

**Pediatric Exclusivity Board
December 14, 1998**

DRAFT

Pediatric Exclusivity Board Members

Liz Dickinson, OCC
Leanne Cusumano, RPS
Mary Fanning, OGD
Roger Williams, OPS
Dianne Murphy, ODE4
Khyati Roberts, EOS
Murray Lumpkin, OCD, Chair

Review Division/Office Representatives

Melissa Truffa, DAVDP
Therese Cvetkovich, DAVDP
Debbie Birnkrant, DAVDP

Pediatric Exclusivity Determination for Abacavir by Glaxo

Written Request issued:	August 20, 1998
Timeframe for submission of report of studies:	October 30, 1998
Date report of studies submitted:	October 30, 1998
Due Date for Pediatric Exclusivity Determination:	January 28, 1999

- This is a 'gap group' application (i.e., the study reports were submitted after November 21, 1998, but before June 30, 1998, (date of issuance of FDA's guidance document)).
- The Written Request (WR) was issued to NDAs 20-977 (tablets) and 20-978 (oral solution).
- Sponsor has submitted reports of studies to both applications in response to the WR.
- The terms of the WR letter have been met by the reports.
- The information requested will provide dosing information for all ages greater than 3 months. This drug is not a first line therapy; therefore, information was not requested below 3 months of age. Once postmarketing safety data is obtained on the older age group, the Division may wish to obtain information on use of the product for the age group of less than 3 months. If additional pediatric information is needed, the Division will prepare a second WR letter.
- If granted, pediatric exclusivity will apply to all patents listed or exclusivity protection granted for NDA 20-978 and 20-977 upon approval.

Recommendation: Grant pediatric exclusivity.

Prepared by: **DRAFT**
Khyati N. Roberts

Date

Murray M. Lumpkin
Chair, Pediatric Exclusivity Board

Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20977 Trade Name: ZIAGEN (ABACAVIR SULFATE) TABLETS
 Supplement Number: Generic Name: ABACAVIR SULFATE TABLETS
 Supplement Type: Dosage Form: Tablet; Oral
 Regulatory Action: PN Proposed Indication: In combination with other antiretroviral agents, for the treatment of HIV-1 infection.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? YES

What are the INTENDED Pediatric Age Groups for this submission?

 NeoNates (0-30 Days) X Children (25 months-12 Years)
 X Infants (1-24 Months) X Adolescents (13-16 Years)

Label Status ADEQUATE Labeling for SOME PEDIATRIC ages
 Formulation Status NEW FORMULATION developed with this submission
 Studies Needed STUDIES needed. Applicant has COMMITTED to doing them
 Study Status Required studies are ongoing

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

Requested that the sponsor commit to the completion and submission of the ongoing pharmacokinetic study in neonates and commit to the initiation, completion and submission of the results of an evaluation of pharmacokinetics in adolescents. 12/7/98

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MELISSA TRUFFA

Signature

Date

12-9-98

NDA 20-977

Ziagen™ Tablets (abacavir sulfate 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.



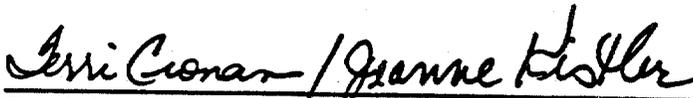
16 JUN 98

Charles E. Mueller
Head, US Clinical Compliance
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.



16 Jun 98

Terri Cronan/Jeanne Kistler
Compliance Standards & Information Administrator
World Wide Compliance

Date

What are the possible or reasonably likely side effects of Ziagen?

Some people have had a hypersensitivity reaction (a serious allergic reaction) to Ziagen, which can be fatal. Instructions on how to recognize a possible reaction, as well as what to do if such a reaction is suspected, are discussed in the section "What is the most important information I should know about Ziagen?"

The class of medicines to which Ziagen belongs (NRTIs) can cause a condition called lactic acidosis, together with an enlarged liver. In some cases, this condition can be fatal. Women are more likely than men to experience this rare but serious side effect.

Ziagen can cause other side effects. In studies, the most common side effects with Ziagen were nausea, vomiting, malaise or fatigue, headache, diarrhea, and loss of appetite. Most of these side effects did not cause people to stop taking Ziagen. This listing of side effects is not complete. Your doctor or pharmacist can discuss with you a more complete list of side effects with Ziagen. Talk to your doctor promptly about any side effects you have.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Ask a health care professional about any concerns about Ziagen. Professional labeling is available to your doctor and other health care professionals.

GlaxoWellcome

Glaxo Wellcome Inc.

Research Triangle Park, NC 27709

Date of Issue RL no.

This Medication Guide has been approved by the US Food and Drug Administration.

NEW DRUG APPLICATION
NDA 20-977
Ziagen™ (abacavir sulfate) Tablets
Volume 5.14

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Division Director Memorandum

NDA: - 20-977 (tablets) and 20-978 (solution)

Drug and indication: Abacavir sulfate (300 mg tablets and 20 mg/mL solution) for use in combination with other antiretroviral agents for the treatment of HIV-1 infection

Dose: Adults - 300 mg twice daily
Ages 3 months to 16 years - 8 mg/kg twice daily up to a maximum of 300 mg twice daily

Applicant: Glaxo Wellcome Inc.

Submission received: June 24, 1998

Date of Memorandum: December 13, 1998

In this application, the sponsor has requested accelerated approval for abacavir tablets and solution for the treatment of HIV-infection. In support of this request, the sponsor has submitted full study reports of two ongoing studies, CNAB3003 (conducted in 173 treatment naive adults) and CNAA 3006 (conducted in 205 treatment-experienced pediatric patients), and a third completed trial, CNAB3001 (conducted in 105 patients with AIDS-dementia). After initial review of this application and at the division's request, preliminary data and executive summaries have been provided from additional ongoing or recently completed studies.

I am in concurrence with the consensus of the Antiviral Drugs Advisory Committee that this application should be approved under the 21 CFR 314 Subpart H provisions for accelerated approval. However, as noted in the clinical and biometrics reviews, there are several reservations about the adequacy of certain aspects of this database that merit comment and additional investigation in phase IV.

1. Antiviral efficacy in treatment naive patients

Evidence of efficacy in treatment naive patients has been provided by the results of interim surrogate marker analyses of ongoing studies CNAB3003 and CNAB3005. In the former study, a significantly higher portion of patients treated with abacavir in combination with lamivudine and zidovudine had a viral load measurement below the limit of quantification at 16 weeks compared to the comparator group. A lower mean CD4 response, however, was also observed in the abacavir-containing group. The finding of a lower CD4 response was consistently observed in a variety of subgroups, and has not been explained by additional exploratory analyses of this study. The CD4 result may be due to one of several factors: a) the clinical observation in practice that virologic and CD4 response do not always correlate in a given patient; b) triple nucleoside analogue therapy may result in a relatively higher degree of myelosuppression than

dual nucleoside therapy; or c) a chance observation. This finding, in the context of CD4 response rates in other studies, is further discussed in the medical officer's review.

Because of concerns raised by the above finding and other questions raised by the original NDA submission, preliminary results of study CNAB3005, an equivalence trial comparing triple drug regimens with either abacavir or indinavir, were requested. In these preliminary analyses, no remarkable differences in virologic or CD4 responses were observed between treatment groups. Therefore, these results provide additional support of the antiviral activity of abacavir in treatment naive patients, with two important caveats: a) only preliminary analyses of HIVRNA and CD4 through 16 and 24 weeks are available for review, and b) the confidence intervals are too broad and the treatment duration is insufficiently brief to allow conclusions of comparability between regimens at this time.

2. Antiviral efficacy in treatment experienced patients

This application is notable for including the first phase III study in pediatric patients to be submitted in support of an accelerated approval. In this pediatric study, a modest increase was found in the rate of virologic response (proportion with HIVRNA < 400 copies/mL) in patients who received a regimen containing abacavir, lamivudine and zidovudine compared to lamivudine and zidovudine. No significant difference in virologic response was found between groups in the primary analysis (proportion with HIVRNA < 10,000 copies/mL), however virologic and CD4 response rates were numerically higher in the abacavir-containing regimen. The study design may have limited the potential to demonstrate effectiveness since most patients had previous experience with zidovudine and lamivudine. Therefore, the use of abacavir in combination with these agents may have resulted in the addition of only a single new agent to an otherwise failing regimen in many patients.

As noted by the biometrics reviewer, several other studies (some submitted in executive summary form, only) with abacavir in treatment experienced patients have not been able to demonstrate the contribution of abacavir to other combination therapies. Study results that raise questions about the limited efficacy of abacavir in treatment experienced patients include: ACTG 368, where there was no apparent advantage of the addition of abacavir to a regimen containing indinavir and efavirenz; and CNAB3001, where abacavir was added to background therapy in a trial designed to assess an impact on AIDS-dementia.

Considered together, the available database suggests that abacavir may have limited efficacy in patients with prolonged prior experience with other nucleoside analogues. As discussed in the microbiology review, this observation is likely attributable to cross-resistance between abacavir and other nucleoside analogues. Further, the results of these studies highlight the difficulty in establishing a new product's relative antiviral contribution when used in combination with more potent antiviral agents in treatment experienced patients. The development of novel clinical trial design approaches for these situations is warranted.

3. Role of triple nucleoside analogue therapy

The principal studies in this application investigated a novel regimen of triple nucleoside analogue therapy, including abacavir, in treatment naive and treatment experienced patients. In treatment naive patients, there are insufficient data at present to fully evaluate the adequacy of this regimen in sustaining viral suppression. As noted below, it is anticipated that data through 48-weeks of treatment from study CNAB3005 (comparing this regimen to an indinavir-containing regimen) will provide information to address this question, and will be submitted in support of traditional approval.

Based on data in treatment experienced pediatric patients, the triple nucleoside regimen resulted in viral suppression below the limit of assay detection in only a small proportion of patients (12%) at week 24. Therefore, preferential use of combinations including more potent therapies should be considered in this population.

4. Lack of efficacy in AIDS-dementia

The applicant's study, CNAB3001, a 12-week study to investigate the potential effect of abacavir on neurocognitive endpoints, did not demonstrate a difference between treatment groups. Consequently, the applicant has not requested a labeling claim for specific use in the setting of AIDS-dementia.

5. Safety - Hypersensitivity reactions

Hypersensitivity is the most important safety concern with abacavir. Hypersensitivity may be manifested by a variety of clinical symptoms and can result in fatality if abacavir treatment is not permanently discontinued. Explicit warnings about the risk of hypersensitivity are provided in the professional labeling as a "black boxed warning" and in the Contraindications, Warnings, Precautions, Adverse Reactions and Dosage and Administration Sections. Importantly, the manufacturer has been required to provide this information to all patients receiving new or refilled prescriptions as a mandatory Medication Guide and wallet warning card. Phase IV commitments to further investigate and address this serious concern are described below.

6. Adequacy of the traditional approval package

Based on review of data in this application, the applicant has been advised that their initial proposal for their traditional approval package (submission of 48-week results of studies 3003, 3005 and 3006) may not be adequate to support approval. This assessment was based on: the unblinding of study 3003 after 16 weeks and the low rate of virologic response in study 3006 at 24 weeks. Ongoing study 3005 appears to be adequate for submission in the traditional approval package and the applicant has committed to the conduct of an additional study of a 48-week treatment duration.

7. Evolving nature of database

The evolving nature of this database merits comment. Because the majority of the studies reviewed in this application are still ongoing, the database remains open and in evolution. The incompleteness of the database has certain consequences: the incidence of hypersensitivity in

There are no additional outstanding regulatory issues at this time that would preclude approval of this application.

/S/

Heidi M. Jolson
Heidi M. Jolson, M.D., M.P.H.
Director, Division of Antiviral Drug Products

cc:

NDA20-977, 20-978

HFD-530/Cvetkovich/Truffa

HFD-104/Murphy

CDER Establishment Evaluation Report
for October 27, 1998

Page 1 of 2

Application: NDA 20977/000 Priority: P Org Code: 530
Stamp: 24-JUN-1998 Regulatory Due: 24-DEC-1998 Action Goal: District Goal:
Applicant: GLAXO WELLCOME Brand Name: ZIAGEN (ABACAVIR SULFATE)
5 MOORE DR TABLETS
RESEARCH TRIANGLE PARK, NC 27 Established Name:
Generic Name: ABACAVIR SULFATE TABLETS
Dosage Form: TAB (TABLET)
Strength: 300 MG/TABLET

FDA Contacts: M. TRUFFA (HFD-530) 301-827-2335 , Project Manager
R. KAMBHAMPATI (HFD-530) 301-827-2395 , Review Chemist
S. MILLER (HFD-530) 301-827-2392 , Team Leader

Overall Recommendation:

ACCEPTABLE on 26-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: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 18-AUG-1998
Decision: **ACCEPTABLE**
Reason: DISTRICT RECOMMENDATION

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

Establishment: 1035048
GLAXO INC
5 MOORE DR
RESEARCH TRIANGLE PARK, NC 2

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 11-JUN-1998
Decision: **ACCEPTABLE**
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE STABILITY
TESTER

Establishment: 9610411
GLAXO OPERATIONS UK LTD
PRIORY ST
WARE, HERTFORDSHIRE, UK

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION

Responsibilities: FINISHED DOSAGE
MANUFACTURER

CDER Establishment Evaluation Report
for October 27, 1998

Milestone Date 26-OCT-1998
Decision: **ACCEPTABLE**
Reason: DISTRICT RECOMMENDATION

FINISHED DOSAGE RELEASE
TESTER
FINISHED DOSAGE STABILITY
TESTER

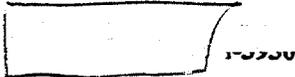
Establishment: 9610419
GLAXOCHEM LTD
COBDEN ST
MONTROSE ANGUS, SCOTLAND, UK

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 11-JUN-1998
Decision: **ACCEPTABLE**
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE
MANUFACTURER
DRUG SUBSTANCE RELEASE
TESTER
DRUG SUBSTANCE STABILITY
TESTER

Establishment: 9614411

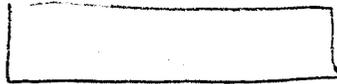


DMF No:
AADA No:

Profile: CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 15-JUN-1998
Decision: **ACCEPTABLE**
Reason: DISTRICT RECOMMENDATION

Responsibilities: INTERMEDIATE MANUFACTURER
INTERMEDIATE RELEASE TESTER

Establishment: 9617068



DMF No:
AADA No:

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

Responsibilities: INTERMEDIATE MANUFACTURER
INTERMEDIATE RELEASE TESTER

ANTIVIRAL DRUGS ADVISORY COMMITTEE
QUICK MINUTES
November 2, 1998

This report contains public information that has not been reviewed by the agency or the Antiviral Drugs Advisory Committee. The official summary minutes will be prepared, circulated, and certified as usual. Transcripts should be available in about 10 days. All external requests should be submitted to the Freedom of Information office.

TOPIC: Ziagen™ (abacavir sulfate tablets and oral solution), Glaxo Wellcome Incorporated, for the treatment of HIV infection in adults and pediatric patients ≥ 3 months.

The meeting was held at the Holiday Inn, Gaithersburg, Maryland. There were approximately 275 persons in attendance. The following members were present: Henry Masur, MD (Acting Chair), Pamela S. Diaz, MD, Wafaa El-Sadr, MD, James J. Lipsky, MD, Roger J. Pomerantz, MD, and John D. Hamilton, MD. The SGE consultants were Joseph S. Bertino, Jr., PharmD (consumer representative), Wm. Christopher Mathews, MD, MSPH, Brian Wong, MD, Robert F. Woolson, PhD and Ram Yogev, MD. The Committee guests were Jeff Bloom (patient representative), Frank Gigliotti, MD, and Joseph Hogan, Sc.D.

The meeting introduction was given by Heidi Jolson, MD, Director, Division of Antiviral Drug Products, FDA. The sponsor's presenters were M. Lynn Smiley, MD, Stephen LaFon, M.Sc., and Seth Hetherington, MD. The FDA's presenters were Therese Cvetkovich, MD and Michael Elashoff, PhD. The open public hearing participants were Jerald Breitman, Mike Donnelly, and Jules Levin.

Questions to the Committee
(Total votes=9)

1. Are the available data sufficient to support the accelerated approval of abacavir for the treatment of HIV infection?

If no, what additional studies are recommended?

If yes, please address the following questions 2 - 7.

Vote: Yes=7
No=2

The majority of the Committee supported the accelerated approval of abacavir for the treatment of HIV infection. There was consensus regarding abacavir's safety data and the risk of an associated hypersensitivity reaction. However, some members felt that the efficacy data did not support accelerated approval due to issues such as the inconsistencies in the virologic and immunologic responses of adult treatment naïve patients in Trial 3003.

2. The principal abacavir-containing regimen studied in phase 3 trials consisted of three nucleoside analogues. Please comment on the appropriate use of this regimen and the appropriate patient population.

The majority of the Committee agreed that a triple nucleoside regimen could be an option for certain patient populations. Additional studies to further define these populations were recommended.

3. Please provide your assessment of the risk/benefit ratio for abacavir, and its implications for clinical use.

It was acknowledged that there is data to suggest abacavir's efficacy in pediatric treatment experienced (Trial 3006) and adult treatment naïve patients (Trial 3005). However, in general, the members stated that abacavir's risk/benefit ratio does not support its use in a first line therapeutic regimen.

4. Several marketed antiretroviral agents associated with rash are likely to be used in combination with abacavir. Please provide your recommendations for the management of patients developing rash while receiving abacavir in combination with these agents.

The Committee agreed that the abacavir-associated hypersensitivity reaction could be confounded by other concurrent antiretroviral therapies and disease symptoms. The majority of the members recommended discontinuing abacavir in the presence of a rash and fever until further studies of this reaction are available.

5. Please provide recommendations for disseminating information on abacavir-associated hypersensitivity reactions to patients and providers, and recommendations for further study of these reactions.

The Committee recommended the widespread dissemination of information on abacavir-associated hypersensitivity to patients and providers. Current awareness methods such as patient and provider wallet cards and proposed awareness methods were discussed. Recommendations for studies of the abacavir-associated hypersensitivity reaction included additional analyses to identify predictive factors associated with its occurrence.

6. Please comment on the applicant's proposed traditional approval package.

The applicant's proposed traditional approval package includes Trial 3003 (adult treatment naïve), Trial 3006 (pediatric treatment experienced), and Trial 3005 (adult treatment naïve). The majority of the Committee agreed that (1) Trial 3003 has supportive viral load results but inconsistent CD4 responses and that (2) Trial 3006 and Trial 3005 suggest abacavir's efficacy. However, several members recommended that the applicant not rely on the pediatric data as a pivotal trial and suggested that the applicant provide an additional study for traditional approval. A trial in adult treatment experienced patients was suggested.

7. Please provide recommendations for any additional Phase 4 studies of abacavir.

The Committee agreed that additional Phase 3 and Phase 4 studies need to be conducted. The majority of the Committee commented on the need for studies to provide insight into the mechanism and management of the abacavir-associated hypersensitivity reaction. Studies to further evaluate abacavir's safety and efficacy in several patient populations based on age, gender, treatment experience, and concomitant antiretrovirals were also suggested. Additionally, several members stressed the need for trials to assess the durability of treatment response at 24 weeks and the importance of long-term patient follow-up.

Prepared 11/3/98 by
Rhonda W. Stover, RPh
Executive Secretary, Antiviral Drugs Advisory Committee

Final Draft

Doug Stokke
(919) 483-2311

Mary Faye Dark
(919) 483-8580

Food and Drug Administration Approves New Drug to Treat HIV/AIDS; Ziagen® is Potent New Option for Inclusion in Combination Drug Therapy

Research Triangle Park, NC (December , 1998) – A new drug with proven antiviral activity that is conveniently dosed with one pill twice daily and easily incorporated into multi-drug regimens, has been granted accelerated approval by the U.S. Food and Drug Administration for use in combination with other drugs to treat HIV and AIDS. Ziagen® (abacavir sulfate) becomes the 13th drug approved by the FDA to treat HIV and AIDS and is the first new drug in its class (nucleoside analogue reverse transcriptase inhibitor) to be approved in more than three years.

Ziagen has been studied in clinical trials that have included previously untreated patients as well as heavily pre-treated patients – including a large, well-controlled study in heavily pre-treated children. Studies show that combinations containing Ziagen have proven antiviral activity in patients who have not previously received treatment with antiretroviral drugs. Patients who have had prolonged prior exposure to zidovudine and lamivudine may have a minimal response to combinations containing Ziagen. However, studies have shown some of these patients to have experienced significant antiviral activity as a result of switching to new combinations containing Ziagen.

Today's approval of Ziagen was based on preliminary results from three phase III studies. In one 16-week study of adults with no previous treatment history, the three-drug combination of Ziagen+Epivir+Retrovir was shown to be superior to the combination of Epivir+Retrovir. A large 24-week study in children with extensive prior nucleoside treatment for HIV that compared the same two treatment arms also showed the arm containing Ziagen to have a superior antiviral effect over the double nucleoside arm. In a third study, a special preliminary analysis suggested that the combination of Ziagen+Combivir® (lamivudine/zidovudine) may, at 24 weeks of treatment, be comparable to the activity seen with the combination of Crixivan® (indinavir, protease inhibitor; Merck)+Combivir.

"Ziagen appears to be a highly potent drug that will have potential in a variety of drug combinations because of its ease of dosing and the fact that it has a low likelihood of interactions with other antiretroviral drugs," said Robert Schooley, M.D., professor of medicine at the University of Colorado Health Sciences Center.

Ziagen will be dosed as one 300-mg tablet twice daily with no food or water restrictions or requirements. It is expected that Ziagen will be available in pharmacies within _____.

The Glaxo Wellcome price to wholesalers for Ziagen will be \$9.70/day, or \$3,540 annually, though retail prices paid by patients will be different. However, the price to state ADAP programs is 15 percent less, or approximately \$3,000 annually. This price is expected to enable ADAPs to quickly add Ziagen to state formularies. The company's pricing decision related to Ziagen included and reflected input from HIV treatment advocates and ADAP administrators who requested a meeting with company representatives prior to a pricing decision in order to share information on the current HIV treatment funding environment.

"The insights provided by community representatives and ADAP administrators were one of many factors considered in the ultimate decision related to the pricing of Ziagen," said Dean Mitchell, general manager of specialty divisions at Glaxo Wellcome. "This price represents a win-win-win situation in that it should greatly enhance patient access to an important new drug, should not unduly affect ADAP budgets, and supports the company's unparalleled long-term commitment to the field of HIV and AIDS."

In clinical trials to date, Ziagen – primarily taken with Epivir and Retrovir but used in combinations with all marketed and most investigation compounds as well – has demonstrated an acceptable safety profile with the most commonly reported adverse events consisting of headache, nausea, vomiting, malaise and diarrhea. All of the nucleoside reverse transcriptase inhibitors, including Ziagen, have been associated with lactic acidosis and severe hepatomegaly with steatosis, including fatal cases.

The most serious adverse event associated with Ziagen is a hypersensitivity reaction that can be life threatening and has been fatal in some cases. The hypersensitivity reaction has been observed in approximately 3-5 percent of patients receiving Ziagen in clinical trials and is generally characterized by fever with nausea and/or malaise, and possibly an accompanying skin rash. The symptoms of this reaction get progressively worse if treatment continues. Patients experiencing these symptoms should stop taking Ziagen and contact a physician immediately. Symptoms of this

reaction usually occur within the first six weeks of treatment and generally resolve following permanent discontinuation of Ziagen. Patients experiencing this reaction must not take Ziagen again as restarting the drug after a hypersensitivity reaction has resulted in cases of life-threatening and fatal reactions. Glaxo Wellcome will be issuing to patients a Medication Guide for Ziagen to provide further information on optimizing care with this drug. This may be the first such Medication Guide issued under the FDA's new regulations announced on December 1, 1998.

"Though it only occurs in a small percentage of patients, the potential for a hypersensitivity reaction is something that patients and physicians should be aware of, particularly during the first six weeks of treatment with Ziagen," said Margaret Fischl, M.D., professor of medicine at the University of Miami.

Ziagen was discovered and is being developed by Glaxo Wellcome. The rights to related compounds and technology, including intermediates used in the manufacture of Ziagen, resulting from the research by Dr. Robert Vince, et. al, were licensed to Glaxo Wellcome by the University of Minnesota.

Glaxo Wellcome is the pharmaceutical industry leader in HIV research and therapies. In addition to Ziagen, Glaxo Wellcome also recently submitted a New Drug Application to the FDA for the investigational protease inhibitor Agenerase™ (amprenavir). Glaxo Wellcome also manufactures and markets the widely used anti-HIV medicines Epivir, Retrovir and Combivir. The company is currently conducting a unique expanded access program for Agenerase, is engaged in basic research programs designed to investigate new targets to treat HIV, and is continuing to lead the way in pioneering efforts to study the viability of increasing access to HIV therapies in the developing world.

#

For complete prescribing information for Ziagen, Epivir, Retrovir and/or Combivir, please call (919) 483-2311 or (919) 483-8580.

GlaxoWellcome

TO: Emergency Departments

ZIAGEN™ (abacavir sulfate) is a nucleoside reverse transcriptase inhibitor for the treatment of HIV-1 infection. It is given as part of combination therapy to reduce plasma HIV-1 RNA and increase CD4+ cell counts. While this medication is generally well tolerated, 3% to 5% of patients develop a hypersensitivity reaction.

You may provide care for individuals receiving ZIAGEN who present with signs and symptoms consistent with a hypersensitivity reaction. The attached information sheet should help you identify and manage these patients. Please share this information with your staff. Full Prescribing Information is enclosed for your convenience.

If you receive a phone call from a patient who exhibits the symptoms detailed in the attached information sheet, please advise them to stop taking ZIAGEN and seek medical attention immediately. Also, if you are providing care for a patient and determine that they may be experiencing this reaction, ZIAGEN must be discontinued and should never be restarted. In this instance, please contact the patient's primary physician so that alternative therapy can be provided.

Sincerely,

Name _____, M.D.

Title _____, Clinical Affairs

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

Hypersensitivity Reactions to ZIAGEN™ (abacavir sulfate)

ZIAGEN is a nucleoside reverse transcriptase inhibitor for the treatment of HIV-1 infection. Hypersensitivity reactions have been reported in 3% to 5% of patients who initiate therapy with abacavir. These reactions are potentially fatal. Once the reaction is identified, treatment with ZIAGEN must be discontinued, which should result in the resolution of symptoms. When ZIAGEN is reinitiated in patients with a prior hypersensitivity reaction, symptoms return, usually within hours, with greater severity, and with a greater likelihood of life-threatening hypotension and death. Discontinuation early in the course of a hypersensitivity reaction can prevent serious complications.

Recognition of hypersensitivity to ZIAGEN:

The reaction is characterized by the appearance of symptoms indicating multiorgan/body system involvement. Symptoms usually appear within the first 6 weeks of treatment with ZIAGEN although these reactions may occur at any time during therapy. Frequently observed signs and symptoms include:

- Fever
- Rash
- Fatigue
- Gastrointestinal symptoms (nausea, vomiting, diarrhea or abdominal pain).

Other symptoms may include malaise, lethargy, myalgia, arthralgia, edema, shortness of breath, and paresthesia. Symptoms may be mild initially, increase in severity over the course of days, appear sequentially, and may be temporally associated with administration of the dose of ZIAGEN.

Consider the diagnosis when a patient receiving ZIAGEN develops:

- Fever and any of the above symptoms, OR
- Evidence for abnormalities related to 2 or more organ systems.

Physical findings during an acute hypersensitivity reaction to ZIAGEN:

- Lymphadenopathy that is greater than usual for the patient.
- Rash: maculopapular or urticarial in appearance. Local or generalized, but most often including face and trunk.
- Mucous membrane lesions (conjunctivitis and mouth ulcerations).
- Hypotension.

Laboratory findings during an acute hypersensitivity reaction:

The findings are not specific, but may include:

- Elevation of liver function tests, creatine phosphokinase, or creatinine
- Lymphopenia
- Thrombocytopenia.

Management of hypersensitivity reactions to ZIAGEN:

- Discontinue therapy with ZIAGEN.
- Patients with rash but without other symptoms or evidence of other organ system involvement may continue ZIAGEN with the warning to discontinue ZIAGEN and seek medical attention if other symptoms develop.
- Provide fluid and vasopressor support for those patients who present with hypotension. The utility of glucocorticoids in the management of the acute reaction is not known.
- Collect all unused ZIAGEN Tablets from the patient and dispose of properly.
- Patients who have experienced a hypersensitivity reaction to ZIAGEN should not reinitiate therapy with ZIAGEN.

For additional information on ZIAGEN and hypersensitivity reactions:

Glaxo Wellcome maintains a 24-hour Medical Information phone number: 1-800-334-0089.

GlaxoWellcome

Dear Colleague:

52-56 Glaxo Wellcome Inc. is pleased to announce the availability of ZIAGEN™ (abacavir sulfate)
20-21 Tablets and Oral Solution, a powerful and unique reverse transcriptase inhibitor—the first
21-24 guanosine analogue NRTI. ZIAGEN in combination with other antiretroviral agents is
397-407 indicated for the treatment of HIV-1 infection. This indication is based on analyses of
surrogate markers in controlled studies of up to 24 weeks in duration. At present, there are
no results from controlled trials evaluating long-term suppression of HIV-RNA or disease
progression with ZIAGEN. ZIAGEN is available as 300-mg tablets and a 20 mg/mL oral
solution.

3003 Table 7 **Powerful reduction in viral load in therapy-naive patients**
p. 121 At week 16 of a double-blind, placebo-controlled study, 75% of patients receiving ZIAGEN
300 mg BID in combination with lamivudine + zidovudine had plasma HIV-1 RNA
levels ≤ 400 copies/mL* compared with 35% receiving lamivudine + zidovudine alone.
173-174 Preliminary findings from a second controlled study using ZIAGEN + Combivir®
(lamivudine 150 mg/zidovudine 300 mg) in therapy-naive adults were supportive of the
efficacy of ZIAGEN.

168-170 ZIAGEN + Combivir can achieve viral load ≤ 400 copies/mL in most therapy-naive patients
and may preserve future treatment options.

Efficacy in treatment-experienced patients demonstrated in pediatric trial
175-192 In a placebo-controlled study, ZIAGEN in combination with lamivudine + zidovudine
provided significant decrease in viral load and increase in CD4 cell count when compared to
treatment with lamivudine + zidovudine in treatment-experienced children. Supportive trials in
treatment-experienced adults have shown similar results.

222-225 In clinical trials, patients with uncontrolled viral replication following prolonged prior
zidovudine and lamivudine exposure who had HIV-1 isolates that contained multiple
mutations conferring resistance to NRTIs showed minimal response to the addition of
ZIAGEN as a single new agent.

Convenient dosing encourages adherence
389 The recommended oral dose of ZIAGEN for adults is one 300-mg tablet BID, in combination
388 with other antiretroviral agents. ZIAGEN may be taken with or without food. For children
391-393 3 months to 16 years of age, the recommended dose is 8 mg/kg BID, not to exceed 300 mg
BID. See complete Prescribing Information for dosing guidelines.

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 246 2100

Drug interactions

- 113-114 ZIAGEN is not significantly metabolized by the cytochrome P450 enzyme system.
134-135 Clinically significant P450 drug interactions are unlikely to occur between ZIAGEN and drugs metabolized through this pathway.

Safety Profile

- 3003 p. 7 In a pivotal study with therapy-naive adults, there were no significant differences in the incidence of adverse events between patients receiving ZIAGEN with lamivudine + zidovudine versus lamivudine + zidovudine. The most common adverse events in patients receiving ZIAGEN with lamivudine + zidovudine were: nausea, headache, malaise and fatigue, and nausea and vomiting. Most events were mild to moderate in intensity.
331-332

- 16-18 Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including ZIAGEN and other antiretrovirals.

- Hypersensitivity Reaction.** In clinical studies, 3% to 5% of patients receiving ZIAGEN developed a hypersensitivity reaction. This reaction is characterized by the appearance of symptoms indicating multi-organ/body system involvement. Symptoms usually appear within the first 6 weeks of therapy, although these reactions may occur at any time during therapy.
302
302-304
304-305

- 306-307 Frequently observed signs and symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain). Other signs and symptoms may include malaise, lethargy, myalgia, arthralgia, edema, shortness of breath, and paresthesia.
307-311

- 311 Physical findings may include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and skin rash. The rash usually appears maculopapular or urticarial but may be variable in appearance. Hypersensitivity reactions may occur without rash.
311-313

- Laboratory abnormalities include elevated liver function tests, increased creatine phosphokinase or creatinine, and lymphopenia. Anaphylaxis, liver failure, renal failure, hypotension, and death have occurred in association with hypersensitivity reactions.
313-314

- Symptoms worsen with continued therapy and usually resolve upon discontinuation of ZIAGEN.

- 316-318 ZIAGEN therapy should not be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death. Patients developing signs or symptoms of hypersensitivity should discontinue treatment as soon as a hypersensitivity reaction is first suspected, and should seek medical attention immediately.
318-320

A powerful NRTI offers new options for HIV therapy

- 389 Easy BID dosing and lack of known significant P450 drug interactions allow ZIAGEN to be easily incorporated into multidrug regimens. For more information about ZIAGEN, please contact your local Glaxo Wellcome HIV representative or call the Customer Response Center toll free at 1-800-825-5249.
134-135

Sincerely,

Name _____, MD

Title _____, Clinical Affairs

*Roche Amplicor HIV-1 MONITOR® Test.

Please see accompanying full Prescribing Information for ZIAGEN.

ABC041R0

Tel No:

Subject: USER FEE PAYMENT & ARREARS LIST

IMPORTANT USER FEE NOTICE:

Effective January 1, 1998, applicants must send the full application fee at the time of submission of fee liable applications and supplements. The fee for Fiscal Year 1998, as announced in the Federal Register on December 9, 1997 (62 FR 64849) are:

Application/Clinical Data Required....\$ 256,846
Supplement/Clinical Data Required.....128,423
Application/No Clinical Data Required...128,423

An application should be accepted for filing if a fee is submitted even if the amount of the fee is incorrect. The firm should be contacted and told to promptly remit the balance due (same user fee ID number). As before, applications for which NO FEE has been received by FDA within 5 days of the receipt date of the application should not be accepted for filing.

NOTE: * denotes entries since last report

APPLICATION PAYMENTS

The following application payments have been received:

Date	Firm	Userfee ID	Application #	Payment
24-JUN-98	GLAXO WELLCOME INC	3484	N020978	256,846
[REDACTED]				
05-JUN-98	GLAXO WELLCOME INC	3483	N020977	256,846
[REDACTED]				
[REDACTED]				
[REDACTED]				



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: January 15, 1997

DRUG: 1592U89

SPONSOR: Glaxo Wellcome, Inc.

PARTICIPANTS:

Representative of Glaxo:

Seth Hetherington, M.D.
Lynn Dix
Amy Cutrell
Michael Joyner
Stephen LaFon
Martha Anne Moore, R.Ph.
Mike Rogers, Ph.D.
Gill Pearce
Lynn Smiley, M.D.
William Spreen
William Symonds
Jim McDowell
Robert Watson
Joe Woolley
Anton Zeman

Representatives of DAVDP:

Rachel Behrman, M.D.
Gary Chikami, M.D.
Terrie Crescenzi, R.Ph.
Therese Cvetokovich, M.D.
Babara Davit, Ph.D.
Jim Farrelly, Ph.D.
David Feigal, M.D.
Donna Freeman, M.D.
Paul Flyer, Ph.D.
Rao Kambhapti, Ph.D.
Paul Lui, Ph.D.
John Martin, M.D.
Lalji Mishra, Ph.D.
Jeff Murray, M.D.
Owen McMaster, Ph.D.
Kim Struble, R.Ph.
Anthony Zeccola

BACKGROUND: End of Phase II meeting to discuss status of development program for the Glaxo Wellcome reverse transcriptase inhibitor 1592U89. Background information was provided in correspondence dated 12/20/96 (submission 088). Eight points of discussion were provided in the meeting agenda dated 8/97 (submission 096).

DISCUSSION: After introduction of the meeting participants, the eight points listed in the meeting agenda were discussed in detail:

1. Do the nonclinical toxicology studies and the planned time line for submission of results support the initiation of 16-week/48-week Phase III surrogate marker/durability studies?

Dr. McMaster said yes, but the sponsor will need to submit the impurity profile for the new formulation, if it is similar to the formulation used to conduct the studies that have been discussed it should be OK.

2. Does the antiviral activity observed during Phase II studies merit further study in controlled studies of longer durations of treatment in Phase III.

Dr. Behrman responded yes.

3. The clinical adverse events observed to date in approximately 215 adults and approximately 22 pediatric patients do not present a significant or unreasonable risk to preclude initiation of Phase III studies. Dr. Behrman agreed.

At this point, a discussion of the Phase III development plan took place. The major comments from FDA as a result of this discussion included the following:

- Please ensure that your program will evaluate a broad range of patients including those with CD4 counts under 50 and those with active disease, as well as a broad range of baseline viral RNA.
- Please note that, while we agree your proposed development plan follows the changing paradigm that we have discussed, we remain strongly in favor of your including a clinical endpoint study irrespective of when that study is completed in relation to regulatory milestones
- Please reconsider your plan to have replicate studies conducted in adults and children.
- Our preferred primary endpoint would be to measure patients who achieve and maintain an undetectable level of virus. We believe this endpoint can be "uncoupled" from the planned patient management that would dictate clinical intervention at the level of 5K copies.
- For your analysis of viral RNA at the 16 weeks timepoint you should choose in advance a DAVG or proportion analysis and provide support for your choice. We appreciate that there are advantages and disadvantages to both types of analyses, but believe that the protocol must define, and defend, a prespecified analysis plan.
- For the analysis of viral RNA data at 48 weeks, we believe that the preferred analysis is time to failure, with failure defined as detectable HIV RNA in plasma after being previously undetectable.
- We believe that a clinical event must be considered a treatment failure irrespective of the viral RNA level at that time. A secondary analysis of changes in viral RNA could include viral RNA measurements after the clinical event.

- Please comment on your expectations regarding compliance with 16 week blinded phases of your proposed studies.
- Please comment on why you believe the proposed management of patients in 1592U89 arms who are treatment failures will be safe and reasonable as patients will have a single protease added to a regimen that is, by your definition, failing to provide benefit.

4. Do the animal bioavailability studies and propose human bioequivalence studies comparing the succinate formulation to the hemisulfate formulation support the use of the hemisulfate formulation in future studies.

Dr. Davit indicated that the study design look reasonable. Dr. McMaster said that he still needs to review the impurity profile of the new formulation.

5. Do the proposed 16 week adult and pediatric studies support accelerated approval, and does the 48 week extension support traditional approval?

Dr. Behrman said yes but they plans as presented describe a narrow development and consideration should be given to incorporating the changes discussed above.

6. Based on division review of the draft protocols CNAB3001, CNAAB 3003 and CNAAB 3006 does the division agree in principle with the design of these studies?

Dr. Cvetkovich said that it would be useful to consider the suggestions made regarding for the 141W94 studies during the 1/14 telecon and incorporate these into the 1592U89 studies. Sponsor agreed that this is a reasonable approach.

7. Will a positive outcome CNAB 3001 (AIDS Dementia Study) support labeling for this indication?

Dr. Behrman said that if the study produces robust and significant data then it would be incorporated into the label.

8. Based upon discussions during the End of Phase 2 meeting for 141W94, it is the sponsor's understanding that clinical endpoint trials are not required for traditional approval. If in the future, sponsor wants to include data in the package insert relative to clinical endpoint data, the necessary trials will need to be agreed upon with the FDA and conducted accordingly. Does DAVDP agree this is the current situation regarding clinical endpoint trials?

Dr. Behrman indicated that this question cannot be answered until after the closed session advisory committee meeting, schedule for February 21, 1997

At the conclusion of the discussion of the agenda items, the sponsor said that they will take our suggestions into consideration during finalization of the their development plans and that they will consider these suggestions during the planning of the closed session advisory committee meeting.

Original
End of Phase II Meeting Minutes

CONCURRENCE:

HFD-530/SMO/Behrman
HFD-530/MO/Cvetkovich/1.31.97
HFD-530/ODEIVDir/Feigal
HFD-530/DivDir/Freeman
HFD-530/SBiostat/Flyer
HFD-530/Pharm/McMaster
HFD-530/CSO/Zeccola

CC:

Division File
HFD-530/SMO/Behrman
HFD-530/Micro/Battula
HFD-530/MO/Chikami
HFD-530/MO/Cvetkovich
HFD-530/BioPharm/Davit
HFD-530/SPharm/Farrelly
HFD-530/ODEIVDir/Feigal
HFD-530/DivDir/Freeman
HFD-530/SBiostat/Flyer
HFD-530/Chem/Lui
HFD-530/MO/Martin
HFD-530/Pharm/McMaster
HFD-530/CSO/Zeccola



MEMORANDUM OF MEETING

IND: _____

DATE: December 10, 1997

DRUG: 1592U89

SPONSOR: Glaxo Wellcome, Inc.

PARTICIPANTS:

Representative of Glaxo:

- Chris Beels, Ph.D.
- John Devlin
- Beverly Lewis
- John McCune, Ph.D.
- Martha Anne Moore, R.Ph.
- Chris Wallis, Ph.D.
- James Zisek

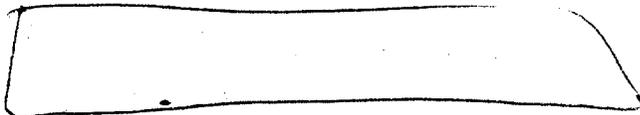
Representatives of DAVDP:

- Therese Cvetkovich, M.D.
- Janice Jenkins, Ph.D.
- Rao Kambhampti, Ph.D.
- Stephen Miller, Ph.D.
- Melissa Truffa, R.Ph.
- Anthony Zeccola

BACKGROUND: Pre-NDA Meeting to discuss CMC issues relating to the submission of 1592U89 Hemisulfate (abacavir sulfate) Tablets and Oral Solution. Background material for this meeting was submitted November 5, 1997 as serial number 233. This background package included discussion items which are indicated in bold typeface. Agency responses are indicated in normal typeface, with additional agency questions indicated in italic typeface.

DISCUSSION:

Drug Substance Change in Synthetic Route



in

ue on

We agree with these statements, given the data submitted thus far. The sponsor agreed to include batch analysis data for final drug substance lots in the NDA submission.

Regarding the final DS manufacturing method (aqueous IMS and filtration in stage 2), how much release data on full scale lots will be available in the NDA?

The sponsor indicated that 20 to 30 batches will be available at filing. They will follow up with the number which will be included in the NDA. The sponsor also agreed to provide physical and chemical comparisons in the NDA.

1592U89 Hemisulfate Starting Materials

- The compounds identified at the March 12, 1997 End-of-Phase II meeting, (1*R*-*cis*)-[4-hydroxymethyl)-2-cyclopenten-yl]carbamic acid, 1,1-dimethylethyl ester and N-(2-amino-4,6-dichloro-5-pyrimidinyl) formamide, are acceptable starting materials.

For the two proposed starting materials, please comment on their commercial availability, and on the level of their documentation in the literature.

The sponsor indicated that these materials are or will be commercially available and that they are documented in the patent literature. Dr. Miller said that the agency is comfortable with the compounds being designated as starting materials.

Proposed Alternate Manufacturers of Intermediate 26U90

- The proposal for the inclusion of _____
manufacturers of the intermediate _____
substance is acceptable in terms of the data that will be provided at the time of the pre-NDA
CMC Submissions and at the time of NDA filings. 3

As part of the justification for the alternate suppliers of 26U90, will HPLC chromatograms be available for some or all of the 9 lots for which batch analysis data will be submitted?

The sponsor agreed to submit the HPLC chromatograms with the NDA. Dr. Miller said that the alternate supplies are acceptable provided chromatograms demonstrate equivalence of the impurity profiles.

1592U89 Hemisulfate Specifications

- The proposal to test for volatiles using a Loss on Drying (LOD) method for 1592U89 Hemisulfate drug substance is acceptable.

Dr. Kambhampati asked for justification to replace the two methods currently being used _____ / the LOD method, since the LOD method is not specific to quantitate organic solvents

Dr. Miller said that if the sponsor wishes to implement this prior to NDA submission/action they should address the two questions listed below prior to implementation, since these data need to be reviewed prior to comment. The sponsor said that they will follow up on this issue and will continue using current methods until they have received Agency feedback.

The Division recommends that the volatile organic impurities be measured by a specific method at release, but that this testing need not be carried out during stability studies of post-approval batches. Loss on drying may be used to quantify moisture at release, and to monitor any uptake of water during stability studies.

In the NDA, will there be release data on volatile organic impurities for the primary NDA DS lots? On stability as well? What are typical levels of 2-propanol in the NDA registration lots?

1592U89 Hemisulfate Drug Substance

- **Because 1592U89 manufactured using Route 1 and Modified Route 1 are equivalent, the proposed stability package which includes drug substance manufactured by both Route 1 and Modified Route 1 is suitable for use as primary stability data.**
- **The proposed stability plan for drug substance is acceptable for NDA filings in terms of number of batches, synthetic route, available data at time of filings, and storage conditions.**

On the basis of the submitted information (primarily data on related substances), the Division concurs with the proposed stability plan for drug substance.

Please submit in the NDA data from all appropriate chemical and physical tests that support the equivalence of drug substance produced by Route 1 and the final commercial process.

1592U89 Hemisulfate Tablets, 300 mg 1592U89 per tablet

- **The proposed stability plan for 1592U89 Hemisulfate Tablets is acceptable for NDA filings in terms of number of batches, drug substance synthetic route, batch size, packaging matrix, available data at time of filings, and stability storage conditions.**

In the proposed stability plan, the PVC blister presentation is represented by three commercial scale lots containing Route 1 drug substance, and one pilot scale lot containing Modified Route 1 drug substance (50 kg batch). This data is intended to support approval and to fulfill the commitment for the first three commercial lots. We would like to discuss the possibility of inclusion of tablets manufactured from Modified Route 1 drug substance at commercial scale in the stability program.

The sponsor proposed replacing the 50 kg batch in blisters with blister-packed samples of the full-scale batch that is being studied in the 80-cc bottles. After internal discussions, the agency proposes that the full-scale lot be added, and the pilot lot be retained in the NDA stability programs. Is this acceptable to the sponsor?

Regarding the post approval stability studies for the drug products, will one production batch of each marketed configuration be studied under the yearly commitment?

The Sponsor proposed several variations on how to provide stability coverage for each of the packaging configurations. This issue will require additional discussion between the agency and the sponsor.

1592U89 Hemisulfate Tablets Dissolution Method and Specifications

- The dissolution method and specifications proposed at the March 12, 1997 End-of-Phase II meeting and subsequently submitted (Amendment Serial #187, dated August 4, 1997) are appropriate for 1592U89 Hemisulfate Tablets. The proposed specifications and dissolution conditions are:

Specification: 

Dissolution Conditions:

Apparatus:

Medium:

Stirring Speed:

Temperature:



We would like to discuss the time point (30-min versus 15-min) for the dissolution specification (Mr. Zeccola conveyed this question to the sponsor verbally on December 5, 1997).

Both the Sponsor and the Agency agreed that the data submitted thus far support a minutes. Dr. Jenkins said that an agreement on the specification is not necessary at this time, rather the specification will be determined at the time of the NDA review. The Sponsor should submit their justification and complete profiles in the NDA. A teleconference can be scheduled, if desired, to address the specific details for the profiles that will be included.

1592U89 Hemisulfate Oral Solution, 20 mg 1592U89 per mL

- The proposed stability plan for 1592U89 Oral Solution is acceptable for NDA filings in terms of number of batches, drug substance synthetic route, drug product formulation, available data at time of filings, and storage conditions.

Regarding the new "Formulation B", have any low pH stress studies been carried out on the oral formulation (either A or B)? With the drop in pH from 6.0 to 4.0, and the increase in citrate concentration from 0.02M to 0.07M, are any additional degradants possibly formed?

Considering that 12-month stability data on the Formulation B will not be available during the review period, we would recommend that microbial limit testing be added to the stability protocol at either the 6 or 9 month time point (for the Formulation B lots).

The sponsor agreed to provide either 6 or 9 month microbial limit testing in the NDA submission.

Please outline the extent of preservative effectiveness testing of 1592U89 hemisulfate oral solution. Were the three Formulation B registration batches tested at release?

Dr. Miller stated that the current position of the Division can be summarized as follows:

For the purposes of approval of drug applications, stability data on pilot or registration batches should include results from microbial challenge studies performed on the drug product at appropriate intervals. Generally, microbial challenge studies conducted initially, annually and at the expiration date are adequate. Chemical assays of preservative content(s) should be performed at all test points.

For post-approval testing, the first three production batches should be tested with a microbiological challenge assay at the start and end of the stability period, and at one point in the middle of the stability period if the test period equals or exceeds 2 years. The first three production batches should be assayed for the chemical content of the preservatives at all appropriate test points. Upon demonstration of chemical content commensurate with microbial effectiveness in the first three production batches, chemical assays may be adequate to demonstrate the maintenance of the specified concentrations of preservatives for subsequent batches placed into stability testing. All testing should be performed according to the Approved Stability Protocol. Changes to the Approved Stability Protocol should be submitted as a supplement to the application.

Dr. Miller also said that we would recommend that preservative effectiveness testing be carried out as follows for the three B-formulation stability batches: at release, at either the 6-month or 9-month time point, and annually out to the longest anticipated expiration dating period.

The sponsor will respond to the comments on preservative effectiveness testing at a later point in time.

Batch Records to be Provided in the Field Copy

- The proposal to provide only the batch records for 1592U89 Hemisulfate Tablets and 1592U89 Hemisulfate Oral Solution used in clinical study CNA1009 is acceptable.

Submission of two executed batch records (one tablet and one oral solution) to our copy of the NDA is acceptable to the review division. Please contact your District Office to discuss the number of batch records that they would like to receive in the field copy.

Questions and Additional Discussion

- Regarding extension of expiry date based on real-time data, this is acceptable for the tablet formulation. For the oral solution, this will be evaluated by comparing the stability data on the A and B formulations
- It was agreed that for both the tablet and oral solution formulations, the first three production batches, post-approval, will not be placed on stability.
- It may be acceptable to replace the current 50 kg blister pack lot with a 300 kg blister pack lot as a stability batch. This issue will require further internal discussion within the agency. After internal discussion, the agency proposed addition of the 300 kg lot in blisters, with the 50 kg lot being retained in the stability program.

- Preservative effectiveness testing will be discussed internally by the sponsor. A proposal will then be made to the agency.

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Truffa
Public Health Service 530

Food and Drug Administration
Rockville MD 20857

Glaxo Wellcome Inc.
Attention: Martha Anne Moore, R.Ph.
Five Moore Drive
Research Triangle Park, NC 27709

MAR 11 1998

Dear Ms. Moore:

Please refer to your Investigational New Drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for 1592U89 (abacavir sulfate) Tablets and Oral Solution.

We also refer to your meeting request and background package submitted on January 15, 1998, (SN 303), to your agenda and list of attendees dated February 5, 1998, (SN 323), to the February 19, 1998, submission (SN 339) that included a copy of the overheads used during this meeting, to our February 10, 1998, telephone facsimile that outlined our points of discussion for the meeting, and to the February 11, 1998, meeting between representatives of your company and members of this Division.

In accordance with the Manual of Policies and Procedures (MAPP) 4512.1, the attachment addresses the discussion items outlined in your and our meeting agendas. Should you have any questions, please contact Melissa M. Truffa, R.Ph., Regulatory Health Manager, at (301) 827-2335.

Sincerely yours,

/s/

Anthony W. DeCicco, R.Ph.
Supervisory Consumer Safety Officer
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Attachment



Record of FDA/Industry Meeting

Meeting Date: February 11, 1998 **Time:** 1300

IND Number:

Drug: Ziagen™ 1592U89 (abacavir) sulfate Tablets and Oral Solution.

Type of Meeting: Pre-NDA meeting

Sponsor: Glaxo Wellcome Inc.

Meeting Chair: Therese Cvetkovich, M.D. **Sponsor Chair:** David Cocchetto, Ph.D.

Regulatory Management Officer: Melissa M. Truffa, R.Ph.

FDA Attendees:

- Heidi Jolson, M.D., M.P.H., Division Director, DAVDP
- Debra Birnkrant, M.D., Acting Deputy Director, Clinical, DAVDP
- Walla Dempsey, Ph.D., Acting Deputy Director, Pre-Clinical, DAVDP
- Rachel Behrman, M.D., M.P.H., Medical Team Leader, DAVDP
- Therese Cvetkovich, M.D., Medical Officer, DAVDP
- Michael Elashoff, Ph.D., Statistical Reviewer, Biometrics
- Paul Flyer, Ph.D., Statistical Team Leader, Biometrics
- Barbara Davit, Ph.D., Reviewing Clin. Pharm. & Biopharmaceutics Officer
- Janice Jenkins, Ph.D., Clin. Pharm. & Biopharmaceutics Team Leader
- Rao Kambhampati, Ph.D., Chemistry Reviewer, DAVDP
- Owen McMaster, Ph.D., Pharmacology/Toxicology Reviewer, DAVDP
- James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader, DAVDP
- Lalji Mishra, Ph.D., Microbiology Reviewer, DAVDP
- Narayana Battula, Ph.D., Microbiology Reviewer, DAVDP
- James Ramsey, Ph.D., Microbiology Team Leader, DAVDP
- Harry W. Haverkos, M.D., Medical Officer, DAVDP
- Stanka Kukich, M.D., Medical Officer, DAVDP
- Barbara Styr, M.D., M.P.H., Medical Officer, DAVDP
- John Martin, M.D., Medical Officer, DAVDP
- Steve Gitterman, M.D., Medical Team Leader, DAVDP
- Jeff Murray, M.D., M.P.H., Medical Officer, DAVDP
- Teresa Wu, M.D., Medical Officer, DAVDP
- Sylvia Lynche, Pharm.D., Regulatory Health Officer, DAVDP
- Melissa Truffa, R.Ph., Regulatory Health Manager, DAVDP

External Constituents:

Seth Hetherington, M.D., Senior Clinical Research Physician
Stephen LaFon, M.S., Clinical Program Head
Lynn Smiley, M.D., Vice President Antivirals
Bill Spreen, Pharm D., Clinical Program Head
David Cocchetto, Ph.D., Regulatory Affairs
Anton Zeman, B.S., Toxicology
Amy Cutrell, M.S., Statistics
Laurene Wang, Ph.D., Clinical Pharmacology/Pharmacokinetics
John McCune, Ph.D., Senior Group Leader/CMC
Randall Lanier, Ph.D., Virology

- Objectives:**
1. Discussion of clinical development plan for abacavir.
 2. Discussion of GW's proposals for the content of their NDA package.

Background:

On January 15, 1998, GlaxoWellcome (GW) requested a Pre-NDA meeting with Division of Antiviral Drug Products (DAVDP) for abacavir (1592U89) sulfate tablets and oral solution. Background material was submitted with the January 15, 1998, meeting request and a meeting was scheduled and confirmed for February 11, 1998. In addition, GW submitted an agenda and a list of participants for the meeting on February 5, 1998. Based on the background package, FDA developed additional points of discussion which were communicated to GW in a February 10, 1998, telephone facsimile.

I. FDA COMMENTS

(GW's responses are in bold type after each FDA comment)

A. Clinical

1. Please clarify whether GW intends to pre-submit to the IND or the NDA.

The CMC Technical Section (Item 4) and Non-clinical Pharmacology and Toxicology Technical Section (Item 5) will be official pre-submissions to the NDA.

The Clinical Technical Section (Item 8), Human Pharmacokinetics and Bioavailability Technical Section (Item 6) and final reports will be pre-submissions and later referenced in the NDA.

2. Please be aware that results from the AIDS dementia trial may require presentation to the Advisory Committee.

GW acknowledged FDA concerns.

3. In order to provide adequate review time, submission of the safety update should take place 60 days after the NDA submission, rather than 120 days.

GW agreed to this proposal and intends to provide Safety Update reports during the first week of August 1998.

4. Prior to the NDA submission, please provide a listing of case report forms (CRFs) for all patients who discontinue due to an adverse event. After review of this submission, we will provide further advice regarding FDA preference for the submission of CRFs of drop-out's. FDA agrees with GW's proposal to submit CRFs for deaths as described on page 13.

GW intends to submit a listing of CRFs as requested for review in April 1998.

B. Pharmacology/Toxicology

Please insert a cover page with each Pharmacology/Toxicology study which includes the following data:

1. Study name
2. Study number for both Glaxo Wellcome's study number and the contract organization's study number.
3. Report number for both Glaxo Wellcome's report number and the contract organization's report number.
4. Related studies (such as pharmacokinetic arm, if reported separately)
5. Dates (start and end of dosing, observation, necropsy)
6. Name and address of contract organization conducting study
7. Lot, batch and reference numbers of drug and vehicle(s) used in the study
8. GLP status
9. Table of significant findings including degree of change from control (%) (see Table).

Table Toxicological changes associated with oral XXXX treatment for 3 months in rats.

	30 mg/kg	100 mg/kg	300 mg/kg	1000 mg/kg
liver necrosis (single cell)		1/10	3/10	10/10
SGOT	20	150	210	400
SGPT	5	50	350	470

10. Name of individual preparing final report submitted to the agency

GW agreed to submit summaries that addressed items 1-8 and item 10 under Pharmacology/Toxicology section.

GW agreed to submit a proposal to address item 9.

C. Chemistry

1. Please include drug substance stability data (see page 46).
2. Please include in the pre-NDA submission the approximate dates of readiness for the inspection of the following facilities: _____
3. Please clarify whether the other manufacturing, packaging, and testing facilities that were listed in the recent IND amendments will be used for commercial batches. For example, Research Triangle Park, _____ Early pre-submission of this information to the NDA will allow more lead-time for any pre-approval inspections which need to be scheduled.

These issues will be addressed in the CMC pre-submissions.

D. Microbiology

Please provide a separate Microbiology Technical Section that includes the following:

1. Virology Studies
2. Viral Resistance Studies from Clinical Trials
3. Biochemical Studies

GW agreed to submit to the NDA a separate Microbiology Technical Section (Item 7) that includes virology studies, biochemical studies and the viral resistance studies from the clinical trials.

E. Biopharmaceutics

Please forward a copy of each of the following reports to Dr. Davit in addition to the Human Pharmacokinetics and Bioavailability section of this NDA:

CMC section: Specifications and analytical methods for drug product, to include dissolution data and data supporting the proposed dissolution specifications

Pharmacology/Toxicology Section:

TEIN/94/0009	RD1997/03644/00
TEIN/94/0010	RD1997/04351/00
TEIN/94/0011	RD1997/04317/00
TESF/93/0002	
TEZA/89/0045	
TBZZ/93/0004	
TBZZ/93/0010	

For the respective human pharmacokinetic and bioavailability studies, please include ASCII files of pharmacokinetic data at the time of pre-submission. Specific data sets requested are: individual demographic data and individual pharmacokinetic parameters.

Please indicate if intestinal permeability of abacavir has been studied in vitro.

GW will evaluate these requests more completely but did not anticipate there would be any difficulty with submitting the requested data.

F. Statistical and Clinical

1. Please clarify whether data from the ultra sensitive Amplicor™ assay will be submitted.

Ultra sensitive assay results will be utilized as a supportive analysis.

GW is currently conducting discussions with the assay sponsor concerning the availability of validation data and agreed to provide any available information to FDA.

2. Please provide preliminary data from all Phase III studies.

GW intends to submit a timeline to address the availability 16-week viral load and CD4 analyses from studies CNAB3002 and CNA3005.

In addition, GW agreed to provide 24 week viral load and CD4 cell count from the principal controlled trials (CNA3003 and CNA3006) in a update to the NDA with a proposed submission date of August 1998.

II. Additional Discussions

1. GW will provide additional copies of AIDS dementia study (CNA3001) for review by the Division of Neuropharmacologic Drug Products and additional desk copies of ISS, ISE and the Summary Volume for use by a secondary medical reviewer.

2. GW agreed to submit FDA compatible electronic datasets that allow for the review and transfer of data from human pharmacokinetic studies prior to filing the NDA. In addition, GW agreed to work with the statisticians to allow for the transfer of compatible statistical data and programs prior to the filing of the NDA.
3. CRF's will be provided as paper copies.
4. GW and FDA agreed to follow-up discussions on viral resistance issues.
5. FDA indicated that the Labeling and Nomenclature Committee had tentatively approved the trademark Ziagen™ for abacavir sulfate tablets and oral solution. However, FDA cautioned GW that the acceptance of the trademark would not be official until such time as the NDA has been reviewed and a regulatory decision is taken.

Signature, minutes preparer, _____
Concurrence Chair _____

/S/

/S/

Attachments: Attendee List
Copy of Glaxo Wellcome's overheads

APPEARS THIS WAY
ON ORIGINAL

