CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-205

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	: 21, 205	**REVIEWER:**	Jooran S. Kim, Pharm.D.
TYPE	: Resubmission of Label	**SUBMISSION DATE**	: 9/13/00
DRUG	: Trizivir (zidovudine 300 mg, lamivudine 150 mg, abacavir sulfate 300 mg)		
FORMULATION:	Oral tablet		
SPONSOR	: Glaxo Wellcome	**DRAFT REVIEW**	: 10/31/00

BACKGROUND: The original NDA has previously been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and was found to be acceptable. The Clinical Division issued an approvable letter dated June 9, 2000. Subsequently, the sponsor resubmitted the Trizivir label on September 13, 2000. This is a review of the label resubmission.

PROPOSED LABELING CHANGES:

1.0 CLINICAL PHARMACOLOGY

1.1 Pharmacokinetics in adults

For consistency throughout the label, "[redacted] was deleted.

1.2 Special Populations

Impaired Renal Function

Currently, ZIAGEN does not have an indication for use in patients with renal impairment. Therefore, the statement, [redacted] was deleted since ZIAGEN cannot be included in this statement.

Pediatric Patients

The statement, [redacted] was deleted.

2.0 PRECAUTIONS

2.1 Patients with Impaired Renal Function

The section on the use of TRIZIVIR in patients with impaired renal function (creatinine clearance ≤ 50 mL/min) was reworded as follows:

"TRIZIVIR: [redacted]

TRIZIVIR is a fixed-dose tablet; therefore, the dose of the individual components cannot be altered."

RECOMMENDATIONS:

The label has been reviewed and is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

/S/ 11/13/00

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Concurrence: /S/ 11/13/2000

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Cc: HFD-530 /NDA 21205
MO/ Cvetkovich
RPM/Truffa
HFD-880 /Kim
/TL/Reynolds
/Viswanathan

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JUN 9 2000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

REVIEWER	: Prabhu Rajagopalan, Ph. D.
NDA (FORMULATION)	: 21205 (Tablet)
TYPE	: Priority
APPLICANT	: GlaxoWellcome
DRUG (STRENGTH)	: Abacavir (300 mg), Lamivudine (150 mg) and Zidovudine (300 mg)
SUBMISSION DATE	: December 20, 1999
DRAFT REVIEW	: March 16, 2000
FINAL REVIEW	: June 7, 2000

BACKGROUND

Abacavir, lamivudine and zidovudine are nucleoside analogs that are approved for the treatment of HIV infection. Currently, these drugs are commercially available under the trade names ZIAGEN, EPIVIR and RETROVIR. Additionally, a fixed combination tablet containing lamivudine and zidovudine is also commercially available under the trade name COMBIVIR. The Applicant has developed a tablet formulation containing a fixed dose of all three nucleoside analogs. The NDA submitted by the Applicant contains results of a study in which the bioequivalence and effect of a high fat meal were assessed. The NDA for this combination tablet product will be acted upon mainly based on the results of the bioequivalence study. No well-controlled clinical trials have been conducted with this combination product.

I. FORMULATION

The composition of the triple combination tablet is given below:

Ingredient	mg/tablet
Abacavir sulfate *	
Lamivudine	
Zidovudine	
Microcrystalline cellulose	
Sodium starch glycolate	
Magnesium stearate	
Total weight	1350.00

* equivalent to 300 mg of abacavir

II. BIOEQUIVALENCE AND FOOD EFFECT ASSESSMENT

STUDY TITLE: An evaluation of the bioequivalence of a combined formulated tablet (300/150/300 mg abacavir/lamivudine/zidovudine) compared to ZIAGEN (abacavir) 300 mg tablet, EPIVIR (lamivudine) 150 mg tablet, and RETROVIR (zidovudine) 300 mg tablet administered concurrently and the effect of food on absorption in healthy volunteers (Protocol AZL10001).

OBJECTIVES: Primary objective was to evaluate the bioequivalence between a combined formulated tablet containing abacavir, lamivudine and zidovudine and individual abacavir, lamivudine and zidovudine tablets swallowed sequentially.

The secondary objective was to assess the effect of food on the absorption of the nucleoside analog from the combined tablet formulation.

SUBJECTS: A total of 24 healthy subjects (15 males and 9 females, mean age: 37.5 years, mean weight: 71 kg) participated in this study.

STUDY DESIGN: This study was conducted in a three-way crossover fashion. Subjects received the following three treatments.
Treatment A: Single dose of combination tablet containing abacavir 300 mg, lamivudine 150 mg and zidovudine 300 mg - fasted
Treatment B: Single dose of individual tablets containing abacavir 300 mg, lamivudine 150 mg and zidovudine 300 mg - fasted
Treatment C: Single dose of combination tablet containing abacavir 300 mg, lamivudine 150 mg and zidovudine 300 mg - fed

Subjects received the three treatments in one of the following six sequences: ABC, ACB, BAC, BCA, CAB and CBA. Treatment C was administered within five minutes after consumption of a high-fat breakfast (2 fried eggs, 2 strips of bacon, 2 slices of toast, 2 ounces hash brown potatoes and 8 ounces whole milk). One deviation from protocol occurred in this study. The washout interval was counted starting from the time the treatments were administered instead of the time after last blood sample collection. As a result, the duration between two treatments was 72 hours instead of the intended 96 hours for all treatments.

FORMULATIONS: Abacavir tablets (300 mg, batch number 9ZP0016), lamivudine tablets (150 mg, batch number 9ZP0027), zidovudine tablets (300 mg, batch number 8ZP0830), and triple combination tablet (batch number 8ZX032T) were used in this study.

SAMPLE COLLECTION: Blood samples were collected at predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours postdose.

ANALYTICAL METHOD: Details regarding the analytical methodology used in the determination of abacavir, lamivudine and zidovudine concentrations are shown in the following table.

[redacted]

PHARMACOKINETIC DATA ANALYSIS: Pharmacokinetic parameters were obtained by non-compartmental methods. In subjects exhibiting quantifiable predose concentrations, the AUC contributed by the predose concentration was subtracted from the total AUC.

Analysis of variance with factors including sequence, subjects within sequence, period and treatment was employed and log transformed C_{max} and AUC values were used in the statistical analyses. The point estimates and 90% confidence intervals were obtained following analysis of variance.

Bioequivalency assessment

The median plasma abacavir, lamivudine and zidovudine concentration-time profiles following administration of the individual tablets and combination tablet are shown in Figure 1 and the results of the statistical analyses are summarized in Table 1.

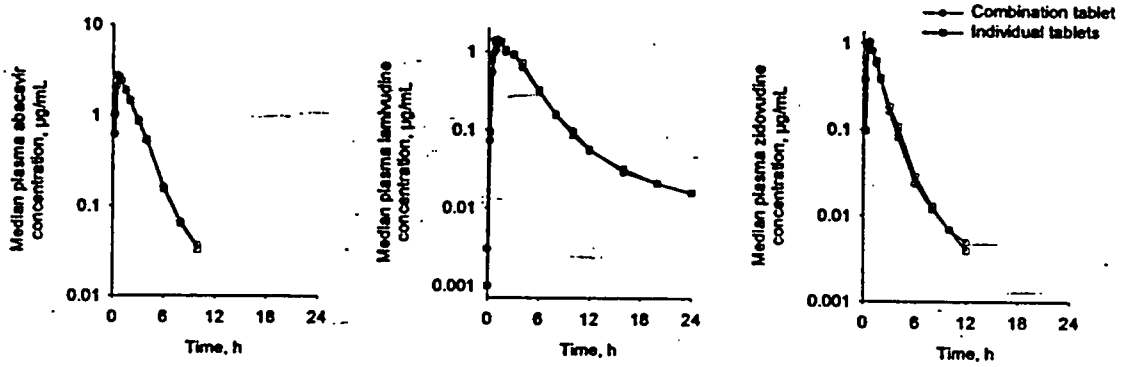


Figure 1

Table 1. Results of statistical analyses (Bioequivalency assessment)

Component	PK parameter	Formulation	Arithmetic mean (%CV)	Geometric mean	% point estimate [90% CI]
Abacavir	C_{max}, µg/mL	Individual	3.23 (30)	3.11	100
		Combined	3.29 (38)	3.10	100 [90 – 111]
	$AUC_{0-\infty}$, µg.h/mL	Individual	7.39 (38)	6.92	100
		Combined	7.31 (37)	6.87	99 [96 – 103]
Lamivudine	C_{max}, µg/mL	Individual	1.78 (41)	1.66	100
		Combined	1.57 (31)	1.49	90 [82 – 99]
	$AUC_{0-\infty}$, µg.h/mL	Individual	6.42 (27)	6.23	100
		Combined	6.04 (23)	5.92	95 [91 – 99]
Zidovudine	C_{max}, µg/mL	Individual	1.43 (48)	1.29	100
		Combined	1.36 (54)	1.24	96 [80 – 115]
	$AUC_{0-\infty}$, µg.h/mL	Individual	2.17 (33)	2.08	100
		Combined	2.07 (35)	1.97	95 [89 – 102]

Statistical analyses indicate that the proposed market formulation is bioequivalent to the three individually marketed formulations. The 90% confidence intervals for all three components were within [80 - 125] for C_{max} and AUC. However, it is noted that the upper limit of the 90% confidence interval did not include 100% in the case of lamivudine.

34 out of 72 predose lamivudine plasma concentrations were above the limit of quantification. The concentrations of 6 of the 34 samples were between ~ and ~ ng/mL and the rest were between — and ~ ng/mL. While unintentional shortening of the washout period might have accounted for some instances of measurable predose concentrations, increased sensitivity of the analytical method (LOQ of previous method = — ng/mL) appears to be responsible for a majority of measurable predose

concentrations. However, the predose concentrations account for a small fraction of the AUC_∞ (average 0.63%, range 0.25% to 1.59%). According to the Applicant, the results of the statistical tests performed after adjusting for measurable predose concentrations were identical to the results shown in Table 1. Zidovudine was measured in only one of the 72 predose samples and abacavir was not measured in any of the predose sample.

Food effect assessment

The median plasma abacavir, lamivudine and zidovudine concentration-time profiles following administration of the combination tablet under fasted and fed conditions are shown in Figure 2 and the results of the statistical analyses are summarized in Table 2.

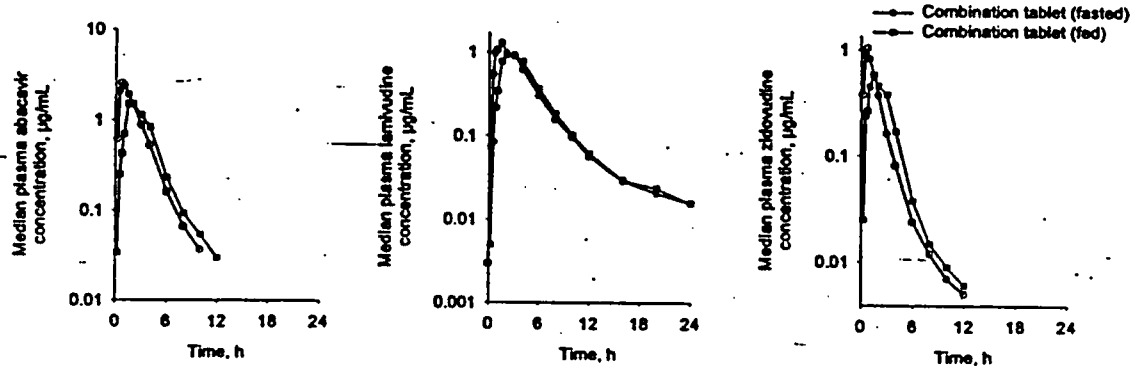


Figure 2

Table 2. Results of statistical analyses (Food effect assessment)

Component	PK parameter		Arithmetic mean (%CV)	Geometric mean	% point estimate [90% CI]
Abacavir	C_{max}, µg/mL	Fasted	3.29 (38)	3.10	100
		Fed	2.28 (37)	2.12	68 [62 – 76]
	$AUC_{0-\infty}$, µg.h/mL	Fasted	7.31 (37)	6.87	100
		Fed	6.57 (32)	6.27	91 [88 – 95]
Lamivudine	C_{max}, µg/mL	Fasted	1.57 (31)	1.49	100
		Fed	1.27 (29)	1.22	82 [75 – 90]
	$AUC_{0-\infty}$, µg.h/mL	Fasted	6.04 (23)	5.92	100
		Fed	5.60 (24)	5.47	92 [88 – 97]
Zidovudine	C_{max}, µg/mL	Fasted	1.36 (54)	1.24	100
		Fed	0.99 (51)	0.89	72 [60 – 87]
	$AUC_{0-\infty}$, µg.h/mL	Fasted	2.07 (35)	1.97	100
		Fed	2.05 (26)	1.99	101 [94 – 108]

Administration of the combination tablet immediately following a high fat meal resulted in an 18 to 32% decrease in average C_{max} values of the nucleoside analogs. However, consumption of a high fat meal had only a minor impact on the exposure to nucleoside analogs. The maximum decrease in the average AUC_∞ was less than 10%.

In the case of lamivudine and zidovudine, it should be noted that the decrease in average C_{max} and AUC_∞ with the combination tablet is no more than the decrease observed with the individual tablets (as per the package insert). According to the package insert for lamivudine, the average decrease in C_{max} when lamivudine is administered in the fed state was 40%. Similarly, according to the package insert for zidovudine, approximately 50% decrease in C_{max} was observed when zidovudine is administered in the fed state. Information contained in NDA 20977 (for abacavir)

indicates that administration of abacavir with high-fat meal results in a 25% decrease in the average C_{max}. However, with the combination tablet, the average drop in C_{max} is 32%. The impact of slightly greater decrease in C_{max} in the case of the combination tablet is not known.

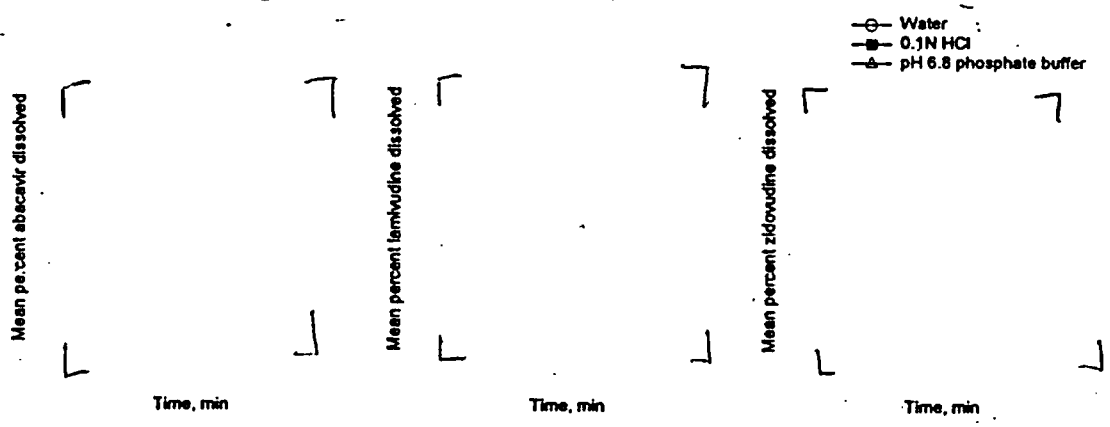
CONCLUSIONS: The conclusions of this study are:

(a) The combination tablet containing abacavir, lamivudine and zidovudine is bioequivalent to individual tablets of these nucleoside analogs.

(b) Administration of the combination tablet after a high fat meal does not affect the exposure to nucleoside analogs, but results in decreased C_{max} values. However, the decrease in average C_{max} is comparable to the decrease observed with individual drugs (as per their respective package inserts).

III. DISSOLUTION

The dissolution profiles for abacavir, lamivudine and zidovudine from the triple combination tablet using different media are shown below.



The average (range) values for the percent dissolved are shown in the following table.

	% abacavir dissolved		
	15 min.	30 min.	45 min.
Water 0.1N HCl pH 6.8 buffer	[ ]	[ ]	[ ]

	% lamivudine dissolved		
	15 min.	30 min.	45 min.
Water 0.1N HCl pH 6.8 buffer	[ ]	[ ]	[ ]

	% zidovudine dissolved		
	15 min.	30 min.	45 min.
Water 0.1N HCl pH 6.8 buffer	[ ]	[ ]	[ ]

The dissolution profiles were generated under the following conditions

Apparatus	: USP Apparatus II (Paddle)
Media	: As noted above
Volume	: 900 mL
Speed of rotation	: 75 RPM

The dissolution specification proposed by the Applicant, Q= — at 30 minutes, is acceptable. The dissolution medium will be 0.1 N HCl and the paddle speed will be 75 RPM.

The dissolution specifications for approved zidovudine, lamivudine and abacavir tablets are Q= — in 30 minutes, Q= — in 30 minutes and Q= — in — minutes, respectively.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS BRIEFING

Dr. Ajayi, Dr. Lazor, Dr. Reynolds, Dr. Selen, Dr. Tandon, and Dr. Wang attended the briefing on April 20, 2000.

RECOMMENDATION

The human pharmacokinetic studies submitted under NDA 21205 provide an understanding of the pharmacokinetics of the combination tablet containing abacavir, lamivudine and zidovudine and fulfills the requirements of Section 320 of the Code of Federal Regulations (21 CFR). The submitted pharmacokinetic information is acceptable.

/S/ 6/7/00

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/S/ 6/9/00

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cc: HFD-530 /NDA 21205
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