CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-003
21-004

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

GlaxoWellcome

DESK COPY

December 9, 1998

Heidi M. Jolson, M.D., M.P.H.
Director, Division of Antiviral Drug Products
HFD-530
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 21-003; Epivir-HBV (lamivudine) Tablets;
NDA 21-004; Epivir-HBV (lamivudine) Oral Solution;
General Correspondence: FDA-Approved Version of Draft Labeling

Dear Dr. Jolson:

Reference is made to the approval letters of December 8, 1998 for NDA 21-003 and NDA 21-004. We acknowledge and appreciate the sustained effort by the review team and Divisional management on these applications. We have every confidence that Epivir-HBV products will make an important contribution to the care of patients with chronic hepatitis B. In addition, we are hopeful that development and approval of Epivir-HBV products is the first step in our collective effort towards the development and registration of even more effective therapeutic options for these patients.

The approval letter of December 8 states that the final printed labeling must be identical to the draft package insert submitted on December 3, 1998 with the deletion of the proposed virologic references numbered 1 and 2, as agreed during the teleconference of December 8, 1998 between Mr. Zeccola and I. This was agreed and I appreciate everyone's effort to bring this to closure on December 8. As follow up to the approval letter and teleconference of December 8, I am now submitting the FDA-approved version of draft labeling. As agreed, we deleted the two references by Melegari *et al.* and Allen *et al.* from the draft labeling of December 3, so that the enclosed labeling only retains one reference (i.e., the publication by Knodell *et al.*).

Please also note that the HOW SUPPLIED section in the enclosed draft labeling describes the bottles of 60 tablets, but it does not describe the bottles of 180 tablets. Although both the 60 count and 180 count bottles are approved, we are concentrating solely on the 60 count

Glaxo Wellcome Research and Development
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709
Telephone
919 248 2100
A Division of
Glaxo Wellcome Inc.

bottle for initial distribution of Epivir-HBV Tablets. Therefore, since the 180 count bottle will not be available to pharmacies and prescribers, we deleted this item from the HOW SUPPLIED section of the enclosed draft labeling. We have initiated preparation of final printed labeling and will submit copies to the Division, in the format requested in the letter of December 8.

This submission is provided in duplicate to NDA 21-003. A copy of the cover letter only has been submitted to NDA 21-004. Seven desk copies (with a WORD file on diskette) have been provided directly to Mr. Zeccola for use by the review team. Please contact me at (919)-483-5127 for any matters regarding this application. Thank you.

Sincerely,

David M. Cocchetto, Ph.D.
Group Director, Regulatory Affairs

cc: A. Zeccola (HFD-530)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338.
Expiration Date: April 30, 2000.
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Glaxo Wellcome Inc.

DATE OF SUBMISSION
December 9, 1998

TELEPHONE NO. (Include Area Code)
(919) 483-2100

FACSIMILE (FAX) Number (Include Area Code)
(919) 483-5756

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued):
Five Moore Drive
Research Triangle Park, NC 27709

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-003

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
Lamivudine Tablets

PROPRIETARY NAME (trade name) IF ANY
Epivir®-HBV™ (lamivudine) Tablets

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)
(2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one

CODE NAME (if any)
GR109714X

DOSAGE FORM:
Tablets

STRENGTHS:
100 mg

ROUTE OF ADMINISTRATION:
oral

(PROPOSED) INDICATION(S) FOR USE
Treatment of Chronic Hepatitis B

APPLICATION INFORMATION

APPLICATION TYPE (check one)
[X] NEW DRUG APPLICATION (21 CFR 314.50)
[ ] ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
[ ] BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE
[X] 505 (b) (1)
[ ] 505 (b) (2)
[ ] 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug
Holder of Approved Application

TYPE OF SUBMISSION (check one)
[ ] ORIGINAL APPLICATION
[ ] AMENDMENT TO A PENDING APPLICATION
[ ] RESUBMISSION
[ ] PRESUBMISSION
[ ] ANNUAL REPORT
[ ] ESTABLISHMENT DESCRIPTION SUPPLEMENT
[ ] SUPAC SUPPLEMENT
[ ] EFFICACY SUPPLEMENT
[ ] LABELING SUPPLEMENT
[ ] CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
[X] OTHER

REASON FOR SUBMISSION
General Correspondence: FDA-Approved Version of Draft Labeling

PROPOSED MARKETING STATUS (check one)
[X] PRESCRIPTION PRODUCT (Rx)
[ ] OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS
[X] PAPER
[ ] PAPER AND ELECTRONIC
[ ] ELECTRONIC

ESTABLISHMENT INFORMATION N/A

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IN
IN
IN

This application contains the following items: *(Check all that apply)*		
	1. Index	
X	2. Labeling (check one)	[X] Draft Labeling [ ] Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))	
	4. Chemistry section	
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
	C. Methods Validation Package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2), 21 CFR 601.2)	
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3) , 21 CFR 601.2)	
	7. Clinical Microbiology (21 CFR 314.50 (d) (4))	
	8. Clinical data section (21 CFR 314.50 (d) (5))	
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b) , 21 CFR 601.2)	
	10. Statistical section (21 CFR 314.50 (d) (6) , 21 CFR 601.2)	
	11. Case report tabulations (21 CFR 314.50 (f) (1) , 21 CFR 601.2)	
	12. Case reports forms (21 CFR 314.50 (f) (2) , 21 CFR 601.2)	
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))	
	15. Establishment description (21 CFR Part 600, if applicable)	
	16. Debarment certification (FD&C Act 306 (k)(1))	
	17. Field copy certification (21 CFR 314.5 (k) (3))	
	18. User Fee Cover Sheet (Form FDA 3397)	
	19. OTHER (Specify)	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biologic product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
David M. Cocchetto	David M. Cocchetto, Ph.D. Group Director, Regulatory Affairs	December 9, 1998

ADDRESS (Street, City, State, and ZIP Code)	Telephone Number
Five Moore Drive Research Triangle Park, NC 27709	(919) 483-5127

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338. Expiration Date: April 30, 2000. See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Glaxo Wellcome Inc.	DATE OF SUBMISSION December 9, 1998
TELEPHONE NO. (Include Area Code) (919) 483-2100	FACSIMILE (FAX) Number (Include Area Code) (919) 483-5756
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued): Five Moore Drive Research Triangle Park, NC 27709	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-004

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Lamivudine Oral Solution	PROPRIETARY NAME (trade name) IF ANY Epivir®-HBV™ (lamivudine) Oral Solution
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one	CODE NAME (if any) GR109714X

DOSAGE FORM: Oral Solution	STRENGTHS: 5 mg/mL	ROUTE OF ADMINISTRATION: oral

(PROPOSED) INDICATION(S) FOR USE
Treatment of Chronic Hepatitis B

APPLICATION INFORMATION

APPLICATION TYPE (check one)
[X] NEW DRUG APPLICATION (21 CFR 314.50) [ ] ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
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Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
[ ] ORIGINAL APPLICATION [ ] AMENDMENT TO A PENDING APPLICATION [ ] RESUBMISSION
[ ] PRESUBMISSION [ ] ANNUAL REPORT [ ] ESTABLISHMENT DESCRIPTION SUPPLEMENT [ ] SUPAC SUPPLEMENT
[ ] EFFICACY SUPPLEMENT [ ] LABELING SUPPLEMENT [ ] CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT [X] OTHER

REASON FOR SUBMISSION
General Correspondence: FDA-Approved Version of Draft Labeling

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ESTABLISHMENT INFORMATION N/A

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
David M. Cocchette	David M. Cocchette, Ph.D. Group Director, Regulatory Affairs	December 9, 1998

ADDRESS (Street, City, State, and ZIP Code)	Telephone Number
Five Moore Drive Research Triangle Park, NC 27709	(919) 483-5127

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DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

GlaxoWellcome

June 17, 1998

Mellon Bank
Food and Drug Administration
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

Re: NDA 21-003; Epivir®-HBV™ (lamivudine) Tablets
User Fee# 3462

Please find enclosed Glaxo Wellcome ... This Payment is 100% of the application fee for the New Drug Application for Epivir®-HBV™ (lamivudine) Tablets for treatment of chronic hepatitis B infection.

A full supplemental fee is being paid for this new drug application. For further clarification, reference is made to the telecon between Dr. David Cocchetto of Glaxo Wellcome and Mr. Anthony Zeccola of the Agency on April 22nd, 1998. As was discussed during this telecon, the original intent regarding this application was to file a Supplemental New Drug Application to NDA 20-564 (Epivir® Tablets) and, in accordance with PDUFA requirements, pay a supplemental application fee at the time of submission. Mr. Anthony Zeccola acknowledged this understanding but requested, for internal administrative reasons and to facilitate review, that this application be the subject of a separate New Drug Application, NDA 21-003. Glaxo Wellcome agreed to submit a new NDA, providing that the user fee would be that for a supplemental application.

Mr. Zeccola noted that this matter had been discussed with Mr. Michael Jones, who agreed that current procedures within the User Fee division do accomodate this situation, and that because a new NDA is an FDA proposal for FDA's administrative needs, that a fee appropriate for a supplemental application would be assessed for this application.

This application will be submitted to the Center for Drug Evaluation and Research, FDA by the end of June, 1998.

Glaxo Wellcome Research and Development
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709
Telephone
919 248 2100
A Division of
Glaxo Wellcome Inc.

Please find below requested information regarding this application

Type of Application:	New Drug Application with Clinical Data	X
	New Drug Application without Clinical Data	
	Supplemental New Drug Application with Clinical Data	

Should you have any questions, please contact me at (919) 483-5107. Thank you.

Sincerely,

Leslie C. Rogers, M.D.
Project Director, Regulatory Affairs

enclosure

ITEM 18
User Fee Cover Sheet
Statutory Exemption from User Fee for New Drug Application for Epivir®-HBV™ (lamivudine) Oral Solution

Reference is made to the teleconference held between Dr. David Cocchetto of Glaxo Wellcome and Mr. Anthony Zeccola of the Agency on April 22nd, 1998. As was discussed during this teleconference, the original intent regarding this application was to file a Supplemental New Drug Application to NDA 20-596 (Epivir® Oral Solution). In accordance with the Prescription Drug User Fee Act, as amended by Section 103(a)(2)(C) of the Food and Drug Administration Modernization Act of 1997, such a Supplemental New Drug Application would be statutorily exempt from a user fee as the supplement would be submitted to seek approval for a pediatric indication. Mr. Zeccola acknowledged this understanding but requested, for intra-agency administrative reasons and to facilitate review, that this application be the subject of a separate New Drug Application, NDA 21-004. Glaxo Wellcome agreed to submit a new NDA, providing no user fee would be applied to this application.

Mr. Zeccola noted that this matter had been discussed with Mr. Michael Jones, who agreed that current procedures within the User Fee division do accommodate this situation, and that because a new NDA is an FDA proposal for FDA's administrative needs, no user fee would be assessed for this application.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-003

Epivir®-HBV™ Tablets
(lamivudine 100mg tablets)

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that to the best of its knowledge and belief, it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

10 Jun 98

Richard D. Kieman
Vice President & World Wide Director
World Wide Compliance

Date

.....

The list of Glaxo Wellcome Principal Investigators for the above titled submission has been compared with the 12Nov97 Food and Drug Administration Debarment List and the 27Apr98 Disqualified, Restricted, and Given Assurances lists.

Jeanne Kistler

08-Jun-98

Jeanne Kistler
Compliance Standards & Information Administrator
World Wide Compliance

Date

PATENT INFORMATION
for
NDA 21-003
Epivir®-HBV™ Tablets

Active Ingredient:	Lamivudine
Dosage Form:	Tablets
Strength of Drug Product:	100mg of lamivudine per tablet
Route of Administration:	Oral
Applicant Firm Name:	Glaxo Wellcome Inc.

Patent Number: 5,047,407

Owner	BioChem Pharma (IAF Biochem International, Inc.) License owned by Glaxo Wellcome Inc.
Coverage:	Lamivudine per se, formulations and methods of use
Issue Date:	September 10, 1991
Expiration Date:	February 8, 2009

Patent Number: 5,532,246

Owner	BioChem Pharma, Inc. License owned by Glaxo Wellcome Inc.
Coverage:	The use of lamivudine in patients with hepatitis B infection
Issue Date:	2 July, 1996
Expiration Date:	2 July, 2013

The undersigned certifies to the best of his knowledge and belief that the above-listed patents cover the composition and method of use of Epivir® Tablets the subject of a New Drug Application.

2 June, 1998
Date

Charles E. Dadswell
Registered Patent Attorney
United States Registration No. 35,851

APPEARS THIS WAY
ON ORIGINAL

PATENT INFORMATION
for
NDA 21-004
Epivir®-HBV™ Oral Solution

Active Ingredient:	Lamivudine
Dosage Form:	Solution
Strength of Drug Product:	5 mg/ml
Route of Administration:	Oral
Applicant Firm Name:	Glaxo Wellcome Inc.

Patent Number: **5,047,407**

Owner	BioChem Pharma (IAF Biochem International, Inc.) License owned by Glaxo Wellcome Inc.
Coverage:	Lamivudine per se, formulations and methods of use
Issue Date:	September 10, 1991
Expiration Date:	February 8, 2009

Patent Number: **5,532,246**

Owner	BioChem Pharma, Inc. License owned by Glaxo Wellcome Inc.
Coverage:	The use of lamivudine in patients with hepatitis B infection
Issue Date:	2 July, 1996
Expiration Date:	2 July, 2013

The undersigned certifies to the best of his knowledge and belief that the above-listed patents cover the composition and method of use of Epivir® Oral Solution the subject of a New Drug Application.

2 June, 1998
Date

Charles E. Dadswell
Registered Patent Attorney
United States Registration No. 35,851

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA #: 21-003, 21-004
Trade Name: Epivir®-HBV™ Generic Name: lamivudine
Applicant Name: Glaxo Wellcome, Inc. HFD #: 530
Approval Date If Known: December 8, 1998

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 question 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

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?
Applicant's request did not specify

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

YES /___/ NO /X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 /X/ NO /___/

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

NDA# 20-564 Epivir® (lamivudine) Tablets

NDA# 20-596 Epivir® (lamivudine) Oral Solution

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 /X/

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

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

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 /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 /X/ 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 8:

(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 /X/

(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 /X/

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 /X/

If yes, explain:

© 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:

NUCB3009, NUCA3010, NCAB3011

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /__/ NO /X/

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

_____ _____

_____ _____

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 /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /__/ NO /X/

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

_____ _____

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"):

NUCB3009 NUCA3010
NUCAB3011

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 YES /X/ NO /__/

Investigation #2 YES /X/ NO /__/

Investigation #3 YES /X/ NO /__/

(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 _____

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 /X/

If yes, explain: _____

_____

/S/ 12/21/98

Anthony M. Zeccola Date
Regulatory Management Officer, HFD-530

/S/ 12/21/98

Heidi M. Jolson, M.D., M.P.H. Date
Division Director, HFD-530

cc:
NDA 21-003
NDA 21-004
HFD-85

APPEARS THIS WAY
ON ORIGINAL

Marketing Exclusivity

NDA 21-003

Epivir®-HBV™ (lamivudine) Tablets

Request for Marketing Exclusivity

Pursuant to Section 505(c)(3)(D)(iii) and 505(j)(5)(D)(iii) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.108(b)(4), Glaxo Wellcome Inc. requests three years of exclusivity from the date of approval Epivir®-HBV™ (lamivudine) Tablets for the treatment of chronic hepatitis B in patients with evidence of hepatitis B viral replication.

Glaxo Wellcome Inc. is entitled to exclusivity as this application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and sponsored by Glaxo Wellcome Inc. The following investigations are "essential to the approval of the application" in that there are no other data available that could support FDA approval of the application.

Indication – Treatment of chronic hepatitis B in patients with evidence of hepatitis B viral replication.

Protocol NUCA3010. A Study of Lamivudine or Placebo in Patients with Chronic Hepatitis B Infection Who are Treatment Naïve (Report RM1997/00785/00)

Protocol NUCAB3011. A Placebo Controlled Study of Lamivudine and Intron A® in Patients with Chronic Hepatitis B Infection Who are Interferon α Non-Responders (Report RM1998/0006/00)

Protocol NUCB3010. A Study of Lamivudine and Alpha-Interferon in Patients with Chronic Hepatitis B Infection Who are Interferon Treatment Naïve (Report RM1997/00182/00)

Protocol NUCB3009. A Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of Two Dosage Regimens of Lamivudine in Patients with Chronic Hepatitis B Infection (Report GM1997/00071/00)

The clinical investigations are defined as "new" as they have not been relied on by the FDA to demonstrate substantial evidence of effectiveness of previously approved drug products for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the FDA to demonstrate the effectiveness or safety in a new patient population of a previously approved drug application.

The investigations were "conducted or sponsored by Glaxo Wellcome" in that Glaxo Wellcome Inc. was the sponsor of the investigational new drug application under which these investigations were conducted.

Leslie C. Rogers, M.D.
Project Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

[redacted] THIS WAY
[redacted]ORIGINAL

Marketing Exclusivity

NDA 21-004

Epivir®-HBV™ (lamivudine) Oral Solution

Request for Marketing Exclusivity

Pursuant to Section 505(c)(3)(D)(iii) and 505(j)(5)(D)(iii) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.108(b)(4), Glaxo Wellcome Inc. requests three years of exclusivity from the date of approval Epivir®-HBV™ (lamivudine) Oral Solution for the treatment of chronic hepatitis B in patients with evidence of hepatitis B viral replication.

Glaxo Wellcome Inc. is entitled to exclusivity as this application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and sponsored by Glaxo Wellcome Inc. The following investigations are "essential to the approval of the application" in that there are no other data available that could support FDA approval of the application.

Indication – Treatment of chronic hepatitis B in patients with evidence of hepatitis B viral replication.

Protocol NUCA3010. A Study of Lamivudine or Placebo in Patients with Chronic Hepatitis B Infection Who are Treatment Naïve (Report RM1997/00785/00)

Protocol NUCAB3011. A Placebo Controlled Study of Lamivudine and Intron A® in Patients with Chronic Hepatitis B Infection Who are Interferon α Non-Responders (Report RM1998/0006/00)

Protocol NUCB3010. A Study of Lamivudine and Alpha-Interferon in Patients with Chronic Hepatitis B Infection Who are Interferon Treatment Naïve (Report RM1997/00182/00)

Protocol NUCB3009. A Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of Two Dosage Regimens of Lamivudine in Patients with Chronic Hepatitis B Infection (Report GM1997/00071/00)

The clinical investigations are defined as "new" as they have not been relied on by the FDA to demonstrate substantial evidence of effectiveness of previously approved drug products for any indication or of safety for a new patient population and do not duplicate

the results of another investigation that was relied on by the FDA to demonstrate the effectiveness or safety in a new patient population of a previously approved drug application.

The investigations were "conducted or sponsored by Glaxo Wellcome" in that Glaxo Wellcome Inc. was the sponsor of the investigational new drug application [redacted] under which these investigations were conducted.

Leslie C. Rogers, M.D.
Project Director, Regulatory Affairs

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 21-003, 21-004 Trade (generic) names Epivir®-HBV™ (lamivudine)
Check any of the following that apply and explain, as necessary, on the next page:

___ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(C) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate).

_X_ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children.

___ a. The applicant has committed to doing such studies as will be required.

_X_ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sonsor 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 do not need to be encouraged because the drug product has little potential for use in children.

___ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

/S/ _____ 12/8/98
Anthony M. Zeccola Date
Regulatory Management Officer, HFD-503

cc: Orig NDA 21-004
HFD-530/Div File
NDA Action Package

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 21-003, 21-004 Trade (generic) names Epivir®-HBV™ (lamivudine)
Check any of the following that apply and explain, as necessary, on the next page:

___ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(C) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate).

_X_ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children.

___ a. The applicant has committed to doing such studies as will be required.

_X_ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sonsor 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 do not need to be encouraged because the drug product has little potential for use in children.

___ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:_____

_____

_____

_____ _____
Anthony M. Zeccola Date
Regulatory Management Officer, HFD-503

cc: Orig NDA 21-004
HFD-530/Div File
NDA Action Package

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	HFD#	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
835	530	EPIVIR-HBV	lamivudine tablets
ATTENTION: George Lunn –			

A. Look-alike/Sound-alike

Potential for confusion:

____	Low	____	Medium	____	High
____	Low	____	Medium	____	High
____	Low	____	Medium	____	High
____	Low	____	Medium	____	High
____	Low	____	Medium	____	High

B. Misleading Aspects:

C. Other Concerns:

The suffix HBV for hepatitis-B virus is acceptable for the new indication of this product.

D. Established Name

xxx Satisfactory

____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

xxx ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/E /S/ 8

CDER Establishment Evaluation Report for December 07, 1998

Application: NDA 21003/000
Stamp: 24-JUN-1998 Regulatory Due: 24-DEC-1998
Applicant: GLAXO WELLCOME
5 MOORE DR
RESEARCH TRIANGLE PARK, NC 27

Priority: P
Action Goal:
Brand Name: EPIVIR (LAMIVUDINE) 150MG TABS
Established Name:
Generic Name: LAMIVUDINE
Dosage Form: TAB (TABLET)
Strength: 100 MG
Org Code: 530
District Goal:

FDA Contacts:

A. ZECCOLA	(HFD-530)	301-827-2335	, Project Manager
G. LUNN	(HFD-530)	301-827-2393	, Review Chemist
S. MILLER	(HFD-530)	301-827-2392	, Team Leader

Overall Recommendation:

ACCEPTABLE on 23-SEP-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1033964
GLAXO INC
1011 NORTH ARENDELL AVE
ZEBULON, NC 27597

DMF No:
AADA No:

Profile: TCM
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 29-MAY-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

Establishment: 9615283
GLAXO WELLCOME INC
7333 MISSISSAUGA RD. NORTH
MISSISSAUGA, ONTARIO, CA L5N 6

DMF No:
AADA No:

Profile: TCM
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 23-SEP-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: 9610419
GLAXOCHEM LTD
COBDEN ST
MONTROSE ANGUS, SCOTLAND, UK

DMF No:
AADA No:

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 29-MAY-1998
Decision: ACCEPTABLE

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Reason: **BASED ON PROFILE**

Application: NDA 21004/000
Stamp: 30-JUN-1998 Regulatory Due: 31-DEC-1998
Applicant: GLAXO WELLCOME
5 MOORE DR
RESEARCH TRIANGLE PARK, NC 27

Priority: P
Action Goal:
Org Code: 530
District Goal: 01-MAR-1999
Brand Name: EPIVIR-HBV (LAMIVUDINE) ORAL SOL 5MG/ML
Established Name:
Generic Name: LAMIVUDINE
Dosage Form: LIQ (LIQUID)
Strength: 5 MG/ML

FDA Contacts:

A. ZECCOLA	(HFD-530)	301-827-2335	, Project Manager
G. LUNN	(HFD-530)	301-827-2393	, Review Chemist
S. MILLER	(HFD-530)	301-827-2392	, Team Leader

Overall Recommendation:

ACCEPTABLE on 28-OCT-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1033964
GLAXO INC
1011 NORTH ARENDELL AVE
ZEBULON, NC 27597

DMF No:
AADA No:

Profile: LIQ
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 05-OCT-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment: 9611170
GLAXO OPERATIONS UK LTD
SPEKE BOULEVARD
SPEKE, LIVERPOOL, UK

DMF No:
AADA No:

Profile: LIQ
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 26-OCT-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

Establishment: 9610421
GLAXO WELLCOME LTD
HARMIRE RD, DL128DT
BARNARD CASTLE, , UK

DMF No:
AADA No:

Profile: CTL
OAI Status: OAI ALERT
Last Milestone: OC RECOMMENDATION
Milestone Date 28-OCT-1998

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9610419**
GLAXOCHEM LTD
COBDEN ST
MONTROSE ANGUS, SCOTLAND, UK

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **14-AUG-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM

Date: July 7, 1998

To: David Lepay, M.D.
Director, Division of Scientific Investigations
HFD-344

From: Anthony M. Zeccola, Regulatory Management Officer, HFD-530 /S/

Through: Heidi Jolson, M.D., M.P.H. /S/
Director, Division of Antiviral Drug Products
HFD-530

Subject: Request for clinical site inspections for NDA 21-003

Dear Dr. Lepay:

In support of NDA 21-003 for Epivir-HBV, Glaxo Wellcome has submitted the results of four phase 3 clinical trials, studies NUCA3010, NUCAB3011, NUCB3009, NUCB3010.

For protocols NUCA3010 and NUCAB3011, we request that the following domestic sites be audited:

Center	Investigator	Location
		Miami

For protocol NUCB3009, which was conducted in Asia, we would like to request that either the Taiwan or the Hong Kong sites be inspected with preference being for the Hong Kong sites listed below:

Center	Investigator	Location
		Hong Kong
		Hong Kong

Should you require any additional information please contact Mr. Anthony Zeccola, Regulatory Management Officer, at 301-827-2419.

Concurrence
HFD-530/MOTL/Kukich /S/ 7/6/98
HFD-530/MO/Styrt /S/ 7/6/98

cc
NDA 21-003
NDA 21-004

MEMORANDUM

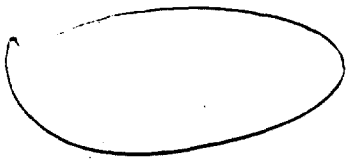
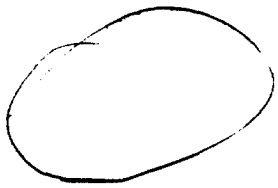
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: NOV -3 1998

FROM: Antoine El-Hage, Ph.D. (HFD-344)

SUBJECT: Inspection of two clinical studies conducted in Hong Kong in support of NDA 21-003 Epivir (lamivudine). Sponsored by Glaxo Wellcome, Inc. - Early Overview - EIR not yet available.

TO: File

Site(s):	Dr. C L Lai	Dr. Nancy WY Leung
	 icine	 ng
Dates of Inspections:	October 12-15, 1998	October 19-23, 1998

PROTOCOL NUCB3009: A Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of Two Dosage Regimens of Lamivudine in Patients with Chronic Hepatitis B Infection.

FDA PARTICIPANTS: Antoine El-Hage, Ph.D. (Rockville Headquarters)
Leah Andrews, Field Investigator (Atlanta, GA)

INDUSTRY PARTICIPANTS: Dr. Julie E. Dent, Principal Clinical Research Scientist and Susan Forskitt, Clinical Compliance Auditor both from Glaxo Research and Development, Middlesex WB6OHE, England. Richard Cheung, Clinical Research Manager, Glaxo Wellcome China Ltd.

FOREIGN GOVERNMENT PARTICIPANTS: NONE

HONG KONG INSPECTIONAL PROGRAM: NONE

GENERAL COMMENTS:

These studies were not conducted under an IND status. A total of 384 subjects (Dr. Lai site) were screened and 296 subjects were screen failures due to inclusion criteria and some refused biopsy. A total of 164 subjects (Dr. Leung site) were screened; only 62 subjects were enrolled into the study.

Eighty-eight (88) subjects were enrolled and summarized at the Lai site and 62 were enrolled at the Leung site. Although these studies had not been conducted under an IND, both investigators had knowledge that their studies would be submitted to FDA. We were told and found that the protocol and informed consent forms were submitted to and approved by the local hospital ethics committee and by the state and federal government prior to study initiation (local requirements). All subjects signed written informed consent forms (exception at Dr. Leung site 9 subjects signed informed consent after screening). There was sufficient documentation (except for concomitant medication and adverse events - Dr. Lai) to assure that all audited subjects did exist and were available for the duration (ongoing-open label) of their stated participation in the study (exception noted). The case report forms and data tabulations (primary and secondary efficacy end points, e.g., hepatic activity index (HAI), HBV-DNA, HbeAg and HbsAg, etc.,) listing of adverse events and hepatic function provided by the sponsor were compared against the medical charts, laboratory records, biopsy reports and drug accountability records. The correspondence files maintained by the principal investigators were reviewed. The study was monitored by the sponsor at both sites.

1) [redacted], Dr. Lai.

We were informed by Dr. Lai that the study subjects were drawn from Hong Kong area; about 95% had a chronic hepatitis B infection since child birth and a few were referrals. The study site personnel (Dr. Lai) seems to be familiar with every subject's condition. Our review of the records for 48 subjects of 88 enrolled and completed 52 weeks of treatment found adequate documentation to assure that all of the subjects did exist and were alive (except 3 withdrew) and available for the duration of their stated participation in the study. Subjects who were discontinued from the study were also reviewed and the reason(s) were adequately documented (except subject 2949). The submitted data were verifiable, exceptions noted in the FDA-483 (copy attached).

The analysis for quantitations of HBV-DNA was not performed on site. It was performed in Singapore and results were not provided to the respective sites in order to keep the investigators blinded (except for screening). Therefore, a cross reference examination of the results could not be performed. However, the screening results were verified.

The inspectional observations were presented and discussed with the doctor at the close of the inspection. The investigator (Dr. Lai) was very cooperative and agreed with the findings and promised corrective measures in the ongoing and future studies.

2) [redacted], Dr. Leung.

We were informed by Dr. Leung that the study subjects were all referrals from the Hong Kong area. The study site seems to be familiar with the subjects's conditions. Few subjects (2) received Interferon for their condition, but the drug was discontinued prior to their enrollment in the NUCB3009 study. Records available confirmed the discontinuation of Interferon.

Our review of the records for 31 subjects of 62 enrolled who completed 52 weeks of treatment found adequate documentation to assure that all of the subjects did exist and were alive (except one death of 2871 - see brief summary), and were available for the duration of their stated participation in the study. Subjects who were discontinued from the study were also reviewed and the reason(s) were adequately documented. The submitted data was verifiable.

INSPECTIONAL FINDINGS:

The following findings were noted and discussed with the principal investigator at the close of the inspection.

1) For at least 5 subjects, the biopsy reports at the end of week 52 were not available during the inspection.

2) Subject 2871 received prohibited concomitant medication (Prednisolone) during the study.

3) Subject 2870 had an elevated CPK of 1260 at week 20, an adverse event that was not reported.

4) The use of Wellferon during the 2nd follow-up period (2864).

Dr. Leung agreed with the observation and promised corrective action.

A BRIEF SUMMARY OF SUBJECT 2871/DEATH (SEPTICEMIA)

Subject 2871 was randomized to placebo on 3/15/95 and completed week 52 treatment with no response. This subject continued on open label and completed the first year on or about 4/9/97. Shortly after completing the first year his HBV-DNA level was 5.07pg/ml on May 7,

1997 and rose to 201.45 pg/ml around June 4, 1997. On July 3, 1997 the subject stated he had epigastric discomfort and nausea since June 18, 1997. Blood tests showed evidence of hepatitis. The biochemical levels ALT 652 IU/L, AST 284 IU/L and his HBV-DNA rose to 1,000.52 pg/ml while on trial medication. On August 11, 1997, the subject was admitted to the hospital with serve abdominal pain and increasing ascites; placed on triple antibiotics (Cefuroxime, Netilmicin and Metronidazole). An ultrasound revealed a small cirrhotic liver, gross ascites and no biliary obstruction. Septic work-up was performed including peritoneal tapping; E.Coli was found in the peritoneal fluid and blood which responded to antibiotic treatment. His condition rapidly deteriorated, developed septic shock and multi organ (renal & hepatic) failure. A Laparotomy was performed on August 13, 1997 to exclude perforation and the findings were negative, but compatible with spontaneous bacterial peritonitis. On August 14, 1997 his condition deteriorated with multiple organ failure and was confirmed dead on August 15, 1997. Autopsy was performed (copy provided).

The principal investigators (both sites) were very cooperative during the inspections. Although intense negotiation (Dr. Leung/Chief Counsel) took place to allow complete access to medical records and copying.

It is worth mentioning that at both sites 13 of 48 subjects (Dr. Lai) and 12 of 31 subjects (Dr. Leung) records reviewed found that during the follow-up period these subjects did not respond to treatment or had relapsed. The virological levels (HBV-DNA) rose with no significant change in the biochemical level (LFT's). It is not clear why some subjects did not respond to long term treatment. A possible explanation could be related to the progression of the disease or genotypic mutation. The rebound elevation in HBV-DNA level may be attributed to genotypic mutation rather than disease progression since the biochemical levels (LFT's) remained within the normal limits (except for subject 2861 who experienced occasionally, a corresponding increase in liver function tests (ALT).

In summary, the overall compliance with protocol directives (exceptions noted) and capture of data (efficacy) was adequate and acceptable. I conclude that both investigators did adhere to acceptable clinical investigations and that their data are reliable. I recommend that the data generated and summarized from these two sites be used in support of NDA claims.

During the inspections, I kept the review division aware of the progress of the inspectional findings.

On October 27, 1998, I met with Barbara Styrt, M.D. and discussed the data in general and our findings (adverse events, withdrawals and death). I expressed my concern that several subjects who are continuing on the open label had relapsed (13/48 Dr. Lai and 12/31 Dr. Leung). I stated that it is clear some subjects responded to treatment within the 52 weeks of Lamivudine Therapy. However, several subjects who continued on the open label did not respond to long term treatment. Whether the lack of efficacy is due to disease progression or genetic mutation is not known at the present time. I strongly recommend that

the sponsor should be asked to provide a summary from the follow-up open label study to include those subjects who have not responded to assigned therapy after the 1st and/or 2nd year of follow-up. The sponsor should also provide a plan or specific rationale for the optimal treatment and or whether higher-than recommended doses of Lamivudine should be used or whether multiple combination therapy should be considered as an alternative treatment for high risk patients.

/S/

Antoine El-Hage, Ph.D.

cc:
HFD-344
HFD-530 (Drs. Styrt and Kukich, CSO Zecolla)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 5, 1998

FROM: Antoine El-Hage, Ph.D.
CIB/HFD-344

TO: Project Manager - HFD-530
Anthony Zecolla - CSO
Barbara Styrt - M.D.

SUBJECT: NDA 21-003
SPONSOR: Glaxo Wellcome, Inc.
PRODUCT: Epivir (lamivudine)

SNAME	CITY	ST	IN	ASSIGN	ACTN DATE	CL	REVIEWER
Domestic							
Grimm			DA	16-Jul-98	5-Nov-98	NAI	AEH
Schiff			DA	16-Jul-98	5-Nov-98	VAI	AEH
Foreign							
Lai		IC	DA	16-Jul-98	15-Oct-98	VAI	AEH
Leung		IC	DA	16-Jul-98	22-Oct-98	VAI	AEH

All 4 requested inspections have been completed. No objectionable conditions were found which would impair the use of the data submitted in support of the pending NDA (See memo dated November 3, 1998).

Key to Classifications
NAI = No deviation from regulations
VAI = Minor deviations(s) from regulations. Data acceptable

Antoine El-Hage, Ph.D.

cc:CAC

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Antoine El-Hage, Ph.D.

cc:CAC

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF MEETING

IND:

DATE: October 8, 1997

DRUG: lamivudine

SPONSOR: Glaxo Wellcome, Inc.

PARTICIPANTS:

Representative of Glaxo:
Nathaniel Brown, M.D.
David Cocchetto, Ph.D.
Lynn Condreay, Ph.D.
Lynn Crowther
Randy Davis, Dr.P.H.
Steven Gardner, M.S.P.H.
Mark Johnson
Leslie Rogers, M.D.
Marc Rubin, M.D.
Thomas Shumaker
Mary Woessner
James Zisek

Representatives of DAVDP:
Rachel Behrman, M.D.
Debra Birnkrant, M.D.
Barbara Davit, Ph.D.
Walla Dempsey, Ph.D.
Paul Flyer, Ph.D.
Janice Jenkins, Ph.D.
Stanka Kukich, M.D.
George Lunn, Ph.D.
John Martin, M.D.
Lalji Mishra, Ph.D.
Greg Soon, Ph.D.
Barbara Styrt, M.D.
Pritam Verma, Ph.D.
Anthony M. Zeccola

BACKGROUND:
Pre-NDA meeting to discuss submission of the supplemental NDA for lamivudine for the treatment of hepatitis B virus (HBV), which will be submitted at the end of second quarter 1998. Background material was submitted September 12, 1997 as submission number 291.

DISCUSSION:
The meeting began with an overview of the Glaxo Wellcome development plan for the HBV indication for lamivudine. This discussion included their rationale for their planned Summer 1998 submission as well as their plans for international submission and a presentation of proposed labeling for this indication.

DA

Clinical Issues

- The proposed labeling includes a PEDIATRIC USE section and a Pediatric Patients subsection under the DOSAGE AND ADMINISTRATION section. Glaxo wanted to know if the proposed pediatric database, which will include 50 patients in the U.S. and 20 patients in Canada, will be sufficient to support the proposed labeling. Dr. Styrt said that the proposal concerning a pediatric indication will need to be further addressed in the sNDA submission and during the review process. The sponsor would need to present convincing evidence to the review team that the data in the submission support such an indication. Issues that may arise include, but are not limited to, the following: demonstration that the database includes a sufficient number of vertically infected patients and that their disease and treatment response is sufficiently similar to that of the relevant pediatric age groups; demonstration of power to detect meaningful differences if absence of treatment-by-subgroup interaction in statistical analysis is used to help support generalizability of results; demonstration of adequate size of pediatric safety database among patients with chronic liver disease; etc. Dr. Berhman added that we generally like to see over 100 patients.

- The sponsor wanted to know if the pediatric HIV indication safety database could be used to support the pediatric database for this submission. Dr. Behrman said that since HBV and HIV infection are different diseases, the proposed pediatric HBV database of 70 subjects seems small. These issues can be discussed further during a teleconference. HBV resistance in pediatric patients may also require further discussion.

- Several parts of the proposed draft labeling, for example the Indications and Usage section, will need work; and the review team will try to provide initial comments on the labeling proposal shortly after submission of the sNDA, so that a dialogue can be carried out during the review process.

- It is unclear from the draft whether an indication for combination lamivudine/interferon therapy is proposed in addition to lamivudine monotherapy. If so, the safety database for lamivudine/interferon should be clarified. The sponsor indicated that the submission would be for lamivudine monotherapy but that some information from studies of combination therapy would be submitted.

- The sponsor requested an exemption from submission of the 4-month safety update. Dr. Styrt said that the 4-month safety update may be a regulatory requirement, we will follow-up on this. FDA and the sponsor will discuss a modified 4-month safety update that will be submitted 2 months after submission and will include focused data such as important adverse events from follow-on studies, and provide a written assurance of absence of other serious events.

- The sponsor presented their proposal to submit data on HIV/HBV co-infected patients and data from studies conducted in Japan. Only the translated summaries from the japan studies conducted will be provided, since these studies will not be used to support efficacy claims in the U.S. label. Dr. Behrman indicated that this is acceptable, if we need any detailed information from these studies we will request it.

Pre-clinical Issues

- The sponsor agreed to provide complete methodology for microbiology and validation for any unapproved assays that are used.

- Full reports of HBV virology studies will be included in Pharmacology, Microbiology, and Clinical sections. The Integrated Summary of Resistance will be included in Clinical, Microbiology, and Statistics sections of submission.

- One of the issues on preliminary review of the label outline is that Clinical Pharmacology information should be a common section since all information therein will be relevant to patients infected with both HIV and HBV.

Statistical Issues

- FDA requested clarification of the statement that case report tabulations will not be submitted but by-variable listings will be submitted. The sponsor indicated that detailed line listings by variable will be provided for each study. FDA asked if it is feasible to have these in a searchable electronic format in addition to the paper copy.

- Sponsor agreed to provide a 10% sample of all case report forms from the key studies, in addition to those specified in the briefing document.

- The sponsor agreed to a detailed analysis plan for IND studies, the same for non-IND studies, and for how these will be integrated. The plan of analysis should incorporate consistent use of endpoints and an approach to defining optimal duration of therapy.

- The sponsor agreed to provide line listings of cause of death in compassionate use studies.

- FDA and the sponsor may have further discussions of what parts of application may be submitted electronically (from initial discussions, everything will be submitted on paper except case report forms which may be electronic; electronic submissions of some other material may be agreed upon as duplicates of the paper material; datasets will also be submitted on diskette with programs that reproduce the key analyses of the phase III studies).

CMC Issues

Questions presented by the FDA Chemistry review team, and response from the sponsor, are listed below. Sponsor responses are indicated in bold typeface.

- It is possible that inspections may be scheduled for the two drug product manufacturing sites. When do you anticipate that the [redacted] plants will be ready for inspection? **At the time of pre-submission of CMC data. This should be March/April 1998 for tablets ([redacted]) and April/May 1998 for oral solutions [redacted]**

- Please specify the data that are currently available regarding the suitability of the dissolution method for the tablet product. In addition, please specify whether dissolution profiles or single time point measurements are being obtained on the stability samples. **Profiles will be supplied.**

- If any type of electronic submission of CMC data is anticipated, it would be beneficial to discuss content and submission medium at some future date. **Submission will probably be paper only.**

- At an appropriate point in time we would like to discuss how the statistical analysis of the stability data will be presented within the NDA. **The statistical analysis will mirror that of the HIV application.**

General Issues

- The sponsor agreed to provide, as part of the sNDA submission in addition to individual citations within the submission, a detailed listing in one place of all presubmitted material with the locations where it may be found.

- Since this application will likely be presented to the advisory committee, we will need to discuss the timing of the submission. Glaxo agree to provide a time-line showing anticipated submission dates for this and other 1998 submissions. Dr. Cochetto expressed that he had not expected to have this application presented to the Advisory Committee. Dr. Behrman said that the first drug to seek a particular indication usually is brought before the committee.

- It was agreed that a post-submission would be useful. This will be arrange at the time of submission.

[redacted] THIS WAY
[redacted]GINAL

Original IND 40,916
Pre NDA Meeting Minutes

CONCURRENCE:
HFD-530/SMO/Behrman
HFD-530/DivDir/Birnkrant
HFD-530/BioPharm/Davit
HFD-530/SBiostat/Flyer
HFD-530/Chem/Lunn
HFD-530/Micro/Mishra
HFD-530/MO/Styrt
HFD-530/Pharm/Verma
HFD-530/CSO/Zeccola

CC:
Division File
HFD-530/SMO/Behrman
HFD-530/DivDir/Birnkrant
HFD-530/BioPharm/Davit
HFD-530/SBiostat/Flyer
HFD-530/Chem/Lunn
HFD-530/Micro/Mishra
HFD-530/MO/Styrt
HFD-530/Pharm/Verma
HFD-530/CSO/Zeccola