CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-977
20-978

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

GlaxoWellcome

December 17, 1998

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

DESK COPY

RE: **NDA 20-977; Ziagen ™ (abacavir sulfate) Tablets;**
NDA 20-978; Ziagen (abacavir sulfate) Oral Solution;
Phase IV Activities for Abacavir

Dear Dr. Jolson:

Reference is made to NDAs 20-977 and 20-978 for Ziagen Tablets and Oral Solution, i.e., applications under active review in your Division. Please also refer to our submission of November 4, 1998 which provided draft commitment letters from Glaxo Wellcome (GW). Reference is also made to the facsimiles of December 7 and 11, 1998 from your Division which listed recommendations for Phase IV activities and to our conference calls on December 7, 14 and 16, 1998 to discuss Phase IV activities. In view of the Division's recommendations, the purpose of this letter is to provide a statement of our commitment to Phase IV activities with abacavir.

Background Information

At the outset, allow us to explain the format of this letter. The initial part of the letter provides a straightforward list of Phase IV activities, recognizing the need for such a list that can be quoted in the action letter. The latter part of the letter provides expanded information on each Phase IV activity; this expanded information enables GW to summarize the work that is already ongoing on each of these topics, give examples of other work that is under consideration, and explicitly state our understanding of key operational aspects of the activities. Finally, please note that our intent is to keep FDA informed on a regular basis of our progress toward completion of these activities. Specifically, we intend to include a progress report on these Phase IV activities in our Annual Reports to NDA 20-977.

We also believe it is important to assure a shared understanding of the nature of these Phase IV activities. Glaxo Wellcome is committed to conducting these activities as a logical extension of our multiyear investment in this important compound. We have applied for accelerated approval of NDAs 20-977 and 20-978; therefore, upon issuance of an approval letter, Glaxo Wellcome's understanding is that our Phase IV activities are subject to the NDA Annual Reporting requirement [21 CFR 314.81(b)(2)], but are not subject to any special reporting requirements under Section 130 ("*Reports of Postmarketing Approval*

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.

Studies") of the FDA Modernization Act. As you know, a proposed regulation to implement Section 130 has not yet been issued by FDA; therefore, in the absence of such a regulation, we believe it is helpful to explicitly state Glaxo Wellcome's view in the interest of assuring a shared understanding.

List of Phase IV Activities

Glaxo Wellcome agrees to the submission of completed reports of the results from the following studies or a report of the ongoing status of these investigations in the supplement for traditional approval for Ziagen unless the individual reports become available during an earlier submission.

1. Glaxo Wellcome agrees to provide a proposal for a comprehensive plan to study abacavir hypersensitivity reactions. GW commits to provide plans with the following components, within the timeframe specified below.

   Prior to Accelerated Approval:
   - Inclusion of a toll-free 1-800 number in the abacavir physician's labeling to facilitate reporting of postmarketing hypersensitivity reactions.

   Ongoing Effort Beginning Immediately After Accelerated Approval:
   - We commit to conduct an ongoing review of the safety-related information in professional labeling, Medication Guide and Warning Card in order to assure that such labeling remains current and effectively conveys warnings.

   Within 45 Days After Accelerated Approval:
   - Submit a draft protocol for a prospective, population-based epidemiologic study to evaluate abacavir hypersensitivity reactions.
   - Capture and describe abacavir hypersensitivity reactions occurring in ongoing clinical studies.

   Within 60 Days After Accelerated Approval:
   - Submit a proposal for study of the biologic mechanism/immunologic basis of abacavir HSR.
   - Submit a concept sheet for a labeling comprehension study for subjects reading the Medication Guide and Warning Card. Following consultation with experts, Glaxo Wellcome will submit a complete protocol for this study to FDA under

2. Glaxo Wellcome will continue to study and report on:
   - available information on the management of rash developing in patients who are being treated with multiple antiretroviral agents (including protease inhibitors and nonnucleoside RTIs) and other commonly used drugs (e.g. TMP/SMX) that may cause rash

- the safety and efficacy of abacavir used in combination with other antiretroviral agents,
- the role of abacavir in therapy experienced patients.

3. Glaxo Wellcome agrees to diligently endeavor to conduct the following pharmacokinetic studies and submit resulting reports to FDA:
   - evaluation of abacavir in neonates,
   - evaluation of abacavir in adults with hepatic impairment,
   - evaluation of abacavir in adolescent patients.

4. Glaxo Wellcome agrees to include with the submission for traditional approval of abacavir an evaluation of the safety, efficacy, and pharmacokinetics of abacavir in women and minorities.

5. Glaxo Wellcome agrees to complete and submit results of resistance and cross resistance assessments in ongoing GW-sponsored clinical studies.

6. Glaxo Wellcome agrees to complete the ongoing carcinogenicity studies and submit reports of the studies to FDA in a timely manner.

7. Glaxo Wellcome agrees to the submission of biannual reports of the rates of clinical endpoints by treatment group in ongoing clinical trials.

Our understanding is that this list of seven items will be quoted in the action letter. Expanded information on each of these Phase IV activities is provided in the following section.

Expanded Information on Phase IV Activities

1. Glaxo Wellcome agrees to provide a proposal for a comprehensive plan to study abacavir hypersensitivity reactions. GW commits to provide a plan with the following components, within the timeframes specified below. It is likely that some information will be available prior to, at the time of, and post-submission of our traditional approval package for Ziagen products.

   Prior to Accelerated Approval:
   - Glaxo Wellcome agrees to include a toll-free 1-800 telephone number in the revised draft physician's labeling for Ziagen products.
   - Glaxo Wellcome proposes to actively seek and collect detailed descriptive data such as patient characteristics, time course, laboratory evaluations, and potential risk factors for hypersensitivity. Information will be actively sought by sending a "Hypersensitivity Case Report Form" and a prepaid return mailer to each health care professional who uses the toll-free number to report a putative hypersensitivity reaction. All such data will be captured in a database that will be available for

periodic analysis. Following accelerated approval, each putative case of hypersensitivity reported to Glaxo Wellcome will be reported to FDA in accordance with the regulations in 21 CFR 314.80.

Ongoing Effort Beginning Immediately After Accelerated Approval:

- We commit to conduct an ongoing review of the safety-related information in professional labeling, Medication Guide and Warning Card in order to assure that such labeling remains current and effectively conveys warnings.

Within 45 Days After Accelerated Approval:

- GW will submit a proposal for a prospective, population-based epidemiologic study of abacavir hypersensitivity reactions. This proposal will be provided to DAVDP for your review and comment.
- GW will continue to collect data on any hypersensitivity reactions to abacavir in ongoing GW-sponsored clinical studies. Data being collected include detailed descriptive data on events, including patient characteristics, time course, laboratory evaluations and potential risk factors. A new case report form specific to hypersensitivity reactions will be implemented to capture this information.

Within 60 Days After Accelerated Approval:

- GW will submit an outline of potential studies on the biologic mechanism/immunologic basis of hypersensitivity reactions to abacavir. After additional consultation with experts in this field, Glaxo Wellcome will revise and submit a complete proposal for studying the biologic mechanism/immunologic basis of these reactions.
- GW will submit a concept sheet describing the general objectives of a labeling comprehension study for subjects reading the Medication Guide and Warning Card. Following consultation by GW with experts in this field, GW will submit to FDA a complete protocol for the proposed labeling comprehension study. GW's intent is to conduct this labeling comprehension study [redacted]1. Once the results of the study are available, GW understands that the regulations permit certain safety-related changes to be made in labeling via a Special Supplement/Changes Being Effected [21 CFR 314.70(c)].

2. Glaxo Wellcome will continue to study and report:
   - The management of rash developing in patients who are being treated with multiple agents that may cause rash. GW will send the Division a text description/summary of completed clinical trials. Our proposal would include further defining the algorithm of rash management post review of continuing studies.
   - Glaxo Wellcome is committed to continuing to study the safety and efficacy of abacavir in a variety of clinical settings, as part of a variety of antiretroviral regimens, and in collaboration with other reputable sponsors. With respect to clinical settings, abacavir will be studied in both therapy-naive and therapy-

experienced patients. With respect to antiretroviral regimens, abacavir will be studied as part of a wide variety of combination regimens, including various nucleoside RTIs (e.g., 3TC, d4T, and ZDV), nonnucleoside RTIs (e.g., efavirenz and nevirapine), and protease inhibitors (e.g., indinavir, saquinavir, amprenavir, and nelfinavir). With respect to other sponsors, Glaxo Wellcome is continuing its decade-long historical commitment to collaborating with established associations (e.g., ACTG, ICC, and various European investigative groups) and other pharmaceutical companies to develop and implement proposals for further assessment of the properties of abacavir. Attachment I provides a more detailed tabular summary of clinical studies with abacavir that are currently ongoing or planned for initiation. Based on our extensive prior experience with Retrovir and Epivir, we fully anticipate that, following accelerated approval, additional new studies will be designed and implemented as a collaborative effort in response to requests from extracompany investigators, other companies, and associations.

3. Glaxo Wellcome agrees to diligently endeavor to conduct the following pharmacokinetic studies:
   - We will evaluate abacavir in neonates. Study ACTG321 in neonates is currently ongoing; results of this trial will be submitted to FDA post completion of the study.
   - We will evaluate abacavir in patients with impaired hepatic function. We have recently terminated study CNAB1006 which is a study of abacavir therapy in patients with hepatic impairment. Patient enrollment into the groups with mild and moderate hepatic impairment was completed; however, no patients with severe hepatic impairment were enrolled in the study. A study report will be submitted after completion of the study. GW believes this study will adequately address the request made by FDA.
   - We will evaluate abacavir in adolescent patients. GW will commit to study the safety and single-dose pharmacokinetics of abacavir in adolescent patients. A report will be submitted after completion of the study.

4. Glaxo Wellcome agrees to include with the submission for traditional approval of abacavir an evaluation of the safety, efficacy and pharmacokinetics in women and minorities. The evaluations of safety and efficacy in minorities (e.g., African-Americans, Hispanic-Americans) will be done using approaches already used in integrated summaries in the NDA. Pharmacokinetic evaluations in women and patients of various races will be assessed using population pharmacokinetic methods applied to selected Phase III studies.

5. Glaxo Wellcome agrees to complete and submit results of virology assessments from ongoing GW-sponsored clinical studies. FDA is aware of Glaxo Wellcome's longstanding commitment to the field of virology. GW intends to continue to study resistance and cross resistance in protocols CNAA2001, CNAB2002, CNAA2003, CNAA2004, CNAB3001, CNAAB3003, CNAA3006 and CNAAB3005 and to submit

results including virology data from these studies in hopes of better establishing the correlation between treatment with abacavir and virologic response to treatment.

6. Glaxo Wellcome agrees to complete the ongoing carcinogenicity studies and submit reports of the studies in a timely manner. As with our previously marketed antiviral medications, Glaxo Wellcome continues to honor the commitment to complete and report the results of carcinogenicity studies.

7. Glaxo Wellcome agrees to the submission of biannual reports of the rates of clinical endpoints by treatment group in ongoing clinical trials. Glaxo Wellcome will provide the requested update for studies CNAAB3003, CNAA3006, CNAAB3005 and the additional, proposed, traditional approval clinical trial.

This letter is submitted in duplicate. A copy of this cover letter is provided to NDA 20-978 to incorporate this information via reference. Two desk copies have been provided directly to Ms. Melissa Truffa for use by the review team. Please contact Martha Anne Moore at (919)-483-9347 for any matters regarding these applications. Thank you.

Sincerely,

M Lynn Smiley

M. Lynn Smiley, M.D.
Vice President
HIV & OI Clinical Development

David M. Cocchetto

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

ABACAVIR - LIST OF STUDIES

Protocol Number (Number and location of Centers)	Study Design	Initiation and Completion Dates	Treatments	Total Number of Subjects Enrolled in Study	Number of Subjects Exposed to ABC
CNAAB3008 (ABC Expanded Access)	MC, OL, international program allowing ABC use in clinical practice setting. Enrollment open to Tx Exp adults	3Q1997 - 1999	ABC used in physician's regimen of choice	11,300 US patients as of Dec 1998	11,300
CNA30,024 (New Traditional Approval Study)	48 weeks MC, DB, PC, R, Tx naïve adults ***Final Design TBD and agreed with FDA***	2Q1999 - 2001	***POTENTIAL REGIMEN:*** d4T + EFV + 3TC or d4T + EFV + 3TC + NFV or d4T + EFV + 3TC + ABC	Est 500	170
ACTG398 (MC in US)	48 weeks, MC, R, partially placebo controlled trial in adults with virologic failure (>1000 c/mL after 16 wks treatment) following PI therapy with IDV, SQV, RTV, or NFV	Sep 1998 - 2000	APV + SQV + ABC + EFV + ADV or APV + IDV + ABC + EFV + ADV or APV + NFV + ABC + EFV + ADV or APV + PI pbo +ABC + EFV + ADV	460	460
ACTG388 (MC in US)	72 weeks, MC, R, controlled trial in adults with limited prior therapy and CD4 <200 c/uL or HIV RNA >100,000 c/mL. Step 1 agents include EFV, NFV, 3TC/ZDV, and IDV	2Q1998 - 2000	ABC will be used as Step 2 regimen (following virologic failure or relapse): ABC (or 2NRTI) + EFV + APV (or PI_2)+ PI_3 choice of ABC or APV based on ViroLogic, Inc. phenotypic assay	444 to enroll to step 1	Not specified - dependent upon phenotypic assay results
ACTG372 (47 centers in the US)	48 weeks MC, DB, R, Tx Exp adults	Oct 1997 - 1999	Group A: ABC + ZDV + 3TC + IDV OR PBO + ZDV +3TC +IDV Group B: ABC + EFV + ADV + NFV or PBO OR Approved nucleoside analogs + EFV + ADV + NFV or PBO Group C: ZDV (or d4T) + 3TC + IDV Group D: ABC + EFV + ADV + NFV	355 Total Grp A = 229 Grp B = 94 Grp C = 12 Grp D = 20	180 Total (approx –blinded)
ACTG368 (47 centers in the US)	48 weeks MC, DB, R, Tx Exp adults	Apr 1997 - 3Q99	ABC + IDV + EFV OR PBO + IDV + EFV	307	165
CHARM Trial (MC in Europe and S Africa)	MC, OL study in Tx naïve adults	Jan 1999 - 2000	ABC + 3TC + ZDV + randomization 1 = +/- HU randomization 2 = +/- NVP	200	200

DB: Double-blind, Tx Exp: Treatment-experienced patients, MC: Multicenter, Tx Naive: Treatment-naive patients, OL: Open-label, PC: Placebo-controlled, Ped: Pediatric study, R: Randomized, SC: Single-center

3TC: lamivudine, NRTI: nucleoside reverse transcriptase inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor PI: protease inhibitors; ART: antiretroviral therapy, ddI: didanosine, d4T: stavudine, ZDV: zidovudine, EFV: efavirenz, NVP: nevirapine, IDV: indinavir, SQV: saquinavir.sgc, RTV: ritonavir, NFV: nelfinavir, APV: amprenavir, ADV: adefovir, Combivir: lamivudine 150mg/zidovudine 300mg tablet, HU: hydroxyurea, IL2: interluekin 2

ABACAVIR - LIST OF STUDIES

Protocol Number (Number and location of Centers)	Study Design	Initiation and Completion Dates	Treatments	Total Number of Subjects Enrolled in Study	Number of Subjects Exposed to ABC
Penta 05 (53 centers in Italy, the UK, Germany, France, Spain, Switzerland, Belgium, and Portugal)	MC, OL, Ped, R, PC study in Tx naive children	Dec 1997 - 2000	ABC + 3TC +NFV OR ABC + 3TC +PBO OR ABC + ZDV +NFV OR ABC + ZDV +PBO OR ZDV + 3TC + NFV OR ZDV + 3TC + PBO	120	80
CNAA2007 (6 centers in the US)	20 weeks MC, OL, Salvage study in Tx Exp adults	Dec 1997 - 3Q99	ABC + APV + EFV	101	101
CNAB3015 (Multicenter in Europe)	48 weeks, MC, OL study in adults with failure to PI containing regimen	4Q1998 - 2000	ABC+APV plus other ART in adults with early failure after an initial PI-containing regimen. 25 subjects/arm assigned to: ABC + 2NRTI or ABC + APV + NRTI(s) or ABC + APV + PI or ABC + NNRTI + NRTI(s)	100	100
CNAA2004 (6 centers in the US)	Up to 48 weeks OL, MC, R, ABC/PI combination in Tx naive adults	June 18, 1997 - end 1998	ABC +IDV OR ABC + SQV OR ABC + RTV OR ABC + NFV OR ABC + APV	82	74
PILLR Trial (Australia)	SC, OL in Tx exp adults	3Q1998 - 2000	2NTRI + PI or 2NRTI + ABC + NVP + HU	80	40

DB: Double-blind, Tx Exp: Treatment-experienced patients, MC: Multicenter, Tx Naive: Treatment-naive patients, OL: Open-label, PC: Placebo-controlled, Ped: Pediatric study, R: Randomized, SC: Single-center

3TC: lamivudine, NRTI: nucleoside reverse transcriptase inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor PI: protease inhibitors; ART: antiretroviral therapy, ddI: didanosine, d4T: stavudine, ZDV: zidovudine, EFV: efavirenz, NVP: nevirapine, IDV: indinavir, SQV: saquinavir.sgc, RTV: ritonavir, NFV: nelfinavir, APV: amprenavir, ADV: adefovir, Combivir: lamivudine 150mg/zidovudine 300mg tablet, HU: hydroxyurea, IL2: interluekin 2

ABACAVIR - LIST OF STUDIES

Protocol Number (Number and location of Centers)	Study Design	Initiation and Completion Dates	Treatments	Total Number of Subjects Enrolled in Study	Number of Subjects Exposed to ABC
CNAAB3007 (ABC Expanded Access)	MC, OL, International program allowing ABC use in clinical practice setting. Enrollment open to Tx exp children	3Q1997 - 1999	ABC used in physician's regimen of choice	75	75
ACTG356 (19 centers in the US and Puerto Rico)	24 weeks MC, OL, Ped, R study in Tx naive children	May 1997 - 1999	ABC + ZDV+ 3TC + NVP OR ZDV + 3TC + NVP OR d4T + 3TC + NVP + NFV	48	16
CNAA2006 (1 center in Switzerland)	48 weeks SC, OL, Tx naive adults	Sep 1997 - end 1999	ABC + APV	41	41
SFGH 001 (SC pilot at San Francisco General Hosp)	OL, study to enroll adults with early vs late IDV or RTV failure	Apr 1998 - 1999	NFV + SQV + ABC + NVP	35	35
CH-97-02 (1 center in Switzerland)	SC, OL in Tx naive adults	Apr 1997 - 1999	ABC + NFV + SQV OR ABC + NFV + SQV + IL-2 OR ABC + NFV + SQV + Remune	30	30
ICC-605 (MC trial via Intercompany Collaboration)	MC, OL, 24 week pilot study in Tx exp adults	Jan 1999 -2000	ABC + ADV + EFV + APV	25	25
CNABERAD (1 center in the Netherlands)	SC, OL in Tx naive adults	Jan 1997 - 1999	ABC + ZDV + 3TC +IDV + NVP OR ABC + d4T + 3TC +IDV +NVP	15	15

DB: Double-blind, Tx Exp: Treatment-experienced patients, MC: Multicenter, Tx Naive: Treatment-naive patients, OL: Open-label, PC: Placebo-controlled, Ped: Pediatric study, R: Randomized, SC: Single-center

3TC: lamivudine, NRTI: nucleoside reverse transcriptase inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor PI: protease inhibitors; ART: antiretroviral therapy, ddI: didanosine, d4T: stavudine, ZDV: zidovudine, EFV: efavirenz, NVP: nevirapine, IDV: indinavir, SQV: saquinavir.sgc, RTV: ritonavir, NFV: nelfinavir, APV: amprenavir, ADV: adefovir, Combivir: lamivudine 150mg/zidovudine 300mg tablet, HU: hydroxyurea, IL2: interluekin 2

GlaxoWellcome

December 15, 1998

DESK COPY

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 20-977; Ziagen™ (abacavir sulfate) Tablets;**
NDA 20-978; Ziagen™ (abacavir sulfate) Oral Solution;
Summary of Our Intent to Pursue Traditional Approval for Abacavir Products

Dear Dr. Jolson:

Pursuant to our discussions with your review team (including the Pre-NDA meeting on February 11, 1998 and the meeting on October 13, 1998) and consistent with the public hearing of the Antiviral Drugs Advisory Committee on November 2, 1998, we have prepared this letter to state Glaxo Wellcome's intent to pursue traditional approval of abacavir products in accordance with the provisions of the accelerated approval regulations.

Ongoing Clinical Studies

Glaxo Wellcome acknowledges the obligation to verify and describe the clinical benefit of abacavir in order to qualify for traditional approval. Glaxo Wellcome intends to submit in the future a Supplemental Application to seek traditional approval of abacavir based on the weight of evidence of several ongoing studies plus a future additional study. As discussed previously with the Division, Glaxo Wellcome fully intends to continue the following ongoing clinical studies:

1. CNAA/B3005: This ongoing GW-sponsored study was designed as an equivalence trial to compare abacavir/ZDV/3TC versus indinavir/ZDV/3TC; 562 therapy-naive adults were enrolled. Preliminary results for 16-24 weeks were reported to FDA in October, 1998 and the study is continuing through 48 weeks of treatment to assess surrogate endpoints (plasma HIV RNA and CD4 cell count) and safety.

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.

2. CNAA3006: This ongoing GW-sponsored study was designed as a superiority trial to compare abacavir/ZDV/3TC versus ZDV/3TC in nucleoside-experienced pediatric patients; 205 patients were enrolled. Results through 16 and 24 weeks have been reported to FDA as part of the application for accelerated approval. The study is continuing through 48 weeks of treatment to assess surrogate endpoints (plasma HIV RNA and CD4 cell count), developmental milestones, and safety.

3. CNAA/B3003: This ongoing GW-sponsored study was designed as a superiority trial to compare abacavir/ZDV/3TC versus ZDV/3TC; 173 therapy-naive adults were enrolled. Results through 16 and 24 weeks have been reported to FDA as part of the application for accelerated approval. The study is continuing through 48 weeks of treatment to assess surrogate endpoints (plasma HIV RNA and CD4 cell count) and safety. Glaxo Wellcome understands the Division's view that the surrogate endpoint data for 48 weeks in this study will not support traditional approval in view of the large proportion of patients in the control group who switched treatment after 16 weeks. Nonetheless, we are committed to completing this study as part of our original commitment to Phase III studies (as described at our End-of-Phase II meeting) and we will provide the results to the Division.

4. ACTG 372-A: This ongoing study (a collaborative effort of the ACTG, Merck, and Glaxo Wellcome) was designed as a rollover study for approximately 200 patients who successfully completed ACTG320 with plasma HIV RNA < 500 copies/mL with the three-drug combination regimen of indinavir 800 mg TID plus zidovudine 300mg BID plus lamivudine 150mg BID. Upon entry into ACTG372-A, these patients were randomized (1:1) to a double-blind comparison of continuation of the three-drug regimen (indinavir/ZDV/3TC) versus intensification to a four-drug regimen (i.e., abacavir 300mg BID plus indinavir/ZDV/3TC). The primary analysis in the study is a comparison by treatment of the time to confirmed virologic failure (defined as two consecutive determinations of plasma HIV RNA ≥ 500 copies/mL). The protocol Chairperson is Dr. Scott Hammer. ACTG372-A is fully accrued and ongoing. This study will also yield additional safety data from concurrent administration of abacavir with indinavir (plus ZDV/3TC).

Within six months of completion of each of these four studies (where "completion" is defined as the time when the last patient completes 48 weeks on randomized, blinded study medication), Glaxo Wellcome intends to provide FDA with a study report of key analyses of safety and efficacy. Glaxo Wellcome will also provide the corresponding data sets for the GW-sponsored studies; the data sets will be sought for the ACTG372-A trial. These reports will be submitted to the GW-sponsored IND for abacavir. Glaxo Wellcome intends to perform the protocol-specified analyses on the results of each study; in addition, Glaxo Wellcome will seek FDA agreement (in advance of our

preparation of these study reports) on any additional efficacy and safety analyses to be requested by the Division.

Additional Clinical Study

1. Glaxo Wellcome acknowledges previous advice from the Division and the Antiviral Drug Products Advisory Committee members regarding the value of initiating one or more additional studies to describe the clinical benefit of abacavir in order to qualify for traditional approval. As discussed previously with the Division on October 13 on November 2 at the Advisory Committee Meeting and on December 7th during a conference call, Glaxo Wellcome commits to design and initiate one additional clinical study intended to describe the clinical benefit of abacavir. In this regard, our diligence has been demonstrated by provision on October 13 of five protocol concept sheets for possible studies. We acknowledge the previous discussions with the Division and the Advisory Committee regarding possible study designs, and we also commit to foster additional, future discussions with the Division and clinical investigators in an effort to finalize a concept sheet and protocol. We estimate that a full draft protocol can be agreed with key clinical investigators and submitted to the Division for comment and agreement by the end of March 1999, thereby enabling initiation of this additional study in second quarter, 1999. No estimate of the date of the completion of this additional study can be provided until the study design is agreed.

2. Major amendments of the design or analysis of each Glaxo Wellcome-sponsored study (i.e., CNAA/B3005, CNAA3006, CNAA/B3003, and an additional clinical study) will be submitted to, and discussed with, the Division prior to enactment.

3. Glaxo Wellcome will submit quarterly progress reports on the progress of each study intended to contribute to a Supplemental Application to seek traditional approval of abacavir. The first such report will encompass our activities during January-March of 1999; this report will be submitted in April, 1999. These quarterly progress reports will include information on total enrollment, approximate number of weeks on treatment of the last patient enrolled, number of deaths, and number of patients remaining on randomized treatment. Since these studies are blinded and ongoing, the quarterly progress reports will not be broken down by treatment group and the information provided will be preliminary. Safety reporting for these ongoing IND studies will continue to be governed by the requirements in 21 CFR 312.32.

We also gratefully acknowledge the Division's contributions of ideas and feedback to date on the development program for abacavir. We appreciate the commitment from Divisional personnel to continue to provide review and feedback on proposals for studies of abacavir.

This submission is provided in duplicate. Four desk copies have been sent directly to Melissa Truffa. Please contact Martha Anne Moore at (919)-483-9347 for any matters regarding these applications. Thank you.

Sincerely,

M. Lynn Smiley, M.D.
Vice President
HIV & OI Clinical Development

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

ITEM 13

PATENT INFORMATION

for

NDA 20-977
ZIAGEN™ (abacavir sulfate) Tablets

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

Trade Name:	Ziagen™ Tablets
Active Ingredient:	abacavir sulfate
Strength(s):	300 mg
Dosage Form:	Tablet
NDA Number:	20-977

Applicable Patent Numbers and Expiration Dates:

Patent No.	5,034,394
Expires:	June 26, 2009
Owner:	Glaxo Wellcome Inc.
Type:	Composition Formulation

Patent No.	5,089,500
Expires:	June 26, 2009
Owner:	Glaxo Wellcome Inc.
Type:	Method of Use (treatment of viral infections, HIV, HBV)

The undersigned declares that U.S. Patent Nos. 5,034,394 and 5,089,500

cover the composition, formulation, and methods of use of ZIAGEN™ (abacavir sulfate) Tablets. These U.S. patents should be included in Item 13 of NDA 20-977.

June 12, 1998
Date

Karen L. Prus, Ph.D.
Registered Patent Attorney
Registration No. 39,337

APPEARS THIS WAY
ON ORIGINAL

Exclusivity Summary Form

EXCLUSIVITY SUMMARY FOR NDA # 20-977

Trade Name: Ziagen™ 300 mg Tablets **Generic Name:** abacavir sulfate

Applicant Name: Glaxo Wellcome Inc. **HFD #** 530

Approval Date If Known: _____

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 /X/ NO /__/

b) Is it an effectiveness supplement?

YES /__/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

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:

_____

_____

Form OGD-011347 Revised 8/27/97
cc: Original NDA Division File HFD-93 Mary Ann Holovac

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?

5 years

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

YES / X / Granted 12/14/98 NO /___/

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

(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 /_X_/

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 /_X_/

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 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 /___/ 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 /___/ 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 /___/

(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:

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 /___/

Investigation #2 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:

_____ _____

_____ _____

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 /___/

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"):

_____ _____

_____ _____

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:
Title: Project Manager

Date: 12-9-98

Signature of Office/Division Director
Signatur

Date: 12/11/98

/S/

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

GlaxoWellcome

December 10, 1998

DESK COPY

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

Re: NDA 20-977; ZIAGEN™ Tablets (abacavir sulfate tablets)
Amendment to Pending Application: Request for Marketing Exclusivity

Dear Dr. Jolson:

Reference is made to NDA 20-977 for Ziagen Tablets. This application is under active review in your Division. The purpose of this submission is to state our request for marketing exclusivity for this product.

The current regulations in 21 CFR 314.50 (j) state that an applicant who believes its drug product is entitled to a period of exclusivity may submit specified information to the New Drug Application record prior to approval. Therefore, we are providing the specified information in accordance with this regulation.

Under sections 505(c)(3)(D)(ii) and 505(j)(4)(D)(ii) of the Federal Food, Drug, and Cosmetic Act, the applicant (Glaxo Wellcome Inc.) requests five years of exclusivity from the date of approval of this New Drug Application for Ziagen (abacavir sulfate) Tablets for the treatment of HIV infection as a new chemical entity pursuant to the definition in 21 CFR 314.108(a).

The active ingredient of the drug product for which approval is being sought under this application is abacavir sulfate. Abacavir sulfate is also known as (1S,cis)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1).

Glaxo Wellcome hereby states that to the best of its knowledge and belief that the drug product which is the subject of the instant application contains no "active moiety" as defined under 21 CFR 314.108(a) that has been approved by the FDA under §505(b) of the Federal Food, Drug and Cosmetic Act and that therefore, the drug product of the instant application falls within the definition of "new chemical entity" under 21 CFR 3414.108(a).

This submission is provided in duplicate. Four desk copies have been provided directly by Ms. Truffa for use by the review team. Please contact me at (919)-483-9347 for any matters regarding this application. Thank you.

Sincerely,

Martha Anne A. Moore

Martha Anne A. Moore, R.Ph.
Antiviral Group - Regulatory Affairs

Glaxo Wellcome Research and Development
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709
Telephone
919 483 2100
A Division of
Glaxo Wellcome Inc.

Extended Market Exclusivity for Pediatric Clinical Work

NDA 20-977: Ziagen™ (abacavir sulfate) Tablets
NDA 20-978: Ziagen™ (abacavir sulfate) Oral Solution

Glaxo Wellcome Inc. requests a determination that marketing submissions and approvals under Subsections (b)(2) or (j) of Section 505 of the Federal Food, Drug, and Cosmetic Act (the "FFDCA"), for any product containing abacavir, will be fully subject to the market-exclusivity extension provisions of new Section 505A of the FFDCA (as added by Section 111 of the Food and Drug Modernization Act of 1997), on the basis of our timely completion of, and submission of reports of, five clinical studies in pediatric patients (i.e., protocols CNAA1001, ACTG 330, CNAA3006, CNAA/B3003, and CNAA/B3007). Glaxo Wellcome Inc. is entitled to such a determination because:

1. FDA and Glaxo Wellcome agreed during regulatory meetings (i.e., End-of-Phase II and Pre-NDA meetings) that information on pediatric use of abacavir sulfate tablets and oral solution may produce health benefits for pediatric patients. This agreement effectively satisfies the requirement of Section 505A(a) that "the Secretary" have made a written request for pediatric studies, on the basis of a determination that additional information relating to pediatric use (of a then unapproved new drug) may produce health benefits.

2. Each of the five pediatric studies was conducted by or with the support of Glaxo Wellcome. Four the five studies were fully funded and explicitly sponsored by Glaxo Wellcom[redacted] the fifth study (ACTG 330) was sponsored by the Pediatric AIDS Clinical Trials Group with active collaboration by Glaxo Wellcome through our membership on the Protocol Team and our provision of all supplies of abacavir used in this study. Each of the five protocols was reviewed by FDA's Division of Antiviral Drug Products, and then discussed with Glaxo Wellcome prior to finalization and implementation. Therefore, this approach complies with the requirement of Section 505A(d) that studies in pediatric patients be conducted according to an agreed-upon protocol.

3. All five studies have progressed and been reported in this NDA in the manner agreed with FDA's Division of Antiviral Drug Products in accordance with discussions at the Pre-NDA meeting on February 11, 1998. We believe that our adherence to these regulatory agreements comprises an adequate basis for stating that the information is complete and reports of the studies have been submitted on a timely basis.

Extended Marketing Exclusivity for Pediatric Clinical Work
NDA 20-977 and NDA 20-978

Please note that Glaxo Wellcome has communicated this position previously to both the Division of Antiviral Drug Products (in our letter of January 8, 1998) and Ms. Khyati Roberts of FDA's Executive Operations Staff (in our letter of May 4, 1998). Both of these letters requested written confirmation from the agency that this body of pediatric studies on abacavir products meets all requirements to merit additional market exclusivity. To date, we have not received a response to these letters.

Glaxo Wellcome Inc. asks that the determination granting extended market exclusivity be published, as provided by Section 505A(f).

NDA 20-977: Ziagen (abacavir sulfate) Tablets
NDA 20-978: Ziagen (abacavir sulfate) Oral Solution

Marketing Exclusivity

Glaxo Wellcome Inc. requests a determination that marketing submissions and approvals under Subsections (b)(2) or (j) of Section 505 of the FFDCA, for any product containing abacavir, will be fully subject to the market-exclusivity extension provisions of new Section 505A of the FFDCA (as added by Section 111 of the Food and Drug Modernization Act of 1997), on the basis of our timely completion of, and submission of reports of Study CNAA3006. Glaxo Wellcome Inc. is entitled to such a determination because (1) FDA issued a Written Request for pediatric studies on abacavir on August 20, 1998; (2) studies CNAA1001, ACTG330, CNAA3006 and CNAAB3007 were conducted according to agreed-upon protocols and (3) the studies were completed and reported to FDA on a timely basis. Glaxo Wellcome Inc. asks that the determination granting extended market exclusivity be published as provided by Section 505A(a).

The clinical investigations are entitled:

CNAA1001 (P131:003): A Phase I Trial to Evaluate the Safety and Pharmacokinetics of Single Oral Doses of 1592U89 in HIV-Infected Children.

ACTG330 (CNAA1013): A Phase I Safety and Pharmacokinetic Study of 1592U89 Alone and in Combination with Other Antiretroviral Agents in Infants and Children with HIV Infection.

CNAA3006: A Double-Blind, Randomized, Multicenter Trial to Evaluate the Safety and Efficacy of the Combination of 1592U89/Zidovudine (ZDV)/Lamivudine (3TC) Versus the Combination of Zidovudine (ZDV)/Lamivudine (3TC) in HIV-1 Therapy-Experienced Patients.

CNAAB3007 1592U89 Open Label Protocol for Pediatric Patients with HIV Infection.

These clinical investigations meet the definition of "new" as they have not been relied on by the FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation relied on by FDA for such purposes [21 CFR 314.108(a)].

Study CNAA3006 is "essential to the approval" of this application in that this New Drug Application can not be approved by the FDA without this investigation [21 CFR 314.108(a)]. Similarly, CNAA001 (P131:003) and ACTG 330 (CNAA1013) are "essential to the approval" of this application since they are the source of essential pharmacokinetic properties and data on safety of abacavir in pediatric patients. Finally, CNAAB3007 is the sole source of data on certain unique abacavir-containing combination regimens of antiretroviral drugs in pediatric patients used in an open-label/expanded access setting.

These clinical investigations were "conducted or sponsored" by Glaxo Wellcome in that Glaxo Wellcome Inc. was named on the From FDA 1571 as the sponsor of the investigational New [redacted] under which these investigations were conducted [21 CFR 314.108(a)] or Glaxo Wellcome contributed to the conduct of the trial in conjunction with a co-sponsor (ACTG 330).

GlaxoWellcome

BZ

October 29, 1998

Dianne M. Murphy, M.D., Office Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 20-977; ZIAGEN™ Tablets (abacavir sulfate tablets)
NDA 20-978; ZIAGEN™ Oral Solution (abacavir sulfate oral solution)
Amendment to Pending Application: SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

Serial No.: 618

Dear Dr. Murphy:

Reference is made to an official Written Request for pediatric data received from your Division dated August 20, 1998. Reference is also made to our submission (serial no. 492) regarding pediatric exclusivity for abacavir products. The purpose of this submission is to provide our response to your request of August 20, 1998.

Glaxo Wellcome is providing, via this submission, clinical study reports for the following four types of studies as requested by your Office:

1. CNAA1001 (P131:003) - Single does pharmacokinetics study assessing different doses of abacavir in patients between the ages of 3 months and 12 years. As agreed with the Division of Antiviral Drug Products (DAVDP), a full copy of this report was submitted to our IND 45,331 on February 18, 1998 (serial no. 336, volumes 4-5 of 5 submitted volumes) for incorporation into NDA 20-977 and 20-978.

2. ACTG 330 (CNAA1013) - Study to evaluate the multiple-dose pharmacokinetics of different doses of abacavir alone, followed by assessment of the safety and antiviral activity of the selected dose of abacavir in combination with other antiretroviral agents in HIV-infected children from age 3 months to 12 years. As agreed with DAVDP, a full copy of this report volumes) for incorporation into NDA 20-977 and 20-978.

3. CNAA3006 - Adequate and well-controlled Phase 3 study comparing an abacavir combination regimen with an established antiretroviral regimen in therapy-experienced HIV-infected patients age 3 months to 12 years. As agreed with DAVDP, a full copy of this report

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

was submitted to our [redacted] submitted volumes) for incorporation into NDA 20-977 and 20-978.

4. CNAAB3007 - Actual use, open-label treatment study to evaluate safety in therapy experienced pediatric patients with HIV disease. A full copy of the report was submitted on October 29, 1998 as an Amendment to a Pending Application to our NDA 20-977 and is incorporated into NDA 20-978 via cross reference.

These four clinical trials have the appropriate objectives/rationale, indication to be studied, pediatric age groups, number of patients studied, entry criteria, study evaluations, drug information and statistical information as outlined in your Written Request of August 20, 1998. We believe we have responded in full to your Written Request.

Also as requested in the August 20, 1998 Written Request, we are submitting proposed product labeling which indicates labeling we believe is warranted based upon results of our submitted pediatric studies. We are also providing a copy of the original Written Request as provided to Glaxo Wellcome.

We recognize the importance of responding to an unmet medical need by providing clinical data in a pediatric HIV patient population. We appreciate FDA's willingness to review these study reports in support of additional exclusivity for abacavir products in accordance with Section 505A(a) of FDAMA. As we believe we have responded in full to your Written Request, please note that we have amended Item 13 of our NDAs to reflect our understanding of additional exclusivity for abacavir products.

As discussed with Ms. Melissa Truffa on October 23, 1998, this submission is made in duplicate to NDA 20-977; one desk copy of this submission has been provided directly to Ms. Melissa Truffa. One copy of this cover letter is provided to NDA 20-978 along with an amended Item 13 in order to incorporate all information into NDA 20-978. A copy of the cover letter is also provided to [redacted] In addition, one copy of this letter has been sent directly to the attention of the Director, Office of Generic Drugs as was requested. If you have any questions regarding this submission, please contact me at (919) 483-9347. Thank you.

Sincerely,

Martha Anne A. Moore

Martha Anne A. Moore, R.Ph.
Antiviral Group - Regulatory Affairs

Cc: Director, Office of Generic Drugs
HFD-600
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-977
NDA 20-978

AUG 20 1998

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

Dear Dr. Cocchetto:

To obtain needed pediatric information on Ziagen™ (abacavir sulfate) Tablets and Oral Solution, the Food and Drug Administration (FDA) is hereby issuing to you an official Written Request, pursuant to Section 505A(a) of the Federal Food, Drug, and Cosmetic Act. FDA requests that you submit information from the following:

Types of studies:
Study 1: Single dose pharmacokinetic study assessing different doses of abacavir in patients between the ages of 3 months and 12 years.

Study 2: Study to evaluate the multiple-dose pharmacokinetics of different doses of abacavir alone, followed by assessment of the safety and antiviral activity of the selected dose of abacavir in combination with other antiretroviral agents in HIV-infected children from age 3 months to 12 years.

Study 3: Adequate and well-controlled Phase 3 study comparing an abacavir combination regimen with an established antiretroviral regimen in therapy-experienced HIV-infected patients, ages 3 months to 12 years.

Study 4: Actual use, open-label treatment study to evaluate safety in therapy-experienced pediatric patients with HIV infection.

Objective/rationale:
Study 1: To assess the single dose pharmacokinetics of different doses of abacavir in the pediatric population.

Study 2: To assess the multiple-dose pharmacokinetics of different doses of abacavir in the pediatric population and to obtain initial assessment of safety and antiviral activity of the selected dose of abacavir in combination with other antiretroviral agents in HIV-infected children between the ages of 3 months and 12 years.

Study 3: Assess the safety and efficacy of abacavir in pediatric patients with HIV infection.

Study 4: Assess safety and provide therapy-experienced pediatric patients access to abacavir.

Indication to be studied: HIV infection.

Study design:
Study 1: Single dose pharmacokinetic study evaluating at least two doses of abacavir.

Study 2: Multiple-dose pharmacokinetic dose-escalating study evaluating the pharmacokinetics of the doses employed in Study 1, followed by a 12 week initial clinical evaluation of a selected dose of abacavir in combination with other antiretroviral therapy.

Study 3: Adequate and well-controlled safety and efficacy study.

Study 4: Open-label safety study.

Age group in which studies will be performed: Studies 1 through 3 should include children between the ages of 3 months and 12 years. Studies 1 and 2 should be appropriately designed and analyzed to determine age-dependent pharmacokinetics.

Number of patients to be studied or power of study to be achieved:
Study 1: A number of completed subjects to adequately characterize the single dose pharmacokinetics for each of the age groups 3-5 months, 6-23 months, 2-5 years, and 6-12 years.

Study 2: In the pharmacokinetic phase of the study, a number of completed subjects to adequately characterize the multiple-dose pharmacokinetics for each of the age groups 3-23 months, 2-5 years, and 6-12 years.

Study 3: A minimum of 100 subjects per study arm.

Study 4: Number of subjects reported at time of submission.

Entry criteria: (i.e., inclusion/exclusion criteria): HIV-infected pediatric patients.

Clinical endpoints, if appropriate:
Study 1: Pharmacokinetic parameters will be assessed (see "Study Evaluations" below).

Study 2: The pharmacokinetic dose escalation phase of this study will assess pharmacokinetic parameters (see "Study Evaluations" below). The second phase of the study will evaluate the preliminary clinical efficacy and safety of abacavir in combination therapy utilizing changes in plasma HIV RNA and CD4 cell percent over 12 weeks.

Study 3: Proportion of patients achieving plasma HIV RNA levels below 10,000 copies/mL through week 24.

Study 4: Comparison of the safety profile in pediatric patients with that described in adults, as well as identification of new or more severe adverse events than described in adults.

***Study evaluations*:**
Study 1: Reports of C_{max}, T_{max}, AUC, and $T_{1/2}$.

Study 2: Reports of C_{max}, T_{max}, AUC, $T_{1/2}$ and antiviral activity assessments over 12 weeks.

Study 3: Safety and efficacy data through week 24.

Study 4: Safety data.

***Drug information*:**

- ***Dosage form*:** oral solution
- ***Route of administration*:** oral
- ***Regimen*:** to be determined by development program
- ***Formulation*:** as appropriate for dosage form and pediatric population

***Safety concerns*:** Hypersensitivity

***Statistical information (statistical analyses of the data to be performed)*:**
Study 1: Descriptive analysis of the pharmacokinetic parameters and comparison of the dose normalized pharmacokinetic parameters between and within the dose groups.

Study 2: Descriptive analysis of the pharmacokinetic parameters and antiviral activity assessments over 12 weeks.

Study 3: Comparative treatment groups using the Cochran Mantel-Haenszel test controlling for randomization stratum (age and prior 3TC/AZT experience).

Study 4: Descriptive statistics.

***Labeling that may result from the studies*:** Information regarding dosing and safety in HIV-infected patients ages 3 months to 12 years.

***Format of reports to be submitted*:** Full study reports or analyses addressing the issues outlined in this request with full analysis, assessment, and interpretation for Studies 1, 2, and 3. Include other information as appropriate.

Timeframe for submitting reports of the studies: On or before October 30, 1998.

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

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

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

If you have any questions, please contact Melissa M. Truffa, R.Ph., Regulatory Health Manager, at (301) 827-2335.

Sincerely yours,

/S/

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