the protocol-defined primary analysis was statistically significant and the magnitude of treatment effect was not strikingly different from those observed with composite serologic/virologic endpoints in adult studies of lamivudine or in the pediatric study supporting approval of the sole alternative licensed treatment for chronic hepatitis B in children. Analyses of secondary endpoints such as transaminase normalization and reduction of HBV DNA below the research assay limit were strongly supportive and showed treatment effects across multiple subgroup evaluations. The principal safety issues arising from the pediatric data included emergence of resistance-associated viral variants with consequent diminished treatment effect, and post-treatment flares of liver enzyme abnormalities, both consistent with the known safety profile in adults.

VII. Conclusions

We agree with the conclusions of the primary reviewers that the study results submitted in this supplement, evaluated in the context of other currently available information regarding antiviral treatment of chronic hepatitis B, are supportive of a treatment effect in the pediatric age group and can be used to provide useful labeling information for practitioners considering such treatment. These evaluations are based on the results of the principal pediatric efficacy study NUC30903 plus limited activity data from pharmacokinetic study NUCB2020 [redacted]

/S/

Barbara A. Styrt, M.D., M.P.H.
Medical Officer, Division of Antiviral Drug Products, HFD-530

/S/ 8/1/01

Stanka Kukich, M.D.
Medical Team Leader, Division of Antiviral Drug Products, HFD-530

Concurrence:

HFD-530/ActDir/DBirnkrant /S/ 8/16/01

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: May 30, 2001

To: Mary Martinson

Address: GlaxoSmithKline
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709
Fax (919) 483-5756

From: Christine Lincoln, RN, MS, MBA, Regulatory Project Manger

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530
Melisse Baylor, M.D., Medical Reviewer, HFD-530

NDA: 21-003 and 21-004

Subject: Pediatric Efficacy Supplement for Epivir-HBV

The following are requests for additional information concerning study NUC30903 in order to facilitate our review of the pediatric efficacy supplement for Epivir-HBV. As we continue this review, additional requests may follow.

1. Please define the exact mode of HBV acquisition when it is listed as "other."

2. According to Listing 16, several patients had biopsies during the study. Please clarify the type of biopsy and the indication for that biopsy in patients 35466, 35256, 35257, 35468, 35631, 35636, and 35644.

3. Please provide separate datasets as SAS transport files to include the following information:

   a. Mode of HBV acquisition and time to diagnosis of hepatitis B infection for each patient in NUC30903.

   b. The Knodell and the Ishak scores for each patient at baseline. The Knodell scores are already provided in datasets, but it is unclear if these biopsies were read by the central or local pathologist. Please provide a data set which includes the results from both the central and local pathologist and clearly specify which is which. In addition, include the results of any liver biopsies done during the study, the indication, and the results.

c. A dataset listing concurrent illnesses by diagnosis, not by organ system for each patient

d. A dataset listing patient identification number, previous treatment of hepatitis, and dates of treatment.

e. A dataset listing concurrent medications received during the study as shown in Table 14.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Christine Lincoln, RN, MS, MBA
Regulatory Health Project Manager
Division of Antiviral Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

RECORD OF TELECONFERENCE

NDA: **21-003 and 21-004**

DATE: **June 6, 2001**

DRUG: **Epivir®(lamivudine) tablets and oral solution**

SPONSOR: **GlaxoSmithKline**

BETWEEN: **Representatives of GlaxoSmithKline**
Mark Atkins, M.D. - Hepatitis project physician
Jeff Johnston, M.D. - Head US Antiviral Clinical Development
Steve Gardner - Hepatitis Clinical Development
Steve Bell - NUC30903 and NUC30926 studies team leader
Randy Davis - Hepatitis clinical statistician
Nancy Little - NUC30903 and NUC30926 studies clinical statistician
Mary Martinson - US Regulatory Affairs

AND: **Representatives of FDA, Div. Of Antiviral Drug Products**
Stanka Kukich, M.D., Medical Team Leader
Melisse Baylor, M.D., Medical Reviewer
Barbara Styrt, M.D., Medical Reviewer
Christine Lincoln, RN, MS, MBA, Project Manger

SUBJECT: **Required data to facilitate pediatric efficacy supplement.**

BACKGROUND: This teleconference was held at the request of FDA to discuss the format and content of additional data needed to facilitate the review of the sponsor's pediatric efficacy supplement for Epivir-HBV. Please refer to the fax sent to the sponsor May 30, 2001.

DISCUSSION:

1. FDA requested that the sponsor clarify the exact HBV mode of acquisition for patients in study NUC30903 when it is listed as "other."

2. According to Listing 16, several patients had biopsies during the study. FDA requested that the sponsor clarify the type of biopsy, the indication for that biopsy, and the timing of the biopsy (i.e., at screening, baseline, or during study treatment).

3. FDA noted that the assay for "e" antigen changed during the study. FDA asked the sponsor to clarify if any "e" antigen results changed after the change to a different assay.

   GSK stated that 9 patients had different assays used at week 48. However, at week 52 all of the patients used the same assay. The sponsor stated that they would submit the results of the "e" antigen by assay.

4. FDA requested that the sponsor provide separate datasets as SAS transport files to include the following information:

   a. Mode of HBV acquisition and time to diagnosis of hepatitis B infection for each patient in NUC30903.

      Please provide a data set, which includes both the Knodell and Ishak histopathology scores along with the baseline ALT and HBV DNA results. In addition, this data set should also include certain endpoints for each patient such as CVR, normalization of ALT, and HBV DNA reduction. Each subject should have be represented by a single line entry similar to the DPOP data set

   b. A dataset listing concurrent illnesses by diagnosis, not by organ system for each patient

   c. A dataset listing patient identification number, previous treatment of hepatitis, and dates of treatment.

   d. A dataset listing concurrent medications received during the study as shown in Table 14.

ACTIONS:

1. The sponsor will provide the information requested above by the end of next week. However, item 4 (c) will be sent later because it will take longer to gather that information. It will be sent as soon as it is available.

2. The sponsor is sending in the safety update next Monday.

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

RECORD OF TELECONFERENCE

NDA: **21-003 and 21-004**

DATE: **June 29, 2001**

DRUG: **Epivir®(lamivudine) tablets and oral solution**

SPONSOR: **GlaxoSmithKline**

BETWEEN: **Representatives of GlaxoSmithKline**
Steve Bell - NUC30903 and NUC30926 Clinical Study Team Leader
Nancy Little - NUC30903 and NUC30926 Study Statistician
Randy Davis - Hepatitis Project Statistician
Bob Watson - US Regulatory

AND: **Representatives of FDA, Div. Of Antiviral Drug Products**
Stanka Kukich, M.D., Medical Team Leader
Barbara Styrt, M.D., Medical Reviewer
Tom Hammerstrom, Ph.D., Statistical Reviewer
Christine Lincoln, RN, MS, MBA, Project Manger

SUBJECT: **Pediatric efficacy supplement**

BACKGROUND: This teleconference was held at the request of FDA to discuss additional data needed for review and the labeling for the sponsor's pediatric efficacy supplement for Epivir-HBV. Please refer to the faxes sent to the sponsor June 26, and 27, 2001.

DISCUSSION:

A. [redacted]

[redacted]

5. **For the applicant's ease of reference, FDA can provide a summary of the above specific analyses needed in addition to those already found in the 6-month interim analysis (additional requests may follow during review).**

   The sponsor agreed to provide all of the above.

ACTIONS:

1. The sponsor stated that they would provide all adverse events in one data set, and all laboratory toxicities in another data set.

2. [redacted]

3. FDA will provide a faxed copy of the requested information from today's teleconference to the sponsor.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

RECORD OF TELECONFERENCE

NDA: **21-003 and 21-004**

DATE: **July 17, 2001**

DRUG: **Epivir®(lamivudine) tablets and oral solution**

SPONSOR: **GlaxoSmithKline**

BETWEEN: **Representatives of GlaxoSmithKline**
David Cocchetto, PhD - US Regulatory Affairs
Mary Martinson - US Regulatory Affairs
Steve Gardener - Clinical Research, Hepatitis
Mark Atkins, MD - Project Physician
Steve Bell - NUC30903 and NUC30926 Clinical Study Team Leader
Randy Davis - Clinical Statistician
Melissa Beaman

AND: **Representatives of FDA, Div. Of Antiviral Drug Products**
Stanka Kukich, M.D., Medical Team Leader
Barbara Styrt, M.D., Medical Reviewer
Lalji Mishra Ph.D., Microbiology Reviewer
Christine Lincoln, RN, MS, MBA, Project Manger

SUBJECT: **Pediatric efficacy supplement**

BACKGROUND: FDA requested this teleconference to clarify issues regarding several of the applicant's responses to previous label comments, and proposed to take the applicant's letter of response dated July 6 as the agenda and briefly go over the principal issues listed in that letter. FDA responses to the applicant's written comments are summarized below, with additional discussion in brackets after each point.

DISCUSSION:

1. Drug resistance: Applicant proposed to restore the sentence about replication competence of YMDD variants.

   FDA noted that deletion of this sentence is based on several points.

   a. The accumulated literature on in vitro studies, which has increased since the original approval, does not support the statement. For example, one of the cited articles did

not control for efficiency of transfection; another found variable effects in different cell lines; one found no effect on levels of RNA transcript and referred to evidence of adequate virus replication in patients; multiple articles have reported that the L528M mutation is compensatory and a recent publication (2001) reported it to be almost fully compensatory.

b. There is a risk that clinicians may take such a statement as implying reduced virulence. The follow-on data from adult studies, cited by the applicant as supporting such an assumption, have not been submitted as a supplement but the IND submissions were noted by DAVDP and were not found to support reduced virulence or improved clinical outcome after emergence of YMDD variants during treatment.

c. Experience over the last several years with antivirals and in vitro data of this type generally does not support inclusion of such a statement in the label even if better supported than in this case, because of enhanced awareness that statements of in vitro results may be interpreted as having more definite clinical implications than they were intended to convey or are capable of supporting.

[Applicant stated there is some evidence in each direction in the in vitro studies. FDA reiterated the importance of avoiding inadvertent confusion between in vitro replication competence and clinical virulence. Applicant agreed.]

2. Description of clinical studies: applicant requested "the remaining clinical comments" before responding to the statement of age variability in treatment response in the principal pediatric study.

FDA clarified that the review team has followed the practice of supplying comments to facilitate dialogue on labeling issues; there will not be a time when "all comments have been sent" short of the time of action, given the potential for additional issues to arise from additional amendments or other sources, but the intent is to ensure adequate opportunity for input. Relationship of age to treatment response was identified as an issue based on the applicant's subgroup analyses of outcomes in NUC30903, and the concern was supported by the applicant's analyses of PK study NUCB2020 although the latter did not provide efficacy data. The review team is continuing to discuss the best way of addressing age groups, and would be very interested in seeing any input from the applicant, as soon as possible if it is to make a constructive contribution to the review process.

[Applicant acknowledged that the sentence regarding age groups "is factually correct" and that they do consider the relationship of age to outcome to be an issue, but have found conclusions difficult to draw because they have not performed a separate adequate and well-controlled study in adolescents. They see this issue as potentially affecting different parts of the label. FDA invited the applicant to provide any alternative wording and rationale they wish to propose & would be glad to review it; would also be interested in any future plans the applicant may have for further study of the issue. Applicant stated the analysis was a retrospective subgroup analysis but it did produce the results stated and

they do not disagree with the proposed wording nor have any alternative to propose. FDA stated there will probably be some modifications based on ongoing internal discussions and these will be conveyed in subsequent label comments.]

3. Observed During Clinical Practice: Applicant requested case documentation for pure red cell aplasia. [redacted]

4. Dosage and administration: Applicant reinstated sentence recommending 5 mg/ml oral solution if a liquid formulation is needed.

   FDA clarified that the concern with this wording is that it suggests the 5 mg/ml oral solution is not the only oral solution of EPIVIR-HBV, thereby risking confusion among the different lamivudine-containing products that major effort has been devoted to distinguishing. The review team has been working on alternative wording and will provide this with subsequent label comments.

5. Other issues in teleconference discussion:

   Applicant said the additional analyses requested in previous teleconference will be mailed today.

   FDA indicated additional label comments will be conveyed within the next few days.

ACTIONS:

1. The sponsor stated that they would be mailing the additional analysis requested by the FDA during the June 29, 2001 teleconference tomorrow.

2. FDA will send additional labeling comments to the sponsor within the next few days.