

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-205/S-002

ADMINISTRATIVE AND CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-205 SUPPL # S-002

Trade Name Trizivir®

Generic Name (abacavir sulfate, lamivudine, and zidovudine)

Applicant Name GlaxoSmithKline HFD- 530

Approval Date February 05, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

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

If yes, what type (SE1, SE2, etc.)? SE8

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

YES / / NO / /

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

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

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

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

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

YES /___/ NO /_X_/

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

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

YES /_X_/ NO /___/

If yes, NDA # 20-977 & NDA 20-978
Drug Name Ziagen® (abacavir sulfate Tablets and Oral Solution)

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

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

YES /___/ NO /___/

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

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

2. Combination product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

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

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

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

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

YES /___/ NO /___/

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

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

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

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

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

YES /___/ NO /___/

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

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /___/

If yes, explain:

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

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

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

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

Investigation #1 YES /___/ NO /___/
Investigation #2 YES /___/ NO /___/
Investigation #3 YES /___/ NO /___/

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

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

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

Investigation #__, Study #
Investigation #__, Study #
Investigation #__, Study #

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

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

Investigation #1 !
!
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!

Investigation #2 !
!
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!
!

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

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

!

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

!

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

YES /___/ NO /___/

If yes, explain: _____

Signature of Preparer
Title:

Date

Signature of Office or Division Director

Date

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

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

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/s/

Jeffrey Murray
3/26/02 11:55:27 AM

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Memorandum of Project Manager's Review: Final Printed Labeling

NDA: 21-205

Date Submitted: April 6, 2001

Date Completed: January 28, 2002

Sponsor: GlaxoSmithKline
5 Moore Drive
Research Triangle Park, NC 27709

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

Materials Reviewed:

1. Final printed labeling (FPL) dated May 3, 2001.
2. Draft labeling dated April 6, 2001.
3. Final printed labeling (FPL) dated November 2000.

Background

NDA 21-205 for Trizivir (abacavir sulfate, lamivudine, and zidovudine) Tablets was originally approved on November 14, 2000. The purpose of Supplement 002 (S-002) is to incorporate appropriate changes into the Trizivir Tablets labeling that have been recently made in labeling for Ziagen (abacavir sulfate) and Retrovir (zidovudine) products. This includes the following changes:

1. Results from studies CNAAB3005 and CNAA1012 which have been incorporated in product labeling for Ziagen Tablets and Ziagen Oral Solution.
2. General updates to the Retrovir products' labeling which include incorporation of statements from PRECAUTIONS, Patient Information, Drug Interactions regarding the concomitant use of doxorubicin, ribavirin and stavudine.

This final printed labeling (FPL) dated May 3, 2001 was compared electronically to the FPL dated November 2000.

Revisions

1. The November 2000 label includes the trademark symbol after the Trizivir name (Trizivir™). The May 3, 2001 FPL has replaced Trizivir™ with Trizivir®.
2. In the **BLACK BOX WARNING**, the following paragraph was deleted in the May 3, 2001 FPL:

TRIZIVIR alone or in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. The indication for TRIZIVIR is based on analyses of surrogate markers in controlled studies with abacavir 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 abacavir.

3. In the **DESCRIPTION** section, under **Abacavir Sulfate**, the words, "In vivo" are italicized in the November 2000 FPL. In the May 3, 2001 FPL, the words are in regular font.
4. In the **MICROBIOLOGY** section, under the **Antiviral Activity in Vitro: Zidovudine**, a comma was removed from the fifth sentence after the word "with." The May 3, 2001 FPL reads: In cell culture drug combination studies, zidovudine demonstrates synergistic activity with delavirdine, didanosine, indinavir, nelfinavir, nevirapine, ritonavir, saquinavir, and zalcitabine, and additive activity with interferon-alpha.
5. In the **MICROBIOLOGY** section, under **Drug Resistance: Abacavir**, the following sentence was deleted in the first paragraph: Mutations M184V and L74V were most frequently observed in clinical isolates.
6. In the **MICROBIOLOGY** section, under **Drug Resistance: Abacavir**, the following paragraph was added:

Genetic analysis of HIV-1 isolates from 21 previously antiretroviral therapy-naive patients with confirmed virologic failure (plasma HIV-1 RNA \geq 400 copies/mL) after 16 to 48 weeks of abacavir/lamivudine/zidovudine therapy showed that 16/21 isolates had abacavir/lamivudine-associated mutation M184V, either alone (11/21), or in combination with Y115F (1/21) or zidovudine-associated (4/21) mutations at the last time point. Phenotypic data available on isolates from 10 patients showed that 7 of the 10 isolates had 25- to 86-fold decreases in susceptibility to lamivudine in vitro. Likewise, isolates from 2 of these 7 patients had 7- to 10-fold decreases in susceptibility to abacavir in vitro.
7. In the **MICROBIOLOGY** section, under **Cross-Resistance: Lamivudine**, a hyphen has been added in the second sentence between the words "lamivudine and resistant".
8. In the **MICROBIOLOGY** section, under **Cross-Resistance**, under **Zidovudine**, a comma was removed in the last sentence after the word "to." The mutation at codon 151 in combination with the mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine.
9. In the **CLINICAL PHARMACOLOGY** section, under **Drug Interactions: Abacavir**, the following paragraph was added: In a study of 11 HIV-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the current recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.
10. In the **CLINICAL PHARMACOLOGY** section, under **Drug Interactions**, in **Table 2**, the May 3, 2001 FPL abbreviates the word "hour" as "h" versus "hr" in the FPL dated November 2000.

11. In the **INDICATIONS AND USAGE** section, the following changes are noted: (The additions are underlined and the deletions are presented as strikethrough.)

INDICATIONS AND USAGE: TRIZIVIR is indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection. The indication for TRIZIVIR is based on ~~two~~ 2 controlled ~~clinical~~ trials with abacavir of ~~16 and 48 weeks in duration that evaluated suppression of HIV RNA and changes in CD4 cell count.~~ 16 and 48 weeks in duration that evaluated suppression of HIV RNA and changes in CD4 cell count. At present, there are no results from controlled trials evaluating ~~the effect of clinical progression of HIV.~~ the effect of clinical progression of HIV.

~~There are limited data on the use of this triple-combination regimen in patients with higher viral load levels (>100,000 copies/mL) at baseline (see Description of Clinical Studies for ZIAGEN).~~

12. In the **INDICATIONS AND USAGE** section, under the **Description of Clinical Studies:** **ZIAGEN**, the last sentence was changed from HIV-1 RNA from ≤ 400 copies/mL to < 400 copies/mL. The sentence now reads:

Proportions of patients with plasma HIV-1 RNA < 400 copies/mL (using Roche Amplicor HIV-1 MONITOR[®] Test) through 16 weeks of treatment are summarized in Figure 1.

13. In the **INDICATIONS AND USAGE** section, under the **Description of Clinical Studies:** **ZIAGEN**, the less than or equal to sign (\leq) was replaced with just the less than sign ($<$) in the title of **Figure 1**. The May 3, 2001 FPL reads:

Proportions of Patients with HIV-1 RNA < 400 copies/mL in Study CNAAB3003.

14. In the **INDICATIONS AND USAGE** section, below **Figure 1**, the November 2000 label reads:

~~Proportions of patients with plasma HIV-1 RNA ≤ 400 copies/mL (using Roche Amplicor HIV-1 MONITOR[®] Test) through 16 weeks of treatment are summarized in Figure 1.~~

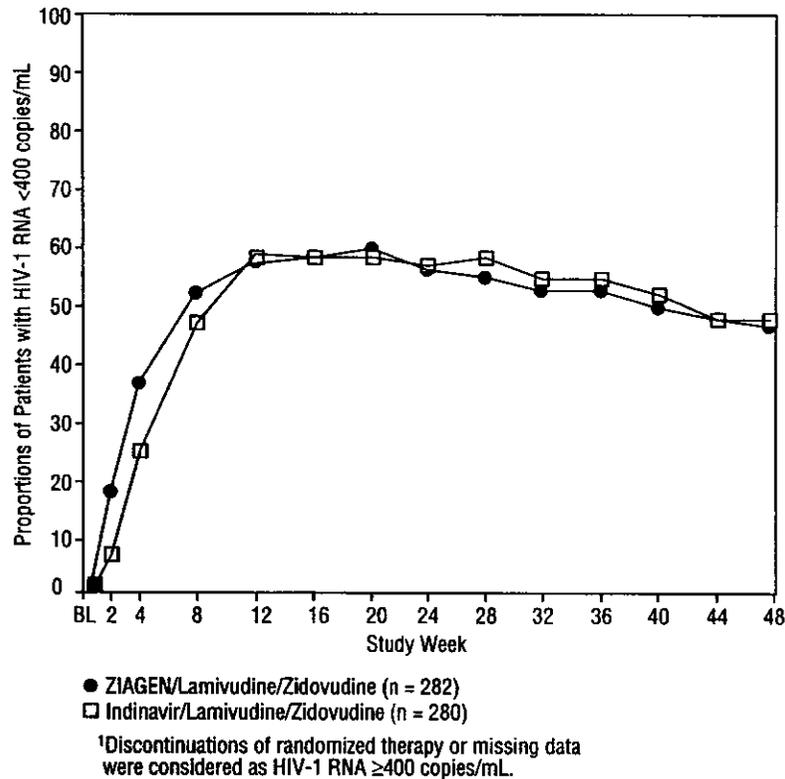
The May 3, 2001 FPL reads:

CNAAB3005 was a multicenter, double-blind, controlled study in which 562 HIV-infected, therapy-naive adults with a pre-entry plasma HIV-1 RNA $> 10,000$ copies/mL were randomized to receive either ZIAGEN (300 mg twice daily) plus COMBIVIR (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times a day) plus COMBIVIR twice daily. Study participants were male (87%), Caucasian (73%), African-American (15%), and Hispanic (9%). At baseline the median age was 36 years, the median pretreatment CD4 cell count was 360 cells/mm³, and median plasma HIV-1 RNA was 4.8 log₁₀ copies/mL. Proportions of patients with plasma HIV-1 RNA < 400 copies/mL (using Roche Amplicor HIV-1 MONITOR[®] Test) through 48 weeks of treatment are summarized in Figure 2.

15. In the **INDICATIONS AND USAGE** section, **Figure 2**, **Table 3**, and the following text were added to the May 3, 2001 FPL:

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Figure 2: Proportions of Patients with HIV-1 RNA <400 copies/mL in Study CNAAB3005¹



Through week 48, an overall mean increase in CD4 cells of about 150 cells/mm³ was observed in both treatment arms.

Table 3: Outcomes of Randomized Treatment Through Week 48 (CNAAB3005)

Outcome	ZIAGEN/Lamivudine/ Zidovudine (n = 282)	Indinavir/ Lamivudine/ Zidovudine (n = 280)
HIV RNA <400 copies/mL	46%	47%
HIV RNA ≥400 copies/mL	29%	28%
CDC Class C event	2%	<1%
Discontinued due to adverse reactions	9%	11%
Discontinued due to other reasons [†]	6%	6%
Randomized but never initiated treatment	7%	5%

[†]Includes viral rebound and failure to achieve confirmed <400 copies/mL by Week 48.

[†]Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, and other.

16. In the **PRECAUTIONS** section, under **Drug Interactions: Abacavir**, the following paragraph was added to the May 3, 2001 FPL:

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the current recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

17. In the **PRECAUTIONS** section, under **Drug Interactions: Zidovudine**, the November 2000 approved label reads:

Zidovudine: Coadministration of ganciclovir, interferon-alpha, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine (see **CLINICAL PHARMACOLOGY**).

The May 3, 2001 FPL reads:

Zidovudine: Coadministration of ganciclovir, interferon-alpha, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine. Concomitant use of zidovudine with stavudine should be avoided since an antagonistic relationship has been demonstrated in vitro. In addition, concomitant use of zidovudine with doxorubicin or ribavirin should be avoided because an antagonistic relationship has also been demonstrated in vitro.

See **CLINICAL PHARMACOLOGY** for additional drug interactions.

18. In the **ADVERSE REACTIONS** section, the November 2000 FPL reads:

Selected clinical adverse events with a $\geq 5\%$ frequency during therapy with ZIAGEN 300 mg twice daily and EPIVIR 150 mg twice daily and RETROVIR 300 mg twice daily compared with EPIVIR 150 mg twice daily and RETROVIR 300 mg twice daily from CNAAB3003 are listed in Table 3.

The May 3, 2001 FPL reads:

The approved label now reads: Selected clinical adverse events with a $\geq 5\%$ frequency during therapy with ZIAGEN 300 mg twice daily, EPIVIR 150 mg twice daily, and RETROVIR 300 mg twice daily compared with EPIVIR 150 mg twice daily and RETROVIR 300 mg twice daily from CNAAB3003 are listed in Table 4.

19. In the **ADVERSE REACTIONS** section, ~~Table 3~~ (in the November 2000 FPL) is now Table 4. In addition, the following text was added after **Table 4**:

Selected clinical adverse events with a $\geq 5\%$ frequency during therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from CNAAB3005 are listed in Table 5.

20. In the **ADVERSE REACTIONS** section, **Table 5** and the following text were added to the May 3, 2001 FPL:

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**Table 5: Selected Clinical Adverse Events Grades 1-4 (≥5% Frequency)
in Therapy-Naive Adults (CNAAB3005) Through 48 Weeks of Treatment**

Adverse Event	ZIAGEN/Lamivudine/Zidovudine (n = 262)	Indinavir/Lamivudine/Zidovudine (n = 264)
Nausea	60%	61%
Nausea and vomiting	30%	27%
Diarrhea	26%	27%
Loss of appetite/anorexia	15%	11%
Insomnia and other sleep disorders	13%	12%
Fever and/or chills	20%	13%
Headache	28%	25%
Malaise and/or fatigue	44%	41%

Five subjects in the abacavir arm of study CNAAB3005 experienced worsening of pre-existing depression compared to none in the indinavir arm. The background rates of pre-existing depression were similar in the 2 treatment arms.

21. In the **ADVERSE REACTIONS** section, under **Laboratory Abnormalities**, the following sentence was added:

In study CNAAB3005, hyperglycemia and disorders of lipid metabolism occurred with similar frequency in the abacavir and indinavir treatment arms.

22. In the **ADVERSE REACTIONS** section, under **Other Adverse Events**, the previous label stated: In addition to the adverse events in **Table 3** other adverse events observed in the expanded access program for abacavir were pancreatitis and increased GGT.

The May 3, 2001 label reads:

In addition to the adverse events in Tables 4 and 5, other adverse events observed in the expanded access program for abacavir were pancreatitis and increased GGT.

23. In the **ADVERSE REACTIONS** section, under **Lamivudine Plus Zidovudine**, the November 2000 refers to _____ The May 3, 2001 FPL refers to "**Tables 6 and 7.**"

24. In the **ADVERSE REACTIONS** section, _____ in the November 2000 label is now **Table 6** in the May 3, 2001 FPL. In addition, the _____ is now **Table 7** and in **Table 7**, a space has been added before the less than sign (<).

25. In the **HOW SUPPLIED** section, the following test was deleted:

Summary

The revisions to the above reference Trizivir Tablets are acceptable. Please refer to the medical

officer's memoranda for concurrence. An approval letter will be issued to the Sponsor.

Karen A. Young, RN, BSN
Regulatory Project Manager
Division of Antiviral Drug Products

Attachment: Medical Officer's memoranda

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/s/

Karen Young
2/6/02 02:31:04 PM
CSO

Trizivir, CSO Labeling Review

Tony DeCicco
2/7/02 11:44:14 AM
CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM

To: NDA 20-977
Trizivir®

From: Joseph Toerner, MD
Medical Officer, DAVDP

Through: Therese Cvetkovich, MD
Medical Officer, Team Leader, DAVDP

Re: SE8-002
Labeling Changes

DAVDP recently approved changes to the zidovudine and abacavir labels. The purpose of this submission is to incorporate those changes into the Trizivir® label. The sponsor submitted draft labeling with changes to the pharmacokinetics and information for patients sections. The sponsor was encouraged to describe the potential antagonistic relationship between stavudine and zidovudine in a separate sentence, rather than describing the potential antagonistic relationship of stavudine, doxorubicin, and ribavirin with zidovudine in a single sentence. The sponsor agreed to incorporate a separate sentence describing the antagonistic relationship between stavudine and zidovudine.

CC: HFD-530: PM/Young, MO/Toerner

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/s/

Joe Toerner
6/11/01 04:07:05 PM
MEDICAL OFFICER

Therese Cvetkovich
7/6/01 09:31:05 AM
MEDICAL OFFICER

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-205/S-002

CBE-30 SUPPLEMENT

GlaxoSmithKline
Attention: Martha Anne A. Moore, R.Ph.
Product Director – AV/AI Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Moore,

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Trizivir® (abacavir sulfate, lamivudine, and zidovudine) Tablets

NDA Number: 21-205

Supplement number: S-002

Date of supplement: April 6, 2001

Date of receipt: April 9, 2001

This supplemental application, submitted as “Special Supplement: Draft - Changes Being Effected, Labeling” proposes to incorporate appropriate changes into the Trizivir Tablets that have been recently made in labeling for Ziagen and Retrovir products. These include:

1. Results from studies CNAAB3005 and CNAAB1012.
2. General updates to the Retrovir products’ labeling which include incorporation of statements from PRECAUTIONS, Patient Information, Drug Interactions regarding the concomitant use of doxorubicin, ribavirin and stavudine.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 8, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-205/S-002

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Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, please call Karen Young, RN Regulatory Project Manager, at (301) 827-2335.

Sincerely yours,

Anthony DeCicco, R.Ph.
Chief Project Manager
Division of Antiviral Drug Products
Office for Drug Evaluation IV
Center for Drug Evaluation & Research

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/s/

Tony DeCicco
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MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: April 13, 2001

To: Martha Anne Moore, R.Ph.
Product Director – Antiviral/Anti-Infective Regulatory Affairs

Sponsor: GlaxoSmithKline

From: Karen A. Young, RN, BSN, DAVDP

Through: Joseph Toerner, M.D., Medical Officer, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP

NDA: 21-205 (Trizivir)

Subject: Special Supplement: Draft – Changes Being Effected, Labeling

The following comments are being conveyed on behalf of the medical review team and are in reference to your submission dated April 6, 2001:

We propose the following changes to Lines 495-500 to the section entitled, "Drug Interactions":

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Based upon your e-mail dated April 5, 2001, we propose the following changes to the Trizivir Medication Guide under the section entitled, "What I should avoid while taking Trizivir?":

You should avoid taking stavudine (Zerit) while taking Trizivir. If your doctor prescribes doxorubicin or ribavirin, tell your doctor that you are taking Trizivir.

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.

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this page is the manifestation of the electronic signature.**

/s/

Karen Young
4/16/01 08:35:52 AM
CSO

Therese Cvetkovich
4/30/01 02:43:40 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**