



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: April 19, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: John Martin, M.D., Medical Officer, DAVDP eso 4/19/00
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP

NDA: 21-205 Trizivir (abacavir sulfate/lamivudine/ zidovudine) Tablets

Subject: Trizivir Labeling.

Comments:

Please model the Trizivir warning card after the currently approved Ziagen warning card.

1. The Trizivir warning card should be a stand-alone item, not a package tear-off.
2. Please use black print on a white background, omitting all color.
3. Please omit all decorative content and logos.
4. The first sentence on the front of the card should begin: _____

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

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: April 20, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: Prabhu Rajagopalan, Ph.D., Pharmacokinetics Reviewer
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader

NDA: 21-205 Trizivir (abacavir sulfate/lamivudine/ zidovudine) Tablets

Subject: Pharmacokinetics

Comments:

1. Please provide a rationale for the use of \checkmark RPM as the --- speed in the dissolution method.
2. Please provide dissolution data at --- RPM as the --- speed using 0.1 N HCl as the dissolution medium.

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

cc:

Original NDA 21-205
Division File
HFD-530/CSO/Truffa

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: May 3, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: Rao Kambhampati, Ph.D., Chemistry Reviewer, DAVDP eso 5/3/00
Stephen Miller, Ph.D., Chemistry Team Leader, DAVDP eso 5/3/00

NDA: 21-205 Trizivir (abacavir sulfate/lamivudine/ zidovudine) Tablets

Please address the following CMC comments that are related to the NDA #21-205 for Trizivir (abacavir sulfate/lamivudine/zidovudine) tablets:

- 1. Based on the batch analyses and stability data, the following impurity limits (see table below) are proposed for the batch release and stability specifications for tablets:

Drug-related Impurities by _____	Proposed Limits
_____ Content	Not more than _____ area
Any Unspecified Impurity	Not more than _____ area
Total Abacavir-related Impurities	Not more than _____ area
Total Lamivudine-related Impurities	Not more than _____ area
Total Zidovudine-related Impurities	Not more than _____ area

- 2. Please change _____ to "300 mg abacavir as abacavir sulfate" in the Sample Printmat and Printmat x 60 for blisters.
- 3. Please change _____ in the *How should I take Trizivir?* section of the Medication Guide.

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

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Date 05/25/00

Job No. 2GLXTZVRM0120

Title Rep Follow-up Letter #1 (MD Seen)

Client GLAXO WELLCOME

Writer

Product TRIZIVIR

[DATE]

[NAME]

[ADDRESS]

[ADDRESS]

Dear Dr. [NAME]:

Thank you for recently taking the time to speak with me regarding new TRIZIVIR™ (abacavir sulfate 300 mg/lamivudine 150 mg/zidovudine 300 mg) Tablets, the first 3-in-1 antiretroviral combination product. As we discussed, TRIZIVIR offers your patients efficacy and simplicity, while preserving future treatment options. The following information highlights the key features and benefits of TRIZIVIR we reviewed together:

Each TRIZIVIR Tablet is bioequivalent to one ZIAGEN® Tablet (abacavir sulfate 300 mg) + one EPIVIR® Tablet (lamivudine 150 mg) also known as 3TC® + one RETROVIR® Tablet (zidovudine 300 mg) taken simultaneously.*

Three antiretrovirals in one tablet BID. The highly simplified dosing of TRIZIVIR—one tablet BID, with or without food—helps simplify combination therapy for your patients.

TRIZIVIR PI
Page 1, 32-34

TRIZIVIR PI
Page 14, 420-424

TRIZIVIR PI
Page 2, 52-58

TRIZIVIR PI
Page 9, 287-288
Page 2, 59

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**

Date 05/25/00

Job No. 2GLXTZVRM0120

Title Rep Follow-up Letter #1 (MD Seen)

Client GLAXO WELLCOME

Writer

Product TRIZIVIR

TRIZIVIR PI
Page 3, 77-78

TRIZIVIR PI
Pages 3-4, 83-101

TRIZIVIR PI
Page 14, 420-424

TRIZIVIR PI
Page 16, 498-500

TRIZIVIR PI
Pages 3-4, 83-101

TRIZIVIR PI
Page 16-17, 508-516

TRIZIVIR PI
Page 6, 160-164

TRIZIVIR may be used alone or in combination with other antiretrovirals. The components of TRIZIVIR have been studied as a complete regimen in therapy-naïve patients. Interim data are supportive of this triple combination.†

When used alone, TRIZIVIR can preserve PIs and NNRTIs for future use.

TRIZIVIR is also easily incorporated into a variety of multidrug regimens. TRIZIVIR is not significantly metabolized through the cytochrome P450 enzyme system, and thus clinically significant drug interactions are unlikely to occur between TRIZIVIR and drugs metabolized through this system.

Potential candidates for therapy with TRIZIVIR include therapy-naïve patients, patients on other regimens who could benefit from the dosing convenience of TRIZIVIR, patients receiving methadone maintenance therapy,‡ and therapy-experienced patients who require a switch in or an intensification of their current regimens due to inadequate viral load response.

Remember that patients with prolonged prior NRTI exposure and HIV-1 isolates that contain multiple mutations conferring resistance to NRTIs, may have limited response to combinations of NRTIs, including the components of TRIZIVIR.

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

Date 05/25/00

Job No. 2GLXTZVRM0120

Title Rep Follow-up Letter #1 (MD Seen)

Client GLAXO WELLCOME

Writer

Product TRIZIVIR

TRIZIVIR PI
Page 1, 25-28

TRIZIVIR PI
Page 2, 70-73

TRIZIVIR PI
Page 2, 66-69

TRIZIVIR PI
Page 1, 28-30

TRIZIVIR PI
Page 5, 122-123

TRIZIVIR PI
Page 4, 113-114

TRIZIVIR PI
Page 4-5, 114-119

TRIZIVIR PI
Page 5, 125-128

Indication: TRIZIVIR is indicated for the treatment of HIV-1 infection, based on analyses of surrogate markers in controlled studies of up to 24 weeks in duration. TRIZIVIR is intended only for patients whose regimen would otherwise include its three components. Because it is a fixed-dose tablet, TRIZIVIR should not be prescribed for adolescents who weigh less than 40 kg, or other patients requiring dosage adjustment. At present, there are no results from studies showing long-term effects of TRIZIVIR on HIV RNA or disease progression.

Important safety information. In ongoing clinical studies, approximately 5% of patients receiving abacavir (a component of ZIAGEN and TRIZIVIR) have developed a hypersensitivity reaction. Some of these reactions have been fatal. Patients developing signs or symptoms of hypersensitivity (which include fever; skin rash; fatigue; gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain; and respiratory symptoms such as pharyngitis, dyspnea, or cough) should discontinue TRIZIVIR as soon as a hypersensitivity reaction is suspected and should seek medical evaluation immediately. Some patients who experienced a hypersensitivity reaction were initially thought to have acute onset or worsening respiratory disease. The diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of acute onset respiratory diseases, even if alternative

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

Date 05/25/00

Job No. 2GLXTZVRM0120

Title Rep Follow-up Letter #1 (MD Seen)

Client GLAXO WELLCOME

Writer

Product TRIZIVIR

diagnoses (pneumonia, bronchitis, pharyngitis, or flu-like illness) are possible.

Neither TRIZIVIR nor ZIAGEN should be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death. Patients should receive a Warning Card explaining this reaction when they get their prescription filled. For details about hypersensitivity reactions, see WARNINGS, PRECAUTIONS: Information for Patients, and ADVERSE REACTIONS in the Prescribing Information.

When therapy with TRIZIVIR or ZIAGEN has been discontinued and reinitiation of therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have a hypersensitivity reaction.

Zidovudine, one of the three active ingredients in TRIZIVIR, has been associated with hematologic toxicity, including neutropenia and severe anemia, especially in advanced HIV disease, and with symptomatic myopathy after prolonged use.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues

APPEARS THIS WAY ON ORIGINAL

TRIZIVIR PI
Page 5, 119-121

TRIZIVIR PI
Page 6-7, 188-190

TRIZIVIR PI
Page 5, 128-131

TRIZIVIR PI
Page 1, 17-20

TRIZIVIR PI
Page 1, 21-25

BEST POSSIBLE COPY

Date 05/25/00

Job No. 2GLXTZVRM0120

Title Rep Follow-up Letter #1 (MD Seen)

Client GLAXO WELLCOME

Writer

Product TRIZIVIR

alone or in combination, including abacavir, lamivudine, zidovudine, and other antiretrovirals.

The safety profile of TRIZIVIR should be the same as that of ZIAGEN + EPIVIR + RETROVIR. Most side effects associated with ZIAGEN + EPIVIR + RETROVIR taken together were mild to moderate. The most common adverse events $\geq 5\%$ were nausea, nausea/vomiting, diarrhea, loss of appetite/anorexia, and insomnia and other sleep disorders.

Thank you for considering TRIZIVIR, a valuable new addition to simplified antiretroviral combination regimens. With the availability of TRIZIVIR, Glaxo Wellcome is furthering our commitment to develop simplified therapies that expand combination treatment options for the management of HIV.

As always, please let me know if I can be of assistance to you. I hope you find the enclosed full Prescribing Information for TRIZIVIR useful, and I look forward to learning about your experiences with TRIZIVIR.

Sincerely,

[REP NAME]

[TITLE]

[PHONE]

Data on file, Glaxo Wellcome Inc.
CNA3003 Study Report
Synopsis, pages 7, 8

TRIZIVIR PI
Page 9, Table 1

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

Date 05/25/00

Job No. 2GLXTZVRM0120

Title Rep Follow-up Letter #1 (MD Seen)

Client GLAXO WELLCOME

Writer

Product TRIZIVIR

[FOOTNOTES]

Data on file,
Glaxo Wellcome Inc.
CNA3003 Study Report
Table 6
HIV RNA ≤ 400 c/mL
(+ Cochran-Haenszel-
Mantel Stats for P value)

HIV RNA < 50 c/mL
Table 13
(+ explanatory note)

TRIZIVIR PI
Page 16-17, 508-516

* ZIAGEN® Tablets, EPIVIR® Tablets, RETROVIR® Tablets, COMBIVIR® (lamivudine/zidovudine) Tablets, and all of their formulations are still available.

† In a clinical trial that led to the accelerated approval of ZIAGEN in 1998, interim 16-week data showed that 71% (62/87) of therapy-naïve patients receiving ZIAGEN + EPIVIR + RETROVIR had plasma HIV-1 RNA levels ≤ 400 copies/mL (HIV-1 MONITOR® Test) compared with 34% (29/86) receiving EPIVIR + RETROVIR alone ($P=0.001$). 54% (47/87) of these patients had levels < 50 copies/mL (HIV-1 MONITOR® UltraSensitive Method) with ZIAGEN + EPIVIR + RETROVIR compared with 15% (13/86) of those taking EPIVIR + RETROVIR alone.¹

‡ A small number of patients may require an increase in their methadone dose due to a modest interaction with abacavir.

Reference: 1. Data on file, Glaxo Wellcome Inc.

(TRZ021R0)

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: May 22, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: Stephen Miller, Ph.D., Chemistry Team Leader, DAVDP eso 5/22/00

NDA: 21-205 Trizivir (abacavir sulfate/lamivudine/ zidovudine) Tablets

SUBJECT: Licensor's name on the Trizivir container label.

We have considered the issue of inclusion of a licensor's name (i.e., BioChem Pharma, Inc.) on the container label. We find 21 CFR 201.1(h)(1) quite clear on this point. We have also reviewed the preamble to this regulation. In the preamble a proposal very similar to yours, i.e., to allow the naming of "developers" on a product's label, was specifically addressed and rejected (see 45 FR 25760 at 25769; April 15, 1980). The Agency, therefore, would prefer that the names listed on your container label be limited to those permitted under 21 CFR 201.1, which are the manufacturer, packer, or distributor. We understand however, that in the past the Agency has approved container labels that happen to include information of the kind you propose. For this reason, and because the Agency may wish to consider more fully its position with respect to label statements of the kind you propose, we will not withhold approval of NDA 21-205 over this statement so long as it does not adversely affect the prominence and conspicuousness that must be accorded words and statements that are required to appear on the label.

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

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

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

DATE: JUN - 2 2000

FROM: Mary E. Willy, Ph.D., M.P.H., Epidemiologist.
Division of Drug Risk Evaluation II, HFD-440

THROUGH: Evelyn Rodriguez, M.D., Director *EW, MPH 06/02/00*
Division of Drug Risk Evaluation I, HFD-430

TO: Heidi Jolson, M.D., Director
Division of Antiviral Drug Products, HFD-530

SUBJECT: Drug: Trizivir
Topic: Hypersensitivity reactions
PID#: D000463

EXECUTIVE SUMMARY

This memorandum is in response to a consult request from Therese Cvetkovich, HFD-530, to comment on a GlaxoWellcome (GW) proposal for postmarketing monitoring of Trizivir-related hypersensitivity reactions (HSR). An early June 2000 target date for action has been set for this product (NDA 21-205) and the Division of Anti-viral Drug Products has concerns about the possibility of an increased incidence of HSR with this combination product. These concerns are based on the expected utilization of this drug by marginalized individuals who, for whatever reason, are less likely to identify and/or respond to HSR symptoms. The Division also anticipates the prescribers of this drug will be less experienced with HIV treatment and more likely to miss HSR symptoms or mis-prescribe (unaware that Trizivir contains abacavir). The sponsor acknowledges the risk for HSR and has proposed a number of different activities to monitor the potential problem. The list of activities does not include a mechanism to study marginalized patients in a prospective fashion. I would suggest that the company include collaboration with a center that treats/studies marginalized patients (prisons, IV drug users, Veterans). Additionally, the data collected from such studies must be consistent with the ongoing prospective study of Ziagen (abacavir) HSR so that comparisons can be made between populations. A retrospective study of health insurance claims databases might also be implemented. Such a study is likely to provide limited insight into drug-related HSR, though, since many of these events, particularly mild ones, will not be identified with an ICD code. Risk management strategies should also be considered along with the development of epidemiologic studies. The addition of the 1-800 number to the box warning and a study of the type of prescribers should be considered.

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

BACKGROUND

Trizivir (NDA 21-205) is a fixed dose combination tablet that contains three synthetic nucleoside analogues: abacavir sulfate (ZIAGEN), lamivudine (EPIVIR, 3TC), and zidovudine (RETROVIR, AZT). Concerns about Trizivir-related HSR result from Ziagen (abacavir) clinical trial data that report a 5% HSR rate among adult and pediatric patients receiving Ziagen. Ziagen (abacavir)-related HSR generally appear within 6 weeks of treatment and are characterized by the appearance of symptoms that suggest multi-organ involvement (fever, skin rash; fatigue; nausea, vomiting, diarrhea; malaise, myolysis, arthralgia, edema, pharyngitis, cough, dyspnea, headache, and paresthesia). Laboratory abnormalities may include elevated liver function tests, increased creatine phosphokinase or creatinine, and lymphopenia. A recent analysis of spontaneous reports of Ziagen (abacavir)-related HSR suggests that delays or breaks in drug administration may increase patient risk for HSR. —

The Division is concerned that Trizivir may be differentially used by populations (poorly compliant, prison, or other marginalized) that may have a higher risk for Trizivir-related HSR (because of delays or breaks in drug administration) or Trizivir-HSR-related mortality (because of decreased awareness of, or response to HSR symptoms). The Division also proposes that the drug may be differentially prescribed by physicians who are less experienced in HIV treatment and perhaps less likely to be monitoring for, and educating the patient about, HSR.

In a February 29, 2000 letter from GW the following HSR surveillance activities were listed: 1) ongoing safety monitoring within clinical trials, 2) analysis of HSR cases within each final study report for completed GW sponsored clinical studies, 3) quarterly reports of HSR, 4) use of 1-800 number in package insert for Ziagen and Trizivir, 5) Ziagen phase 4 commitments related to HSR, and 6) a prospective, population-based epidemiologic study to evaluate abacavir hypersensitivity reactions.

The final item of this list, a prospective, observational study of Ziagen (abacavir) HSR, was described in a January 29, 1999 letter and updated in a May 4, 1999 letter. GW proposed to collect patient data from 5000 HIV-1 infected adults enrolled in the Collaboration in HIV Outcomes Research/U.S. — study. — enrolls patients treated in four centers

REVIEW

GW has proposed a number of different surveillance activities to identify Trizivir-related HSR. Although all of these activities have the potential to identify HSR, none of the populations proposed are likely to be representative of the postmarketing user, if the user is more likely to be, as the Division describes, marginalized and/or the prescriber is less experienced as expected. Clinical trials (options 1 and 2) generally do not enroll marginalized patients, and the reports appearing in quarterly reports and 800 numbers (options 3 and 4) require motivated, informed patients who understand and value the importance of communicating adverse health outcomes.

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**

The challenge is trying to obtain good epidemiologic data from a population of marginalized HIV-1 infected patients and from a population of less experienced prescribers. There are several possible sources of data that GW should consider. A number of databases of marginalized HIV-1 infected patients, for example ALIVE (AIDS link to the Intravenous Experience) and the Veterans Administration, have relatively large patient populations and established research records.

It would be important to make sure Trizivir is listed on the formulary of any center that is included in the study. It would also be important to use methodology consistent with the Ziagen (abacavir) prospective study so that comparisons can be made between Ziagen (abacavir) and Trizivir HSR cases.

A retrospective study comparing Ziagen (abacavir) and Trizivir-HSR rates can be done using health insurance claims data that have these drugs on formulary. Large databases of outpatient prescription and outcome information exist that include marginalized patients and a variety of prescribers (Medicaid, for example). This type of study would be very limited, though, since it is likely that many mild HSR events will not be captured in the claims data. Medical record reviews, that might be more informative, would require the utilization of a very long list of possible ICD codes and involve the abstraction of a large number of records of potential cases for every actual identified case.

In addition to the epidemiologic effort, several risk management strategies should be considered. The 1-800 number should be moved to a more prominent position in the labeling (in the box warning). The Division might request periodic descriptive reports from the sponsor that describe the types of prescribers for Ziagen (abacavir) and Trizivir. A specific educational strategy should be implemented by the sponsor, if these descriptive reports identify new prescribers are using Trizivir (not infectious disease specialists). The sponsor should also describe their plans for measuring the impact of that educational program.

CONCLUSION

Concerns exist about an increased incidence of Trizivir-related HSR with an associated risk for mortality. These concerns are based on the expected utilization of this drug by marginalized individuals who, for whatever reason, are less likely to identify and/or respond to HSR symptoms. The Division also anticipates the prescribers of this drug will be less experienced with HIV treatment and more likely to miss HSR symptoms or mis-prescribe (unaware that Trizivir contains abacavir). The sponsor acknowledges the risk for HSR and has proposed a number of different activities to monitor the potential problem. The list of activities does not include a mechanism to study marginalized patients in a prospective fashion. I would suggest that the company include collaboration with a center that treats/studies marginalized patients (prisons, IV drug users, veterans, medicaid). Additionally, the data collected from such studies must be consistent with the ongoing prospective study of Ziagen (abacavir) HSR so that comparisons can be made between populations. A retrospective study of health insurance claims databases might also be implemented. Such a study is likely to provide limited insight into drug-related HSR, though, since many of these events, particularly mild ones, will not be identified

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

with an ICD code. Risk management strategies should also be considered along with the development of epidemiologic studies. The addition of the 1-800 number in the box warning and a study of the type of prescribers should also be considered.

/S/

Mary E. Wilby, Ph.D. M.P.H.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Copies:

NDA 21-205

Division File

HFD-400 Honig

HFD-440 Rodriguez/Willy/Chron file

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: June 5, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: John Martin, M.D., Medical Officer, DAVDP eso 5/5/00
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP eso 5/5/00

NDA: 21-205 Trizivir (abacavir sulfate/lamivudine/ zidovudine) Tablets

Comments:

We have previously communicated to you our concern that TRIZIVIR therapy may have associated with its use a higher rate of hypersensitivity reactions and/or death than therapy with the already-marketed product, ZIAGEN. For this reason:

1. We anticipate that an Approvable action is to be taken on NDA 21-205.
2. The key provision of this action will be to require you to conduct a prospective epidemiological study to compare rates of hypersensitivity and death in ZIAGEN and TRIZIVIR recipients.
3. Prior to approval of TRIZIVIR, we will require you to: (i) submit a protocol for such a study for review, (ii) obtain Agency agreement with regard to study design, (iii) provide evidence that study centers and investigators have been engaged to conduct the study, (iv) provide a plan for regular reports of information collected from this study, and (v) provide a plan for providing the final study report in a timely manner.

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

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Group Leader Memo

June 8, 2000

NDA 21-205

Trizivir™ (abacavir sulfate 300 mg, zidovudine 300 mg, and lamivudine 150 mg)

Trizivir™ is a fixed dose combination that contains three nucleoside analogues marketed by the applicant, Glaxo Wellcome, Inc. This combination product should be used only by those whose treatment regimens would otherwise include these doses of these three nucleoside analogues. It may be used alone or in combination with other antiretroviral agents for the treatment of HIV infection.

The most important clinical issue raised by this NDA submission is that of adequately conveying to health care providers and patients the serious adverse event of hypersensitivity caused by abacavir. It appears that the applicant plans to widely market this combination product as a convenient treatment for HIV infection, particularly among those for whom compliance may be problematic. Therefore, there may be use of this product by health care providers and patients who are less familiar with the adverse event profile of abacavir. Our concern is that such use may increase the incidence of fatalities due to hypersensitivity reactions. In addition, in order to prevent inadvertent rechallenge with abacavir, patients and prescribers must recognize that Trizivir and Ziagen both contain abacavir, and that neither of these drugs should ever be taken by a person who may have experienced symptoms of a hypersensitivity reaction to abacavir.

The team has put the following in place in order to address these important safety issues:

- The label will highlight the important safety information about abacavir hypersensitivity reactions. It will also convey to prescribers and patients that there are other combinations of antiretroviral agents for which there is more data to support a durable antiviral effect, and that this fixed dose combination should be prescribed only when the three drugs would have been used separately.
- A medication guide for patients highlights the symptoms of hypersensitivity reactions to abacavir; the importance of discontinuation of abacavir when these symptoms occur; the dangers of rechallenge; and, identification of the three names for abacavir with which patients must be familiar in order to prevent rechallenge.
- A wallet warning card similar to the one provided to patients with abacavir prescriptions that summarizes the most important points that patients need to know about hypersensitivity reactions.

In addition to the measures described above, the applicant will be required to design and conduct an epidemiologic study. This study should be designed to answer the question of whether the availability of this combination formulation will lead to increases in the incidence of hypersensitivity reactions and/or rechallenge, and in particular, fatal outcomes. The design of the study should allow the causes of increased incidence (such

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**

as prescribing by those unfamiliar with the adverse event profile of abacavir) to be identified. At this time, we plan to issue an approvable letter for this NDA, contingent upon the applicant's submission of a final protocol that we agree will be likely to provide data that will address our concerns. In addition, we will require evidence that the study is ongoing prior to issuing the approval letter.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

MEMORANDUM

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

DATE: June 8, 2000

FROM: Melissa M. Truffa, R.Ph

SUBJECT: DSI audit for NDA 21-205

NDA: 21-205 Trizivir (abacavir sulfate, lamivudine and zidovudine) Tablets indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The information and data provided by the applicant, Glaxo Wellcome, in NDA 21-205 to support approval of TRIZIVIR, a combination drug product, is based upon the human bioequivalence of the new dosage form to each of the commercially available products (ZIAGEN Tablets, EPIVIR Tablets, and RETROVIR Tablets). This application does not directly contain clinical data. Non-clinical data is incorporated in full by reference from previously approved NDA 20-977, NDA 20-564, and NDA 19-655.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

**Group Leader Memo: Update 11/11/00
NDA 21-205**

Trizivir™ (abacavir sulphar 300 mg, zidovudine 300 mg, and lamivudine 150 mg)

The applicant has submitted final protocols for the epidemiologic study required for approval of Trizivir™. It appears that, in general, the protocols represent a reasonable effort to address our concerns. Comments from OPDRA outline analysis issues that will not delay initiation of the studies. The applicant has agreed to identify another database with sufficient numbers of patients and providers of interest as a phase 4 commitment.

The agreed-upon label contains the elements described in the group leader memo dated June 8, 2000. In addition, we have requested that the applicant agree to submit any labeling supplements that revise safety information contained in the zidovudine, lamivudine, or abacavir labels to the Trizivir NDA, so that changes to these labels may be considered for inclusion in the Trizivir label.

/S/

Therese Cvetkovich, M.D.
Medical Team Leader, DAVDP

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY



Food and Drug Administration
Rockville MD 20857

NDA 21-205

Glaxo Wellcome Inc.
Attention: Martha Anne A. Moore, R.Ph.
Antiviral Group- Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

JUN 19 2000

Dear Ms. Moore:

Reference is made to your correspondence dated May 4, 2000, requesting FDA issue a Written Request under Section 505A of the Food, Drug, and Cosmetic Act for Trizivir™ (abacavir sulfate, lamivudine, and zidovudine) Tablets.

Please also refer to your new drug application dated December 16, 1999 for Trizivir and the approvable letter dated June 9, 2000 that included draft labeling for Trizivir.

We have reviewed your proposed pediatric study request and are unable to issue a Written Request for the following reasons:

- Data submitted in your new drug application for Trizivir already supports labeling for the treatment of HIV-1 infection in adolescents who weigh more than 40 kilograms, and
- Because Trizivir is a fixed-dose combination tablet, it is an inappropriate dosage form for use in children, infants, and neonates.

Therefore, no additional pediatric data are needed to adequately label Trizivir for use in the intended pediatric population.

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

Sincerely yours,

Heidi Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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

DATE: OCT 11 2000

TO: Heidi Jolson, M.D., Director
Division of Antiviral Drug Products, HFD-530

THROUGH: Evelyn Rodriguez, M.D., Director
Division of Drug Risk Evaluation I, HFD-430

FROM: Mary E. Willy, Ph.D., M.P.H., Epidemiologist.
Division of Drug Risk Evaluation II, HFD-440

SUBJECT: Drug: Trizivir
Topic: Hypersensitivity reactions, epidemiologic program
PID#: D000463

S
my
Deputy Dirctn, DRES, OPDRA
10/11/00

I. EXECUTIVE SUMMARY --

This memorandum is in response to a GlaxoWellcome (GW) letter from September 13, 2000 addressing their proposal for a multi-center epidemiologic study of Trizivir-related hypersensitivity reactions (HSR). The sponsor acknowledges the risk for HSR and has proposed a multi-center epidemiologic prospective study to collect population-based data. The study proposals include a comprehensive description of the anticipated objectives and methodology. Several concerns remain regarding this proposal which need clarification by the sponsor. The following action items require further information and clarification:

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

The sponsor's efforts will need ongoing evaluation once the project is initiated to determine whether the Agency's and sponsor's objectives can be met using this multi-center epidemiologic study. Comparison with spontaneous reports may be necessary to determine whether there is an HSR signal.

II. BACKGROUND

A new Drug Application for Trizivir (NDA 21-205), a fixed dose combination tablet that contains three synthetic nucleoside analogues, was submitted in December 1999. In June 2000 GW submitted a proposal for an epidemiologic study of Trizivir-related HSR. A preliminary teleconference in August 2000 and then a follow-up meeting also in August 2000 were arranged to review the proposal and discuss concerns about the methodology. GW submitted a response letter on September 13, 2000 that included updates for the epidemiologic study proposal and the labeling.

III. REVIEW

GW has provided a detailed description of the four final protocols for the epidemiologic databases and addressed the questions identified at the last meeting. The following additional information was included in the September 13 letter:

A. *The Veteran's Administration database:*

The VA Pharmacy Benefits Management group confirmed that all antiretroviral agents are added to the National formulary as soon as they become available and "overall, newly approved antiretroviral agents appear on local VA Pharmacy shelves of larger VA HIV sites within the first week of approval." It remains unclear, though, whether this experience will follow for Trizivir which is a combination drug of three individual drugs that are currently available. Concerns about whether VA patients were actually obtaining both prescription and medical care from the VA system (and not just prescriptions) were investigated by Dr. Deyton of the VA. He reports that 97% of patients received both their medical care and prescriptions from a VA provider during the first four months of 2000. This information does not address the possibility that a certain percentage of emergency treatment for HSR may not be identified for VA patients if they receive treatment outside the VA system, since their data collection system is not based on claims. Some way to survey a sample of study patients should be considered to confirm that most have received all their care within the VA.

APPEARS THIS WAY
ON ORIGINAL

B. _____

As discussed previously, this study utilizes physicians highly trained in HSR and is not likely to be representative of HIV patient experience in the general population. We did not previously discuss the hospitalization information that is collected by _____ but as described there appears to be limited information available.

C. _____

No new comments are identified.

D. _____

This database does not have hospital records, although there are data fields for recording hospitalization information. GW included a proposal for verifying the ability to obtain hospital records for patients in this database. This study is proposed to take 2 months and will summarize: the number of _____ physicians asked to participate in the study and the percentage that participated; the number of hospitalizations in the database which were selected for review and the percentage of which a copy of the hospital record was obtained; and the number of patients sampled in the target population who did not have a documented hospitalization in the database and the percentage of patients for whom the physician recalled a hospitalization during the 90 days following abacavir treatment. Since this study has not been initiated, it is unclear whether the database will provide sufficient inpatient information for the study of HSR events. Additionally, it is not clear whether physicians will continue to be reimbursed for providing hospital data in the prospective study.

Physician participants may be more current on HIV treatment issues, since they are self-selected, and thus not be representative of HIV patient experience in the general population.

E. Review of GW Summary of Epidemiologic Study

The objectives listed include:

1. *Is the incidence of HSR equivalent for Trizivir and Ziagen?*
2. *What is the incidence of rechallenge?*
3. *What is the risk of HSR-associated hospitalization or HSR-associated death?*

Reviewer' comments:

The first objective may not be met unless the denominator used represents only patients at risk for a HSR (i.e. not previously exposed patients treated in other healthcare plans).

The second objective may not be met unless the denominator used includes patients at risk for a HSR rechallenge.

The first part of the last objective may only be achievable for 2 of the 4 databases (VA and _____ and the second part of this objective may not be met by any database given the projected low frequency of HSR-associated death.

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**

In each study there is a description of the methods used to calculate HSR risk for Trizivir and Ziagen. The protocols do not define "initial course" of treatment, so that recently enrolled patients who may have had potential exposure prior to enrollment are not excluded. Without limiting the denominators to patients with known first time exposures (i.e. those members enrolled for at least 60-90 days for example), the HSR rates will be diluted, i.e., the denominator will include patients that are not at risk for an initial HSR event because they have "survived" their initial exposure without an HSR. Although the number of patients with prior exposure to Trizivir and Ziagen may be small, a sub-analysis that includes and excludes newly enrolled patients (less than 60-90 days enrollment) should be completed and compared.

The identification of HSR events varies between the four studies with the VA and _____ studies intending to use _____ while _____ and _____ will use less well defined methods. I would suggest that the two studies using _____ codes utilize a similar list of codes (_____ has a much longer and well described list). The sponsor's plan to aggregate the four study's findings will be limited by the different study methodology used to identify cases.

The timing for study closure is inconsistently addressed in each of the four study protocols with _____ stating the timing will be _____ and _____ stating the _____ . Additionally, the first periodic review of the HSR data is not scheduled until one year after enrollment opens (page 72), this seems too long and might best start 6 months after enrollment begins.

A review of the projected yearly sample size tables show that _____ Ziagen/Trizivir candidates will come from the VA database and _____ will come from _____. Since these may be the only studies able to provide hospitalization data, it is possible that the project may not turn out to be a multi-center study, but primarily a VA study. Since the VA database has not been used for this type of study in the past, it is of some concern that so much of the study depends on this database.

IV. CONCLUSION

Concerns exist about an increased incidence of Ziagen- and Trizivir-related HSR with an associated risk for mortality. The sponsor acknowledges the risk for HSR and has proposed a multi-center epidemiologic prospective study to collect population-based data. The study proposals include a comprehensive description of the anticipated objectives and methodology. Several concerns remain regarding these proposals and need clarification by the sponsor. The following action items require further information and clarification:

[_____]

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

The sponsor's efforts will need ongoing evaluation once the project is initiated to determine whether the Agency and sponsor's objectives can be met using this epidemiologic study. Comparison with spontaneous reports may be necessary to determine whether there is an HSR signal.

/S/

Mary E. Willy, Ph.D. M.P.H.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

cc:
NDA 21-205
Division File

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

WITHHOLD 6 PAGE (S)



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 18, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: Mary Willy, Ph.D., MPH, OPDRA KU eso for MW 10/18/00
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP eso 10/18/00

NDA: 21-205 Trizivir (abacavir sulfate/lamivudine/ zidovudine) Tablets

Comments:

The following comments are being conveyed on behalf of Dr. Mary Willy, Epidemiologist, Division of Drug Risk Evaluation, with our concurrence:

1. The September 13 resubmission addresses many of the outstanding issues identified at our meeting on August 28, 2000. However, we recommend that you plan to include at least one other database in addition to those you have proposed, for the following reasons:
 - It appears that the majority of hypersensitivity reaction (HSR) cases occurring in the populations of interest will come from the Veteran's Administration (VA) database. For this reason, we question the ability to generalize the results of these studies to the larger population of interest.
 - In addition, the VA database does not have a proven "track record" for the conduct of pharmacoepidemiologic studies.
 - Finally, two of the databases _____ and _____, may not be able to provide appropriate hospital medical record information.

The additional database that you choose should have the ability to reflect the occurrence of HSR in the populations of interest (intravenous drug, prisoners, and women) in numbers similar to those projected for the VA database.

2. Please provide a mechanism by which you will be able to quantify the number of Ziagen/Trizivir VA patients who obtained emergency care outside the VA system and the medical reasons for those visits.
3. Please provide a proposal for your alternative plans if the VA does not add Trizivir to the formulary.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

4. Please provide a clear definition of "initial" exposure and a plan for completing an analysis of the data excluding patients who were not part of the health plan for a specific-period of time (60-90 days). Further, please provide a clear definition of rechallenge HSR and the denominator used for calculating rechallenge rates.
5. Please utilize similar ICD-9 codes for the two studies (VA and _____ to identify cases of HSR. Additionally, please note that your plans to aggregate the four studies' findings will be limited by the different methodology used to identify cases in the other two studies.
6. Please clarify the following: 1) whether sufficient hospitalization data can be collected from the four databases, (if not, the sample size calculations are optimistic, particularly if the drug use is low in the study populations), 2) the agreement to begin periodic review of HSR data within 6 months after enrollment, and 3) consistent wording for timing for study closure.
7. Finally, please note that we will evaluate the results from these studies in the context of all the available information.

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

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Record of Teleconference

October 25, 2000

NDA: 21-205

Drug: Trizivir®, (abacavir sulfate/lamivudine/zidovudine) Tablets

Sponsor: Glaxo Wellcome

Sponsor Attendees:

Dr. David Cochetto, Regulatory Affairs
Martha Anne Moore, Regulatory Affairs
Amy Cutrell, Statistics
Dr. Seth Hetherington, Clinical Research
Amy Keller, Clinical Research
Steve LaFon, Clinical Research
Dr. Lynn Smiley, Clinical Research
Dr. Alice White, Epidemiology

FDA Attendees:

Therese Cvetkovich, M.D., Medical Team Leader
Mary Dempsey, Regulatory Project Manager, OPDRA
Mary Willey, Ph.D., M.P.H., OPDRA
Kathy Uhl, M.D., OPDRA
Debbie Birnkrant, M.D., Deputy Director
Heidi Jolson, M.D., M.P.H., Division Director
Leslie Stephens, R.N., M.S.N., Regulatory Project Manager

Background:

The purpose of this teleconference was to discuss the outstanding concerns of the Division and OPDRA related to the Trizivir resubmission of September 13, 2000, and as outlined in the October 18, 2000 facsimile sent to the sponsor. The following issues were discussed:

1. Issues surrounding the databases proposed:

- Majority of hypersensitivity reaction (HSR) cases appear to come from Veteran's Administration (VA) database. We are concerned with the generalizability of these studies to a larger population.
- VA does not have a proven "track record" for the conduct of pharmacoepidemiologic studies.
- Two of the databases _____ and _____ may not be able to provide appropriate hospital medical record information.

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**

2. Mechanism by which the number of Ziagen/Trizivir VA patients who obtained emergency care outside the VA system can be quantified and the medical reasons for those visits.
3. Proposal for an alternate plan if the VA does not add Trizivir to the formulary.
4. Definition of "initial" exposure and a plan for completing an analysis of the data excluding patients who were not part of the health plan for specific period of time (60-90 days).

The sponsor agreed to:

1. Identify a fifth large database that will include the subjects and practitioners of interest.
2. Evaluate our proposal for analysis as outlined in the OPDRA consult of November 6, 2000.
3. Submit the final protocols.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

Concurrence:
HFD-530/MTL/Cvetkovich

11/14/00

/S/

Cc:
Original NDA 21-205
Division File
HFD-530/MTL/Cvetkovich
HFD-530/RPM/Truffa

NDA 21-205

Teleconference minutes

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION**

OPDRA POSTMARKETING SAFETY REVIEW

Debra Birmkrant, M.D.
Acting Director, Antiviral Drug Products

FROM: DDRE II (HFD-440)

OPDRA PID # D000463
Signed 11-08-00

DATE REQUESTED:
November 6, 2000

REQUESTOR/Phone #:
Melissa Truffa/ 7-2335

DATE RECEIVED:
November 6, 2000

DRUG (Est): ABC/ZDV/3TC

NDA/IND # 21-205

SPONSOR: Glaxo Welcome (GW)

DRUG NAME (Trade): Trizivir

THERAPEUTIC CLASSIFICATION:

EVENT: Hypersensitivity reactions (HSR)

Executive Summary:

The Sponsor has provided a detailed response to questions discussed in an October 25, 2000 telecon. Overall, the information addresses most of the concerns identified in that telecon. Specific information that was included in the response letter regarding the analysis plan should be revised to include a previously requested need for an analysis that excludes patients with possible previous exposure to abacavir – a requirement that there be a minimum number of enrolled days (60-90 days) without abacavir prior to initial exposure period.

Reason for Request/Review:

A response was requested to the October 27, 2000 letter from GW that included: responses to seven points on the epidemiologic program listed in October 18, 2000 fax from Agency, a revised draft letter of Phase IV commitments and a protocol for verifying the ability to hospital records from the _____ database

Relevant Product Labeling:

NA

Usage Information:

NA

Search Date: NA

Search Type(s): AERS Literature Other

Search Criteria: Drug Names:

MEDDRA Terms: NA

Search Results:

NA

BEST POSSIBLE COPY

**APPEARS THIS WAY
ON ORIGINAL**

Discussion / Conclusions:

A review of attachment 1, GW's responses to FDA's requests in the fax of October 18, 2000, identified a small number of concerns related to item 4. The company did not describe an analysis plan that would exclude patients who have been enrolled for only a short period prior to exposure to abacavir. The attached table (attachment A) describes in more detail my concerns about their analysis plan. The table highlights the different scenarios that may occur when using patient databases that include patients who have had previous exposure to abacavir while enrolled in other health plans. Although there is always the possibility that some patients included in these types of studies may have had previous drug exposure, requiring a minimum number of enrolled days (60-90 days) prior to the initial abacavir exposure will minimize the number of patients with unrecognized prior abacavir exposure. Including patients with unrecognized prior abacavir exposure will lead to an underestimate of primary HSR rates (by including patients in the denominator who are not receiving their first exposure to abacavir) and a possible misclassification of a rechallenge HSR as a primary HSR. The calculations for rechallenge may also misrepresent the true rate of rechallenge if the denominator does not include all patients at risk for that reaction.

Additionally, the methodology listed on page 7 and 8 of GW's attachment 1 is unclear. The denominators used for generating the relative risks will include patients exposed >90 days in an initial course AND patients exposed > 90 days in subsequent courses. It is not clear why patients exposed to subsequent courses need to be included in the denominators for initial HSR calculations. Different proportions that will be calculated are described on page 7 and 8. The proportion of HSRs that are rechallenged needs to include denominators that include patients exposed to either drug, i.e. # patients with HSR rechallenge in Ziagen group/#patients with HSR in Ziagen and Trizivir group (both groups might be at risk of being rechallenged with Ziagen) AND # patients with HSR rechallenge in Trizivir group/#patients with HSR in Ziagen and Trizivir group (both groups might be at risk of being rechallenged with Trizivir)

Item 7 on page 11 addresses the need to evaluate study results in the context of all available information. Although epidemiologic studies can provide robust information, such studies need a large enough sample to insure reliable and valid conclusions. Given the challenges presented when trying to study an outcome as difficult to identify as HSR and in a population that may be hard to study, a robust study may not result.

Finally, the Phase IV commitment in GW's attachment 2 includes the statement: "conduct a postmarketing epidemiological program that will compare rates of hypersensitivity, HSR-associated hospitalization, and HSR-associated death." This statement should include rechallenge rates in the list.

Mary Willy/signed 11-08-99

Reviewer's Signature / Date:

Team Leader's Signature / Date:

Kathleen Uhl/signed 11-08-00

Acting Division Director Signature / Date:

Office Director Signature / Date:

Attachments:

Cc: NDA #

HFD-530(Division File)/ Birnkrant/Truffa

HFD-440 DD/TL/SE/Chron/Drug

Electronic File Name:

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Group Leader Memo: Update 11/11/00

NDA 21-205

Trizivir™ (abacavir sulphar 300 mg, zidovudine 300 mg, and lamivudine 150 mg)

The applicant has submitted final protocols for the epidemiologic study required for approval of Trizivir™. It appears that, in general, the protocols represent a reasonable effort to address our concerns. Comments from OPDRA outline analysis issues that will not delay initiation of the studies. The applicant has agreed to identify another database with sufficient numbers of patients and providers of interest as a phase 4 commitment.

The agreed-upon label contains the elements described in the group leader memo dated June 8, 2000. In addition, we have requested that the applicant agree to submit any labeling supplements that revise safety information contained in the zidovudine, lamivudine, or abacavir labels to the Trizivir NDA, so that changes to these labels may be considered for inclusion in the Trizivir label.

/s/

Therese Cvetkovich, M.D.
Medical Team Leader, DAVDP

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

GlaxoWellcome

November 14, 2000

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

**Re: NDA 21-205; Trizivir™ (abacavir sulfate, lamivudine, and zidovudine) Tablets;
Other: Phase IV Commitments**

Dear Dr. Birnkrant:

Reference is made to NDA 21-205 for Trizivir Tablets under review by your Division. We would also like to reference our meeting on August 28, 2000 with members of your Division and OPDRA regarding our proposed epidemiologic program for Trizivir, our complete response on September 13, 2000 to the approvable letter of June 9, 2000, comments received from your Division on October 18, 2000, our conference call on October 25, 2000 and our submissions of October 27 and November 8, 2000. The purpose of this letter is to state our commitments regarding Phase IV activities for Trizivir Tablets based upon our October-25, 2000 conference call and other recent discussions with your Division.

Glaxo Wellcome acknowledges its previous Phase IV commitments for abacavir sulfate as the drug substance in Ziagen Tablets and Oral Solution (NDAs 20-977 and 20-978). These commitments were presented in full in our letter of December 17, 1998 and reiterated in DAVDP's approval letter of December 17, 1998. We recognize that these abacavir-related commitments should also apply to abacavir sulfate within Trizivir Tablets. Therefore, Glaxo Wellcome intends to incorporate information on the use of Trizivir (as well as Ziagen products) into our ongoing commitments for abacavir concerning hypersensitivity.

In addition to extending these commitments for Ziagen to Trizivir, Glaxo Wellcome commits to the following specific additional Phase IV activities for Trizivir:

APPEARS THIS WAY
ON ORIGINAL

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398
Telephone
919 483 2100

BEST POSSIBLE COPY

NDA 21-205
November 14, 2000
Page 2

1. Glaxo Wellcome will conduct a postmarketing epidemiological program that will compare rates of hypersensitivity (HSR), HSR-associated rechallenge, HSR-associated hospitalization, and HSR-associated death in patients receiving Trizivir Tablets compared to Ziagen products. This program will be conducted in accordance with the protocols, data analysis plan, and plan for periodic updates to DAVDP, as submitted to your Division by Glaxo Wellcome on November 8, 2000.

Anticipated timeframe for completion: In order to meet the objective of the program it is anticipated that the epidemiologic program for Trizivir will be ongoing for a minimum of 3 years based upon the expected numbers of patients to be enrolled, as described in the data analysis plan of our September 13, 2000 resubmission (attachment C). Summaries of accumulated data will be submitted to FDA following the biannual review, with the first review planned for six months after accelerated approval of Trizivir.

2. GW will strive to identify a fifth database for inclusion in the epidemiologic program by contacting appropriate investigators for databases capturing health care data on prescriber and patient populations of special interest (i.e., non-HIV specialists and marginalized patients), working to identify the research questions that can be answered from each database, and identifying any limitations of each database.

Anticipated timeframe for completion: GW will submit the results of this effort to FDA, along with our recommendation on how to proceed, no later than February 15, 2001.

This submission is made in duplicate to NDA 21-205. If you have any questions regarding this submission, please contact David M. Cocchetto at (919) 483-5127. Thank you.

Sincerely,



David M. Cocchetto, Ph.D.
Vice President
AV/AI Regulatory Affairs



Marc Rubin, M.D.
Vice President
Therapeutic Development and Product Strategy
HIV, Infectious Diseases, and Hepatitis

— APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-205 / _____

This is a complete, Type I RESubmission to our June 9, 2000
 APPROVABLE LETTER

Drug Trizivir (abacavir sulfate, lamivudine, zidovudine) Tablets Applicant Glaxo Welcome

RPM Melissa Truffa Phone 301-827-2335

505(b)(1)
 505(b)(2) Reference listed drug _____

Fast Track Rolling Review Review priority: S P

Pivotal IND(s) IND 58,191

Application classifications: Chem Class _____
 Other (e.g., orphan, OTC) _____

PDUFA Goal Dates: Primary Nov 14, 2000
 Secondary January 14, 2001

Arrange package in the following order:

Indicate N/A (not applicable),
 X (completed), or add a
 comment.

GENERAL INFORMATION:

- ◆ User Fee Information: User Fee Paid
 User Fee Waiver (attach waiver notification letter)
 User Fee Exemption
- ◆ Action Letter..... AP AE NA
- ◆ Labeling & Labels
 - FDA revised labeling and reviews.....
 - Original proposed labeling (package insert, patient package insert)
 - Other labeling in class (most recent 3) or class labeling.....
 - Has DDMAC reviewed the labeling? Yes (include review) No
 - Immediate container and carton labels
 - Nomenclature review
- ◆ Application Integrity Policy (AIP) Applicant is on the AIP. This application is is not on the AIP.
 Exception for review (Center Director's memo)..... _____
 OC Clearance for approval..... _____

APPEARS THIS WAY
 ON ORIGINAL

BEST POSSIBLE COPY

Continued ⇨

- ◆ Status of advertising (if AP action) Reviewed (for Subpart H – attach review) Materials requested in AP letter
- ◆ Post-marketing Commitments
 - Agency request for Phase 4 Commitments.....
 - Copy of Applicant's commitments
- ◆ Was Press Office notified of action (for approval action only)?..... Yes No
 - Copy of Press Release or Talk Paper.....
- ◆ Patent
 - Information [505(b)(1)]
 - Patent Certification [505(b)(2)].....
 - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
- ◆ Exclusivity Summary
- ◆ Debarment Statement
- ◆ Financial Disclosure
 - No disclosable information
 - Disclosable information – indicate where review is located
- ◆ Correspondence/Memoranda/Faxes
- ◆ Minutes of Meetings
 - Date of EOP2 Meeting NA
 - Date of pre NDA Meeting Oct 8, 1999 and Oct 22, 1999
 - Date of pre-AP Safety Conference NA
- ◆ Advisory Committee Meeting NA
 - Date of Meeting NA
 - Questions considered by the committee NA
 - Minutes or 48-hour alert or pertinent section of transcript NA
- ◆ Federal Register Notices, DESI documents NA

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X
- ◆ Clinical review(s) and memoranda X

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

Continued ⇨

- ◆ Safety Update review(s) NA
- ◆ Pediatric Information
 - Waiver/partial waiver (Indicate location of rationale for waiver) Deferred Pediatric Page..... ✓
 - Pediatric Exclusivity requested? Denied Granted Not Applicable
- ◆ Statistical review(s) and memoranda X
- ◆ Biopharmaceutical review(s) and memoranda..... ✓
- ◆ Abuse Liability review(s) NA
 Recommendation for scheduling NA
- ◆ Microbiology (efficacy) review(s) and memoranda ✓
- ◆ DSI Audits NA
 Clinical studies bioequivalence studies

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda ✓
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability NA
- ◆ DMF review(s) NA
- ◆ Environmental Assessment review/FONSI/Categorical exemption NA
- ◆ Micro (validation of sterilization) review(s) and memoranda NA
- ◆ Facilities Inspection (include EES report)
 Date completed June 2, 2000 Acceptable Not Acceptable
- ◆ Methods Validation Completed Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda ✓
- ◆ Memo from DSI regarding GLP inspection (if any) NA

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Continued ⇨

- ◆ Statistical review(s) of carcinogenicity studies NA
- ◆ CAC/ECAC report NA

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

**OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST**

NDA:	21-205
Drug:	TRIZIVIR (abacavir sulfate, lamivudine, zidovudine)
Applicant:	Glaxo Wellcome
Chem/Ther/other Types:	Antiretroviral
CSO/PM:	MELISSA TRUFFA
Phone:	(301) 827-2335
HFD:	530
USER FEE GOAL DATE:	JUNE 17, 2000
CHECKLIST COMPLETE:	June 9, 2000

Tablets

Arrange package in the following order (include a completed copy of this CHECKLIST):

1. ACTION LETTER with supervisory signatures	AP	AE	<input checked="" type="checkbox"/>	NA	<input type="checkbox"/>
Are there any Phase 4 commitments?		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
2. Have all disciplines completed their reviews?	DRAFT	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
3. LABELING (package insert and carton and container labels). Note: If final or revised draft, include copy of previous version with ODEs comments and state where in action package the Division's review is located. If RX-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.	- Draft				
	Revised Draft				<input checked="" type="checkbox"/>
	Final				
4. PATENT INFORMATION		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
5. EXCLUSIVITY CHECKLIST		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
6. PEDIATRIC PAGE (all NDAs)		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
7. DEBARMENT CERTIFICATION (copy of applicant's certification for all NDAs submitted on or after June 1, 1992).		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES: Note: If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo explaining why. <i>No clinical data submitted</i>		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
9. REVIEWS & MEMORANDA					
a. DIVISION DIRECTOR'S MEMO	NA	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
b. GROUP LEADER'S MEMO	DRAFT	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
c. MEDICAL REVIEW	DRAFT Final	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
d. SAFETY UPDATE REVIEW	NA	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
e. STATISTICAL REVIEW		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
f. BIOPHARMACEUTICS REVIEW		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
g. PHARMACOLOGY REVIEW (Include pertinent IND reviews)		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>

MEMO attached

**BEST POSSIBLE COPY
APPEARS THIS WAY
ON ORIGINAL**

1) Statistical Review of Carcinogenicity Study(ies)	NA	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
2) CAC Report/Minutes	NA	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
h. CHEMISTRY REVIEW	DRAFT 1/2/00	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
1) Labeling and Nomenclature Committee Review		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
Memo					
2) Date EER completed	June 2, 2000				
3) EER Results (attach signed form or CIRT's printout)	OK	Yes	<input checked="" type="checkbox"/>	No	<input checked="" type="checkbox"/>
4) FUR needed		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
5) FUR requested		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
6) Have the methods been validated?		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
7) Environmental Assessment Review		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
8) FONSI		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
i. MICROBIOLOGY REVIEW		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
1) What is the status of the monograph?	NA				
10. CORRESPONDENCE, TELECONS, and FAXes		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
11. MINUTES OF MEETINGS		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
a. Date of End-of-Phase 2 Meeting:	NA				
b. Date of pre-NDA Meeting:	GMC Oct 8, 1999			Oct 22, 1999	
12. ADVISORY COMMITTEE MEETING	NA				
a. Meeting Conducted		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
b. Minutes		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
c. Info Alert		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
d. Transcript		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
14. If AP letter, has ADVERTISING MATERIAL been reviewed?		Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
a. If no and this is an AP with draft labeling letter, has advertising material already been requested?		Yes, documentation attached	<input checked="" type="checkbox"/>	No, included in AP letter	<input type="checkbox"/>
15. INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA)		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
16. INTEGRATED SUMMARY OF SAFETY (from NDA)		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>

revision: 5/14/96; edited LR: 5/29/96;

designed for web: Hardeman 7/17/98

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL