

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-205 / S-011

Trade Name: Trizivir

Generic Name: (abacavir, sulfate, lamivudine, and zidovudine)

Sponsor: GlaxoSmithKline

Approval Date: May 13, 2005

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APPLICATION NUMBER:

21-205 / S-011

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-205 / S-011

APPROVAL LETTER



NDA 21-205/S-011

GlaxoSmithKline
Attention: Martha Anne A. Moore, R.Ph.
Antiviral/Antibacterial US Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Moore:

Please refer to your supplemental new drug application dated July 14, 2004, received July 16, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine) Tablets.

We also acknowledge receipt of your submissions dated: 14-Jul. 2004, 23-Sep. 2004 (2), 19-Oct. 2004, 03-Feb. 2005, 03-Mar. 2005, 04-Mar. 2005, 30-Mar. 2005, 19-Apr. 2005, 28-Apr. 2005 and 04-May 2005.

This supplemental application fulfills your accelerated approval commitments as required under CFR 314.510. Specifically, this supplemental new drug application provides for the use of TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine) Tablets in combination with other antiretroviral agents or alone for the treatment of HIV-1 infection.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, this application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the medication guide). Marketing the products with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the FPL electronically according to the guidance for industry titled "*Providing Regulatory Submissions in Electronic Format – NDA.*" Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-205/S-011." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated April 19, 2005. These commitments are listed below; please address each as stated.

1. Complete and report on the ongoing pharmacogenetics assessments to identify genetic markers associated with hypersensitivity to abacavir that may have predictive value alone or in combination with HLA-B*5701 (studies CNA30027 and CNA30032) in Caucasians, Blacks, Hispanics, males and females.
 - Final report submission: by May 31, 2006
2. Supplement the previously completed work to identify genetic markers associated with hypersensitivity to abacavir in additional patient subpopulations (studies CNA30027, CNA30032 and EPV40001).
 - Final report submission: by May 31, 2006
3. Prepare and submit a summary of GlaxoSmithKline's cumulative research on possible genetic correlates of hypersensitivity to abacavir.
 - Final report submission: by May 31, 2006
4. Provide data on the genotypes and phenotypes of baseline and on-therapy isolates from patients receiving Trizivir therapy in the absence of other antiretroviral drugs. Data from study CNA3005 (96 week) will be provided in a virology report with data in the HIV resistance template format.
 - Submission of final 96 week study report and data in the HIV resistance template: by August 31, 2005

Submit clinical protocols to your IND for this product. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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If you have any questions, please contact Tanima Sinha, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely yours,

{See appended electronic signature page}

Debra Birnkrant, M.D.

Director

Division of Antiviral Drug Products

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

Attachment: Approved labeling

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Debra Birnkrant
5/13/05 01:32:41 PM
NDA 21-205

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-205 / S-011

APPROVED LABELING

PRESCRIBING INFORMATION

TRIZIVIR[®]

(abacavir sulfate, lamivudine, and zidovudine)

Tablets

WARNINGS

TRIZIVIR contains 3 nucleoside analogues (abacavir sulfate, lamivudine, and zidovudine) and is intended only for patients whose regimen would otherwise include these 3 components.

Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of TRIZIVIR. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue TRIZIVIR as soon as a hypersensitivity reaction is suspected. Permanently discontinue TRIZIVIR if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Following a hypersensitivity reaction to abacavir, NEVER restart TRIZIVIR or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of TRIZIVIR or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours (see WARNINGS and PRECAUTIONS: Information for Patients).

Hematologic Toxicity: Zidovudine has been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced Human Immunodeficiency Virus (HIV) disease (see WARNINGS). Prolonged use of zidovudine has been associated with symptomatic myopathy.

Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, zidovudine, and other antiretrovirals (see WARNINGS).

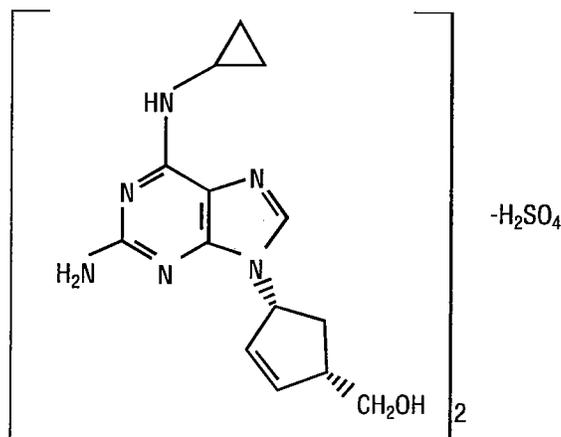
Exacerbations of Hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV) and have discontinued lamivudine, which is one component of TRIZIVIR. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue TRIZIVIR and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see WARNINGS).

DESCRIPTION

TRIZIVIR: TRIZIVIR Tablets contain the following 3 synthetic nucleoside analogues: abacavir sulfate (ZIAGEN[®]), lamivudine (also known as EPIVIR[®] or 3TC), and zidovudine (also known as TROVIR[®], azidothymidine, or ZDV) with inhibitory activity against HIV.

TRIZIVIR Tablets are for oral administration. Each film-coated tablet contains the active ingredients 300 mg of abacavir as abacavir sulfate, 150 mg of lamivudine, and 300 mg of zidovudine, and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film (Opadry® green 03B11434) that is made of FD&C Blue No. 2, hypromellose, polyethylene glycol, titanium dioxide, and yellow iron oxide.

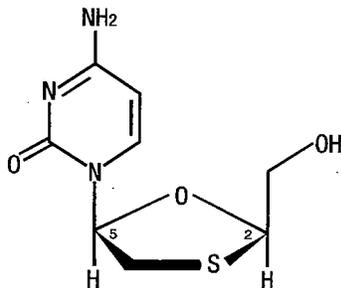
Abacavir Sulfate: The chemical name of abacavir sulfate is (1*S*,*cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with 1*S*, 4*R* absolute configuration on the cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight of 670.76 daltons. It has the following structural formula:



Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25°C.

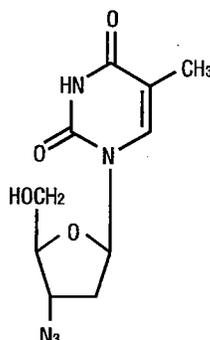
In vivo, abacavir sulfate dissociates to its free base, abacavir. In this insert, all dosages for ZIAGEN (abacavir sulfate) are expressed in terms of abacavir.

Lamivudine: The chemical name of lamivudine is (2*R*,*cis*)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3 daltons. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

Zidovudine: The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. It has a molecular formula of $C_{10}H_{13}N_5O_4$ and a molecular weight of 267.24 daltons. It has the following structural formula:



Zidovudine is a white to beige, crystalline solid with a solubility of 20.1 mg/mL in water at 25°C.

MICROBIOLOGY

Mechanism of Action:

Abacavir: Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5'-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleotide analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA polymerases α , β , and γ .

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. 3TC-TP is a weak inhibitor of cellular DNA polymerases α , β , and γ .

Zidovudine: Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is phosphorylated to its active 5'-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerases α and γ and has been reported to be incorporated into the DNA of cells in culture.

Antiviral Activity:

Abacavir: The in vitro anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50 percent (IC_{50}) ranged from 3.7 to 5.8 μ M (1 μ M = 0.28 mcg/mL) and 0.07 to 1.0 μ M against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μ M against 8 clinical isolates. The IC_{50} values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μ M, and against HIV-2 isolates, from 0.024 to 0.49 μ M. Abacavir had synergistic activity in vitro in combination with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the protease inhibitor (PI) amprenavir; and additive activity in combination with the NRTIs

didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50 μM) had no effect on the in vitro anti-HIV-1 activity of abacavir.

Lamivudine: The in vitro activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. IC_{50} values (50% inhibitory concentrations) were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg/mL). The IC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM , and against HIV-2 isolates from 0.003 to 0.120 μM . In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity. Ribavirin (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold.

Zidovudine: In vitro activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The IC_{50} and IC_{90} values for zidovudine were 0.01 to 0.49 μM (1 μM = 0.27 mcg/mL) and 0.1 to 9 μM , respectively. Zidovudine had anti-HIV-1 activity in all acute virus-cell infections tested. However, zidovudine activity was substantially less in chronically infected cell lines. The IC_{50} values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 μM , and against HIV-2 isolates from 0.00049 to 0.004 μM . In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the NRTIs abacavir, didanosine, lamivudine, and zalcitabine; the NNRTIs delavirdine and nevirapine; and the PIs indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon- α . Ribavirin has been found to inhibit the phosphorylation of zidovudine in vitro.

Resistance:

HIV-1 isolates with reduced sensitivity to abacavir, lamivudine, or zidovudine have been selected in vitro and were also obtained from patients treated with abacavir, lamivudine, and zidovudine, or the combination of lamivudine and zidovudine.

Abacavir: Genotypic analysis of isolates selected in vitro and recovered from abacavir-treated patients demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in RT contributed to abacavir resistance. In a study of subjects receiving abacavir once or twice daily in combination with lamivudine and efavirenz once daily, 39% (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7 to 13).

Lamivudine: Genotypic analysis of isolates selected in vitro and recovered from lamivudine-treated patients showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine.

Zidovudine: Genotypic analyses of the isolates selected in vitro and recovered from zidovudine-treated patients showed mutations in the HIV-1 RT gene resulting in 6 amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of mutations. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Cross-Resistance:

Cross-resistance has been observed among NRTIs.

Abacavir: Isolates containing abacavir resistance-associated mutations, namely, K65R, L74V, Y115F, and M184V, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in vitro and in patients. The K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V mutation can confer

resistance to abacavir, didanosine, and zalcitabine; and the M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

Lamivudine: Cross-resistance to abacavir, didanosine, tenofovir, and zalcitabine has been observed in some patients harboring lamivudine-resistant HIV-1 isolates. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including lamivudine, have emerged (see under Zidovudine below). Cross-resistance between lamivudine and zidovudine has not been reported.

Zidovudine: In a study of 167 HIV-infected patients, isolates (n = 2) with multidrug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from patients treated for ≥ 1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of resistance-associated mutations with such combination therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the Q151M mutation being most commonly associated with multidrug resistance. The mutation at codon 151 in combination with mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine. TAMs are selected by zidovudine and confer cross-resistance to abacavir, didanosine, stavudine, tenofovir, and zalcitabine.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults:

TRIZIVIR: In a single-dose, 3-way crossover bioavailability study of 1 TRIZIVIR tablet versus 1 ZIAGEN tablet (300 mg), 1 EPIVIR tablet (150 mg), plus 1 RETROVIR tablet (300 mg) administered simultaneously in healthy subjects (n = 24), there was no difference in the extent of absorption, as measured by the area under the plasma concentration-time curve (AUC) and maximal peak concentration (C_{max}), of all 3 components. One TRIZIVIR tablet was bioequivalent to 1 ZIAGEN tablet (300 mg), 1 EPIVIR tablet (150 mg), plus 1 RETROVIR tablet (300 mg) following single-dose administration to fasting healthy subjects (n = 24).

Abacavir: Following oral administration, abacavir is rapidly absorbed and extensively distributed. Binding of abacavir to human plasma proteins is approximately 50%. Binding of abacavir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5'-carboxylic acid and glucuronyl transferase to form the 5'-glucuronide.

Lamivudine: Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

Zidovudine: Following oral administration, zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is 3'-azido-3'-deoxy-5'-O- β -D-glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively. A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one fifth of the zidovudine AUC.

In humans, abacavir, lamivudine, and zidovudine are not significantly metabolized by cytochrome P450 enzymes.

The pharmacokinetic properties of abacavir, lamivudine, and zidovudine in fasting patients are summarized in Table 1.

Table 1. Pharmacokinetic Parameters* for Abacavir, Lamivudine, and Zidovudine in Adults

Parameter	Abacavir		Lamivudine		Zidovudine	
	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n
Oral bioavailability (%)	86 ± 25	n = 6	86 ± 16	n = 12	64 ± 10	n = 5
Apparent volume of distribution (L/kg)	0.86 ± 0.15	n = 6	1.3 ± 0.4	n = 20	1.6 ± 0.6	n = 8
Systemic clearance (L/hr/kg)	0.80 ± 0.24	n = 6	0.33 ± 0.06	n = 20	1.6 ± 0.6	n = 6
Renal clearance (L/hr/kg)	.007 ± .008	n = 6	0.22 ± 0.06	n = 20	0.34 ± 0.05	n = 9
Elimination half-life (hr) [†]	1.45 ± 0.32	n = 20	5 to 7		0.5 to 3	

*Data presented as mean ± standard deviation except where noted.

[†] Approximate range.

Effect of Food on Absorption of TRIZIVIR:

TRIZIVIR may be administered with or without food. Administration with food in a single-dose bioavailability study resulted in lower C_{max} , similar to results observed previously for the reference formulations. The average [90% CI] decrease in abacavir, lamivudine, and zidovudine C_{max} was 32% [24% to 38%], 18% [10% to 25%], and 28% [13% to 40%], respectively, when administered with a high-fat meal, compared to administration under fasted conditions. Administration of TRIZIVIR with food did not alter the extent of abacavir, lamivudine, and zidovudine absorption (AUC), as compared to administration under fasted conditions (n = 24).

Special Populations:

Impaired Renal Function:

TRIZIVIR: Because lamivudine and zidovudine require dose adjustment in the presence of renal insufficiency, TRIZIVIR is not recommended for use in patients with creatinine clearance <50 mL/min (see PRECAUTIONS).

Impaired Hepatic Function:

TRIZIVIR: A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Abacavir is contraindicated in patients with moderate to severe hepatic impairment and dose reduction is required in patients with mild hepatic impairment. Because TRIZIVIR is a fixed-dose combination that cannot be adjusted for this patient population, TRIZIVIR is contraindicated for patients with impaired hepatic function.

Pregnancy: See PRECAUTIONS: Pregnancy.

Abacavir and Lamivudine: No data are available on the pharmacokinetics of abacavir or lamivudine during pregnancy.

Zidovudine: Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine were similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. In a nonpregnant adult population, a potential for interaction has been identified (see CLINICAL PHARMACOLOGY: Drug Interactions).

Nursing Mothers: See PRECAUTIONS: Nursing Mothers.

Abacavir: No data are available on the pharmacokinetics of abacavir in nursing mothers.

Lamivudine: Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Zidovudine: After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum.

Pediatric Patients:

TRIZIVIR: TRIZIVIR is not intended for use in pediatric patients. TRIZIVIR should not be administered to adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be dose adjusted for this patient population (see PRECAUTIONS: Pediatric Use).

Geriatric Patients: The pharmacokinetics of abacavir, lamivudine, and zidovudine have not been studied in patients over 65 years of age.

Gender:

Abacavir: A population pharmacokinetic analysis in HIV-infected male (n = 304) and female (n = 67) patients showed no gender differences in abacavir AUC normalized for lean body weight.

Lamivudine and Zidovudine: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no gender differences in zidovudine exposure (AUC_{∞}) or lamivudine AUC_{∞} normalized for body weight.

Race:

Abacavir: There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics.

Lamivudine: There are no significant racial differences in lamivudine pharmacokinetics.

Zidovudine: The pharmacokinetics of zidovudine with respect to race have not been determined.

Drug Interactions: See PRECAUTIONS: Drug Interactions. The drug interactions described are based on studies conducted with the individual nucleoside analogues. In humans, abacavir, lamivudine, and zidovudine are not significantly metabolized by cytochrome P450 enzymes; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Abacavir: Due to the common metabolic pathways of abacavir and zidovudine via glucuronyl transferase, 15 HIV-infected patients were enrolled in a crossover study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently 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.

Lamivudine and Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).

Table 2. Effect of Coadministered Drugs on Abacavir, Lamivudine, and Zidovudine AUC*
Note: ROUTINE DOSE MODIFICATION OF ABACAVIR, LAMIVUDINE, AND ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	Lamivudine Dose	n	Lamivudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 150 mg	11	↑10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	single 300 mg	14	↑43%	90% CI: 32% to 55%	↔
Drugs That May Alter Zidovudine Blood Concentrations					
Coadministered Drug and Dose	Zidovudine Dose	n	Zidovudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑31%	Range 23% to 78% [†]	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑43%	Range 16% to 64% [†]	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑106%	Range 100% to 170% [†]	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑80%	Range 64% to 130% [†]	Not Assessed
Drugs That May Alter Abacavir Blood Concentrations					
Coadministered Drug and Dose	Abacavir Dose	n	Abacavir Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Ethanol 0.7 g/kg	single 600 mg	24	↑41%	90% CI: 35% to 48%	↔

↑ = Increase; ↓ = Decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.

*See PRECAUTIONS: Drug Interactions for additional information on drug interactions.

[†]Estimated range of percent difference.

INDICATIONS AND USAGE

TRIZIVIR is indicated in combination with other antiretrovirals or alone for the treatment of HIV-1 infection.

Additional important information on the use of TRIZIVIR for treatment of HIV-1 infection:

- TRIZIVIR is one of multiple products containing abacavir. Before starting TRIZIVIR, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.
- Limited data exist on the use of TRIZIVIR alone in patients with higher baseline viral load levels (>100,000 copies/mL, see Description of Clinical Studies).

Description of Clinical Studies:

TRIZIVIR: The following study was conducted with the individual components of TRIZIVIR (see CLINICAL PHARMACOLOGY for information about bioequivalence of TRIZIVIR).

CNA3005 was a multicenter, double-blind, controlled study in which 562 HIV-infected, therapy-naive adults 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. The study was stratified at randomization by pre-entry plasma HIV-1 RNA 10,000 to 100,000 copies/mL and plasma HIV-1 RNA >100,000 copies/mL. Study participants were male (87%), Caucasian (73%), black (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 Table 3.

Table 3. Outcomes of Randomized Treatment Through Week 48 (CNA3005)

Outcome	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 265)
Responder*	49%	50%
Virologic failure [†]	31%	28%
Discontinued due to adverse reactions	10%	12%
Discontinued due to other reasons [‡]	11%	10%

*Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL.

[†]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, clinical progression, and other.

Treatment response by plasma HIV-1 RNA strata is shown in Table 4.

Table 4. Proportions of Responders Through Week 48 By Screening Plasma HIV-1 RNA Levels (CNA3005)

Screening HIV-1 RNA (copies/mL)	ZIAGEN plus Lamivudine/Zidovudine (n = 262)		Indinavir plus Lamivudine/Zidovudine (n = 265)	
	<400 copies/mL	n	<400 copies/mL	n
≥10,000 - ≤100,000	50%	166	48%	165
>100,000	48%	96	52%	100

In subjects with baseline viral load >100,000 copies/mL, percentages of patients with HIV-1 RNA levels <50 copies/mL were 31% in the group receiving abacavir vs. 45% in the group receiving indinavir.

Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells/mm³ was observed in both treatment arms. Through Week 48, 9 subjects (3.4%) in the group receiving abacavir sulfate (6 CDC classification C events and 3 deaths) and 3 subjects (1.5%) in the group receiving indinavir (2 CDC classification C events and 1 death) experienced clinical disease progression.

CONTRAINDICATIONS

TRIZIVIR Tablets are contraindicated in patients with previously demonstrated hypersensitivity to abacavir or to any other component of the product (see WARNINGS).

Following a hypersensitivity reaction to abacavir, NEVER restart TRIZIVIR or any other abacavir-containing product. Fatal rechallenge reactions have been associated with readministration of abacavir to patients with a prior history of a hypersensitivity reaction to abacavir (see WARNINGS and PRECAUTIONS).

TRIZIVIR Tablets are contraindicated in patients with hepatic impairment (see CLINICAL PHARMACOLOGY).

WARNINGS

Hypersensitivity Reaction: Serious and sometimes fatal hypersensitivity reactions have been associated with TRIZIVIR and other abacavir-containing products. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue TRIZIVIR if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

Signs and Symptoms of Hypersensitivity: Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups.

Group 1: Fever

Group 2: Rash

Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)

Group 4: Constitutional (including generalized malaise, fatigue, or achiness)

Group 5: Respiratory (including dyspnea, cough, or pharyngitis)

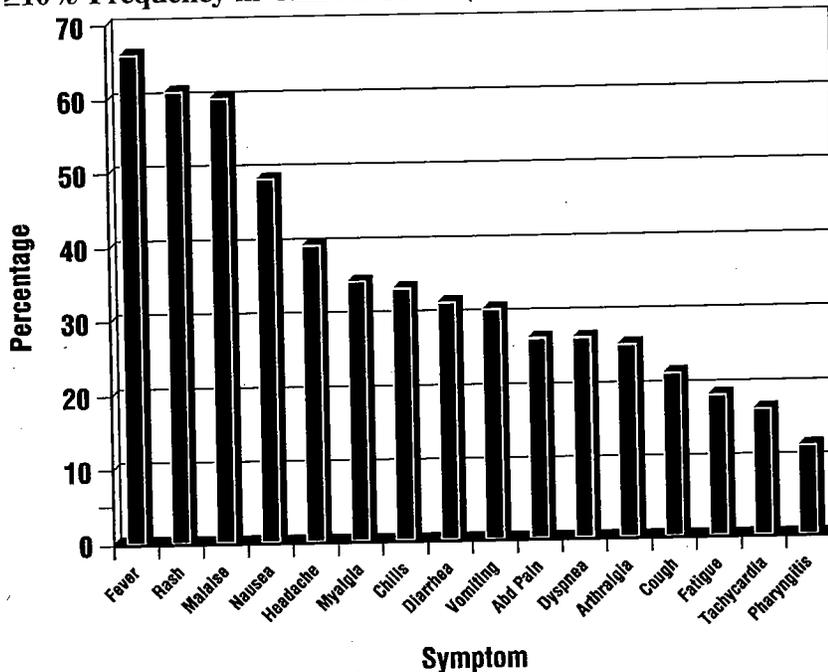
Hypersensitivity to abacavir following the presentation of a single sign or symptom has been reported infrequently.

Hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients (n = 206) in 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data collection module. The frequencies of symptoms are shown in Figure 2. Symptoms usually appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at any time during therapy. Median time to onset was 9 days; 89% appeared within the first 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.

A recent study with ZIAGEN used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the study, suspected hypersensitivity to abacavir was reported

by investigators in 9% of 324 patients in the abacavir group and 3% of 325 patients in the zidovudine group.

Figure 2: Hypersensitivity-Related Symptoms Reported with $\geq 10\%$ Frequency in Clinical Trials (n = 206 Patients)



Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions.

Physical findings associated with hypersensitivity to abacavir in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash. Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

Clinical Management of Hypersensitivity: Discontinue TRIZIVIR as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue TRIZIVIR if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications). Following a hypersensitivity reaction to abacavir, NEVER restart TRIZIVIR or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

When therapy with TRIZIVIR has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of abacavir is under consideration, carefully evaluate the reason for discontinuation to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, DO NOT reintroduce abacavir. If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued

monitoring for symptoms of a hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of abacavir and that abacavir reintroduction needs to be undertaken only if medical care can be readily accessed by the patient or others.

Abacavir Hypersensitivity Reaction Registry: To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. Physicians should register patients by calling 1-800-270-0425.

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, zidovudine, and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering TRIZIVIR to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with TRIZIVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Bone Marrow Suppression: Since TRIZIVIR contains zidovudine, TRIZIVIR should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count $<1,000$ cells/mm³ or hemoglobin <9.5 g/dL. Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with TRIZIVIR. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended.

Myopathy: Myopathy and myositis, with pathological changes similar to that produced by HIV disease, have been associated with prolonged use of zidovudine, and therefore may occur with therapy with TRIZIVIR.

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-infected patients treated with lamivudine for chronic HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

Other: TRIZIVIR contains fixed doses of 3 nucleoside analogues: abacavir, lamivudine, and zidovudine and should not be administered concomitantly with abacavir, lamivudine, emtricitabine, or zidovudine. TRIZIVIR should also not be administered concomitantly with the fixed-dose combination drugs: lamivudine/zidovudine (COMBIVIR), abacavir and lamivudine (EPZICOM™), or emtricitabine and tenofovir (TRUVADA®).

Because TRIZIVIR is a fixed-dose tablet, it should not be prescribed for adolescents who weigh less than 40 kg or other patients requiring dosage adjustment.

The complete prescribing information for all agents being considered for use with TRIZIVIR should be consulted before combination therapy with TRIZIVIR is initiated.

PRECAUTIONS

Therapy-Experienced Patients:

Abacavir: In clinical trials, patients with prolonged prior nucleoside reverse transcriptase inhibitor (NRTI) exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients (see MICROBIOLOGY: Cross-Resistance).

Patients with HIV and Hepatitis B Virus Coinfection:

Lamivudine: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see EPIVIR-HBV[®] package insert for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

Patients with Impaired Renal Function:

TRIZIVIR: Since TRIZIVIR is a fixed-dose tablet and the dosage of the individual components cannot be altered, patients with creatinine clearance <50 mL/min should not receive TRIZIVIR.

Patients with Impaired Hepatic Function:

TRIZIVIR: TRIZIVIR is contraindicated in patients with hepatic impairment since it is a fixed-dose tablet and the dosage of the individual components cannot be altered.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including TRIZIVIR. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Fat Redistribution: Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information for Patients:

Abacavir: Hypersensitivity Reaction: Inform patients:

- that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of TRIZIVIR, and encourage the patient to read the Medication Guide and Warning Card every time to obtain any new

information that may be present about TRIZIVIR. (The complete text of the Medication Guide is reprinted at the end of this document.)

- **to carry the Warning Card with them.**
- how to identify a hypersensitivity reaction (see WARNINGS and MEDICATION GUIDE).
- that if they develop symptoms consistent with a hypersensitivity reaction to discontinue treatment with TRIZIVIR and seek medical evaluation immediately.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if TRIZIVIR is not immediately discontinued.
- **to not restart TRIZIVIR or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.**
- that a hypersensitivity reaction is usually reversible if it is detected promptly and TRIZIVIR is stopped right away.
- that if they have interrupted TRIZIVIR for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- to not restart TRIZIVIR or any other abacavir-containing product without medical consultation and that restarting abacavir needs to be undertaken only if medical care can be readily accessed by the patient or others.
- TRIZIVIR should not be co-administered with COMBIVIR, EMTRIVA™, EPIVIR, EPIVIR-HBV, EPZICOM, RETROVIR, TRUVADA, or ZIAGEN.

Lamivudine: Patients co-infected with HIV and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician.

Zidovudine: Patients should be informed that the important toxicities associated with zidovudine are neutropenia and/or anemia. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced HIV disease.

TRIZIVIR: Inform patients that some HIV medicines, including TRIZIVIR can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly).

TRIZIVIR is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using TRIZIVIR. Advise patients that the use of TRIZIVIR has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

TRIZIVIR Tablets are for oral ingestion only.

Patients should be advised of the importance of taking TRIZIVIR exactly as it is prescribed.

Drug Interactions:

TRIZIVIR: No clinically significant changes to pharmacokinetic parameters were observed for abacavir, lamivudine, or zidovudine when administered together.

Abacavir: Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure (see CLINICAL PHARMACOLOGY: Drug Interactions).

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently 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.

Lamivudine: Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has been shown to increase lamivudine exposure (AUC). The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see CLINICAL PHARMACOLOGY).

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of TRIZIVIR in combination with zalcitabine is not recommended.

Zidovudine: Coadministration of ganciclovir, interferon- α , 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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Carcinogenicity:

Abacavir: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection.

Zidovudine: Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg per day on day 91 and then to 300 mg/kg/day on day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and

lactation with dosing continuing in offspring for 24 months postnatally. At these doses, exposures were approximately 3 times the estimated human exposure at the recommended doses. After 24 months at the 40-mg/kg/day dose, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity:

Abacavir: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y/TK^{+/-} mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Lamivudine: Lamivudine was mutagenic in an L5178Y/TK^{+/-} mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was negative in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Zidovudine: Zidovudine was mutagenic in an L5178Y/TK^{+/-} mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Impairment of Fertility:

Abacavir: Abacavir had no adverse effects on the mating performance or fertility of male and female rats at a dose approximately 8 times the human exposure at the recommended dose based on body surface area comparisons.

Lamivudine: In a study of reproductive performance, lamivudine, administered to male and female rats at doses up to 130 times the usual adult dose based on body surface area considerations, revealed no evidence of impaired fertility judged by conception rates and no effect on the survival, growth, and development to weaning of the offspring.

Zidovudine: Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

Pregnancy: Pregnancy Category C. There are no adequate and well-controlled studies of TRIZIVIR in pregnant women. Reproduction studies with abacavir, lamivudine, and zidovudine have been performed in animals (see Abacavir, Lamivudine, and Zidovudine sections below). TRIZIVIR should be used during pregnancy only if the potential benefits outweigh the risks.

Abacavir: Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced crown-rump length) were observed in rats at a dose which produced 35 times the human exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at half of the above-mentioned

dose in separate fertility studies conducted in rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 8.5 times the human exposure at the recommended dose based on AUC.
human exposure,

Lamivudine: Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryoletality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times that in humans.

Zidovudine: Reproduction studies with orally administered zidovudine in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of approximately 3,700 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less. Two rodent carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, and Impairment of Fertility).

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to TRIZIVIR or other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

Abacavir, Lamivudine, and Zidovudine: Lamivudine and zidovudine are excreted in human breast milk; abacavir and lamivudine are secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving TRIZIVIR.**

Pediatric Use: TRIZIVIR is not intended for use in pediatric patients. TRIZIVIR should not be administered to adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be adjusted for this patient population.

Therapy-Experienced Pediatric Patients: A randomized, double-blind study, CNA3006, compared ZIAGEN plus lamivudine and zidovudine versus lamivudine and zidovudine in pediatric patients, most of whom were extensively pretreated with nucleoside analogue antiretroviral agents. Patients in this study had a limited response to abacavir.

Geriatric Use: Clinical studies of abacavir, lamivudine, and zidovudine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug

therapy. TRIZIVIR is not recommended for patients with impaired renal function (i.e., creatinine clearance <50 mL/min; see PRECAUTIONS: Patients with Impaired Renal Function and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Hypersensitivity Reaction: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of TRIZIVIR (see WARNINGS and PRECAUTIONS: Information for Patients).

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a $\geq 5\%$ frequency during therapy with abacavir 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 CNA3005 are listed in Table 5.

Table 5. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, $\geq 5\%$ Frequency) in Therapy-Naive Adults (CNA3005) Through 48 Weeks of Treatment

Adverse Reaction	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Nausea	19%	17%
Headache	13%	9%
Malaise and fatigue	12%	12%
Nausea and vomiting	10%	10%
Hypersensitivity reaction	8%	2%
Diarrhea	7%	5%
Fever and/or chills	6%	3%
Depressive disorders	6%	4%
Musculoskeletal pain	5%	7%
Skin rashes	5%	4%
Ear/nose/throat infections	5%	4%
Viral respiratory infections	5%	5%
Anxiety	5%	3%
Renal sign/symptoms	<1%	5%
Pain (non-site-specific)	<1%	5%

Five patients receiving abacavir in study CNA3005 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.

Laboratory Abnormalities: Laboratory abnormalities in study CNA3005 are listed in Table 6.

Table 6. Treatment-Emergent Laboratory Abnormalities (Grades 3-4) in Study CNA3005

Grade 3/4 Laboratory Abnormalities	Number of Subjects by Treatment Group	
	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Elevated CPK (>4 x ULN)	18 (7%)	18 (7%)
ALT (>5.0 x ULN)	16 (6%)	16 (6%)
Neutropenia (<750/mm ³)	13 (5%)	13 (5%)
Hypertriglyceridemia (>750 mg/dL)	5 (2%)	3 (1%)
Hyperamylasemia (>2.0 x ULN)	5 (2%)	1 (<1%)
Hyperglycemia (>13.9 mmol/L)	2 (<1%)	2 (<1%)
Anemia (Hgb ≤6.9 g/dL)	0 (0%)	3 (1%)

ULN = Upper limit of normal.

ANC = Absolute neutrophil count.

n = Number of patients assessed.

Other Adverse Events: In addition to adverse reactions in Tables 5 and 6, other adverse events observed in the expanded access program for abacavir were pancreatitis and increased GGT.

Observed During Clinical Practice: The following events have been identified during post-approval use of abacavir, lamivudine, and/or zidovudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine and/or zidovudine.

Abacavir: Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

There have also been reports of erythema multiforme with abacavir use.

Abacavir, Lamivudine, and/or Zidovudine:

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).

Cardiovascular: Cardiomyopathy.

Digestive: Stomatitis.

Endocrine and Metabolic: Gynecomastia, hyperglycemia.

Gastrointestinal: Anorexia and/or decreased appetite, abdominal pain, dyspepsia, oral mucosal pigmentation.

General: Vasculitis, weakness.

Hemic and Lymphatic: Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly, thrombocytopenia.

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, elevated bilirubin, elevated transaminases, pancreatitis, posttreatment exacerbation of hepatitis B (see WARNINGS).

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Arthralgia, myalgia, muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Dizziness, paresthesia, peripheral neuropathy, seizures.

Psychiatric: Insomnia and other sleep disorders.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

OVERDOSAGE

Abacavir: There is no known antidote for abacavir. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

Lamivudine: One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

Zidovudine: Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. The only consistent findings were nausea and vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy, and confusion. Hematologic changes were transient. All patients recovered. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, GZDV, is enhanced.

DOSAGE AND ADMINISTRATION

A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill. To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. Physicians should register patients by calling 1-800-270-0425.

The recommended oral dose of TRIZIVIR for adults and adolescents is 1 tablet twice daily. TRIZIVIR is not recommended in adolescents who weigh less than 40 kg because it is a fixed-dose tablet.

Dose Adjustment: Because it is a fixed-dose tablet, TRIZIVIR should not be prescribed for patients requiring dosage adjustment such as those with creatinine clearance <50 mL/min, patients with hepatic impairment, or patients experiencing dose-limiting adverse events.

HOW SUPPLIED

TRIZIVIR is available as tablets. Each tablet contains 300 mg of abacavir as abacavir sulfate, 150 mg of lamivudine, and 300 mg of zidovudine. The tablets are blue-green capsule-shaped, film-coated, and imprinted with GX LL1 on one side with no markings on the reverse side. They are packaged as follows:

Bottles of 60 Tablets (NDC 0173-0691-00).

Convenience Pack containing 60 Tablets on one blister roll (NDC 0173-0691-20).

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

ANIMAL TOXICOLOGY

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.



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Lamivudine is manufactured under agreement from
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Basingstoke, UK

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Date of Issue

RL-

MEDICATION GUIDE

TRIZIVIR® (TRY-zih-veer) Tablets

Generic name: abacavir sulfate, lamivudine, and zidovudine

Read the Medication Guide that comes with Trizivir before you start taking it and each time you get a refill because there may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. Be sure to carry your Trizivir Warning Card with you at all times.

What is the most important information I should know about Trizivir?

- **Serious Allergic Reaction to Abacavir.** Trizivir contains abacavir (also contained in Ziagen® and Epzicom™). Patients taking Trizivir may have a serious allergic reaction (hypersensitivity reaction) that can cause death. **If you get a symptom from 2 or more of the following groups while taking Trizivir, stop taking Trizivir and call your doctor right away.**

	Symptom(s)
Group 1	Fever
Group 2	Rash
Group 3	Nausea, vomiting, diarrhea, abdominal (stomach area) pain
Group 4	Generally ill feeling, extreme tiredness, or achiness
Group 5	Shortness of breath, cough, sore throat

A list of these symptoms is on the Warning Card your pharmacist gives you. Carry this Warning Card with you.

If you stop Trizivir because of an allergic reaction, NEVER take Trizivir (abacavir sulfate, lamivudine, and zidovudine) or any other abacavir-containing medicine (Ziagen, Epzicom) again. If you take Trizivir or any other abacavir-containing medicine again after you have had an allergic reaction, **WITHIN HOURS** you may get life-threatening symptoms that may include **very low blood pressure or death.**

If you stop Trizivir, for any other reason, even for a few days, and you are not allergic to abacavir, talk with your doctor before taking it again. Taking Trizivir again can cause a serious or life-threatening reaction, even if you never had an allergic reaction to it before. If your doctor tells you that you can take Trizivir again, **start taking it when you are around medical help or people who can call a doctor if you need one.**

- **Blood problems.** Retrovir®, one of the medicines in Trizivir, can cause serious blood cell problems. These include reduced numbers of white blood cells (neutropenia) and extremely reduced numbers of red blood cells (anemia). These blood cell problems are especially likely to happen in patients with advanced HIV disease or AIDS. Your doctor should be checking your blood cell counts regularly while you are taking Trizivir. This is especially important if you have advanced HIV or AIDS. This is to make sure that any blood cell problems are found quickly.

- **Lactic Acidosis.** Some HIV medicines, including Trizivir, can cause a rare but serious condition called **lactic acidosis with liver enlargement (hepatomegaly)**. Nausea and tiredness that don't get better may be symptoms of lactic acidosis. In some cases this condition can cause death. Women, overweight people, and people who have taken HIV medicines like Trizivir for a long time have a higher chance of getting lactic acidosis and liver enlargement. Lactic acidosis is a medical emergency and must be treated in the hospital.
- **Worsening of hepatitis B virus (HBV) infection.** Patients with HBV infection who take Trizivir and then stop it, may get "flare-ups" of their hepatitis. "Flare-up" is when the disease suddenly returns in a worse way than before. If you have HBV infection, your doctor should closely monitor your liver function for several months after stopping Trizivir. You may need to take anti-HBV medicines.
- **Muscle weakness (myopathy).** Retrovir, one of the medicines in Trizivir, can cause muscle weakness. This can be a serious problem.

Trizivir can have other serious side effects. Be sure to read the section below entitled "What are the possible side effects of Trizivir?"

What is Trizivir?

Trizivir is a prescription medicine used to treat HIV infection. Trizivir includes 3 medicines: Ziagen (abacavir), Epivir[®] (lamivudine or 3TC), and Retrovir[®] (zidovudine, AZT, or ZDV). See the end of this Medication Guide for a complete list of ingredients in Trizivir. All 3 of these medicines are called nucleoside analogue reverse transcriptase inhibitors (NRTIs). When used together, they help lower the amount of HIV in your blood. This helps to keep your immune system as healthy as possible so it can fight infection.

Different combinations of medicines are used to treat HIV infection. You and your doctor should discuss which combination of medicines is best for you.

- **Trizivir does not cure HIV infection or AIDS.** We do not know if Trizivir will help you live longer or have fewer of the medical problems that people get with HIV or AIDS. It is very important that you see your doctor regularly while you are taking Trizivir.
- **Trizivir does not lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood.** For your health and the health of others, it is important to always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

Who should not take Trizivir?

Do not take Trizivir if you:

- **have ever had a serious allergic reaction (a hypersensitivity reaction) to Trizivir or any other medicine (Ziagen, Epzicom) that has abacavir as an ingredient.** See the end of this Medication Guide for a complete list of ingredients in Trizivir. If you have had such a reaction, return all of your unused Trizivir to your doctor or pharmacist.
- **have a liver that does not function properly**
- **are an adolescent who weighs less than 90 pounds.**

Before starting Trizivir, tell your doctor about all your medical problems, including if you:

- **are pregnant or planning to become pregnant.** We do not know if Trizivir will harm your unborn child. You and your doctor will need to decide if Trizivir is right for you. If you use Trizivir while you are pregnant, talk to your doctor about how you can be on the Antiviral Pregnancy Registry for Trizivir.
- **are breastfeeding.** Some of the ingredients in Trizivir can be passed to your baby in your breast milk. It is not known if they could harm your baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.
- **have liver problems including hepatitis B virus infection.**
- **have kidney problems.**
- **Have low blood cell counts (bone marrow problem).** Ask your doctor if you are not sure.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take:

- **methadone**
- **trimethoprim (TMP/sulfamethoxazole (SMX) (Bactrim[®], Septra[®])**
- **ganciclovir (Cytovene[®], DHPG)**
- **interferon-alfa**
- **doxorubicin (Adriamycin[®]).**
- **ribavirin (Copegus[®], Rebetol[®], Virazole[®])**
- **any bone marrow suppressive medicines or cytotoxic medicines.** Ask your doctor if you are not sure.
- **any of the following anti-HIV medicines: Combivir[®] (lamivudine and zidovudine), Emtriva[™] (emtricitabine), Epivir or Epivir-HBV[®] (lamivudine, 3TC), Epzicom (abacavir sulfate and lamivudine), Hivid[®] (zalcitabine, ddC), Retrovir (zidovudine, AZT, or ZDV), Truvada[®] (emtricitabine and tenofovir), Zerit[®] (stavudine, d4T), or Ziagen (abacavir sulfate).**

How should I take Trizivir?

- **Take Trizivir by mouth exactly as your doctor prescribes it.** The usual dosage is 1 tablet twice a day. Do not skip doses.
- **You can take Trizivir with or without food.**
- **If you miss a dose of Trizivir, take the missed dose right away. Then, take the next dose at the usual scheduled time.**
- **Do not let your Trizivir run out.** If you stop your anti-HIV medicines, even for a short time, the amount of virus in your blood may increase and the virus may become harder to treat.
- **Starting Trizivir again can cause a serious allergic reaction or life-threatening reaction, even if you have never had an allergic reaction to it before.** If you run out of Trizivir even for a few days, you must ask your doctor if you can start Trizivir again. If your doctor tells you that you can take Trizivir again, start taking it when you are around medical help or people who can call a doctor if you need one.
- **If you take too much Trizivir, call your doctor or poison control center right away.**

What should I avoid while taking Trizivir?

Do not take **Combivir** (lamivudine and zidovudine), **Epivir** (lamivudine, 3TC), **Epzicom** (abacavir sulfate and lamivudine), **Retrovir** (zidovudine, AZT, or ZDV), or **Ziagen** (abacavir sulfate) while taking Trizivir. These medicines are already in Trizivir.

Avoid doing things that can spread HIV infection, as Trizivir does not stop you from passing the HIV infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Some of the medicines in Trizivir can be passed to babies in breast milk and could harm the baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.

What are the possible side effects of Trizivir?

Trizivir can cause the following serious side effects. See "What is the most important information I should know about Trizivir?" at the beginning of this Medication Guide.

- **Serious allergic reaction that can cause death.**
- **Lactic acidosis with liver enlargement (hepatomegaly) that can cause death.**
- **Blood problems**
- **Muscle weakness.**
- **Changes in body fat.** These changes have happened in patients taking antiretroviral medicines like Trizivir. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

The most common side effects of taking the medicines in Trizivir together are nausea, vomiting, diarrhea, loss of appetite, weakness or tiredness, headache, dizziness, pain or tingling of the hands or feet, and muscle and joint pain.

This list of side effects is not complete. Ask your doctor or pharmacist for more information.

How should I store Trizivir?

- Store Trizivir between 59° to 86°F (15° to 30°C).
- **Keep Trizivir and all medicines out of the reach of children.**

General information for safe and effective use of Trizivir

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use Trizivir for a condition for which it was not prescribed. Do not give Trizivir to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Trizivir. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for the information that is written for healthcare professionals or call 1-888-825-5249.

What are the ingredients in Trizivir?

Active ingredients: abacavir sulfate, lamivudine, and zidovudine

Inactive ingredients: Each film-coated Trizivir Tablet contains the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film (Opadry® green 03B11434) that is made of FD&C Blue No. 2, hypromellose, polyethylene glycol, titanium dioxide, and yellow iron oxide.



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Date of Issue MG-

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

(Front of card)

WARNING CARD

TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine) Tablets

Patients taking Trizivir may have a serious allergic reaction (hypersensitivity reaction) that can cause death. If you get a symptom from 2 or more of the following groups while taking Trizivir, stop taking Trizivir and call your doctor right away.

	Symptom(s)
Group 1	Fever
Group 2	Rash
Group 3	Nausea, vomiting, diarrhea, or abdominal (stomach area) pain
Group 4	Generally ill feeling, extreme tiredness, or achiness
Group 5	Shortness of breath, cough, or sore throat

Always carry this Warning Card with you to help recognize symptoms of this allergic reaction.

(Back of Card)

WARNING CARD

TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine) Tablets

If you must stop treatment with Trizivir because you have had an allergic reaction to abacavir, **NEVER** take Trizivir or any other abacavir-containing medicine (Ziagen®, Ezicom) again. . If you take Trizivir or

another abacavir-containing medicine again after you have had an allergic reaction, **WITHIN HOURS** you may get life-threatening symptoms that may include very low blood pressure or death. You should return all of your unused Trizivir to your doctor or pharmacist for proper disposal.

Please read the Medication Guide for additional information on Trizivir.

Date of Issue

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-205 / S-011

MEDICAL REVIEW

CLINICAL REVIEW

Application Type sNDA
Submission Number 21-205
Submission Code SE7

Letter Date July 14, 2004
Stamp Date July 14, 2004
PDUFA Goal Date May 16, 2005

Reviewer Name Anitra P. Denson, MD
Review Completion Date March 10, 2005

Established Name abacavir sulfate
lamivudine
zidovudine
(Proposed) Trade Name Trizivir
Therapeutic Class nucleoside reverse transcriptase
inhibitor
Applicant Glaxo-Smith-Kline

Priority Designation S

Formulation Fixed dose combination tablet
abacavir 300 mg
lamivudine 150 mg
zidovudine 300 mg

Clinical Review
Anitra P. Denson, MD
21-205 SE7-011
Trizivir

Dosing Regimen	One tablet orally twice daily
Indication	Combination or single treatment of HIV-1
Intended Population	adults and adolescents

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1 Executive Summary

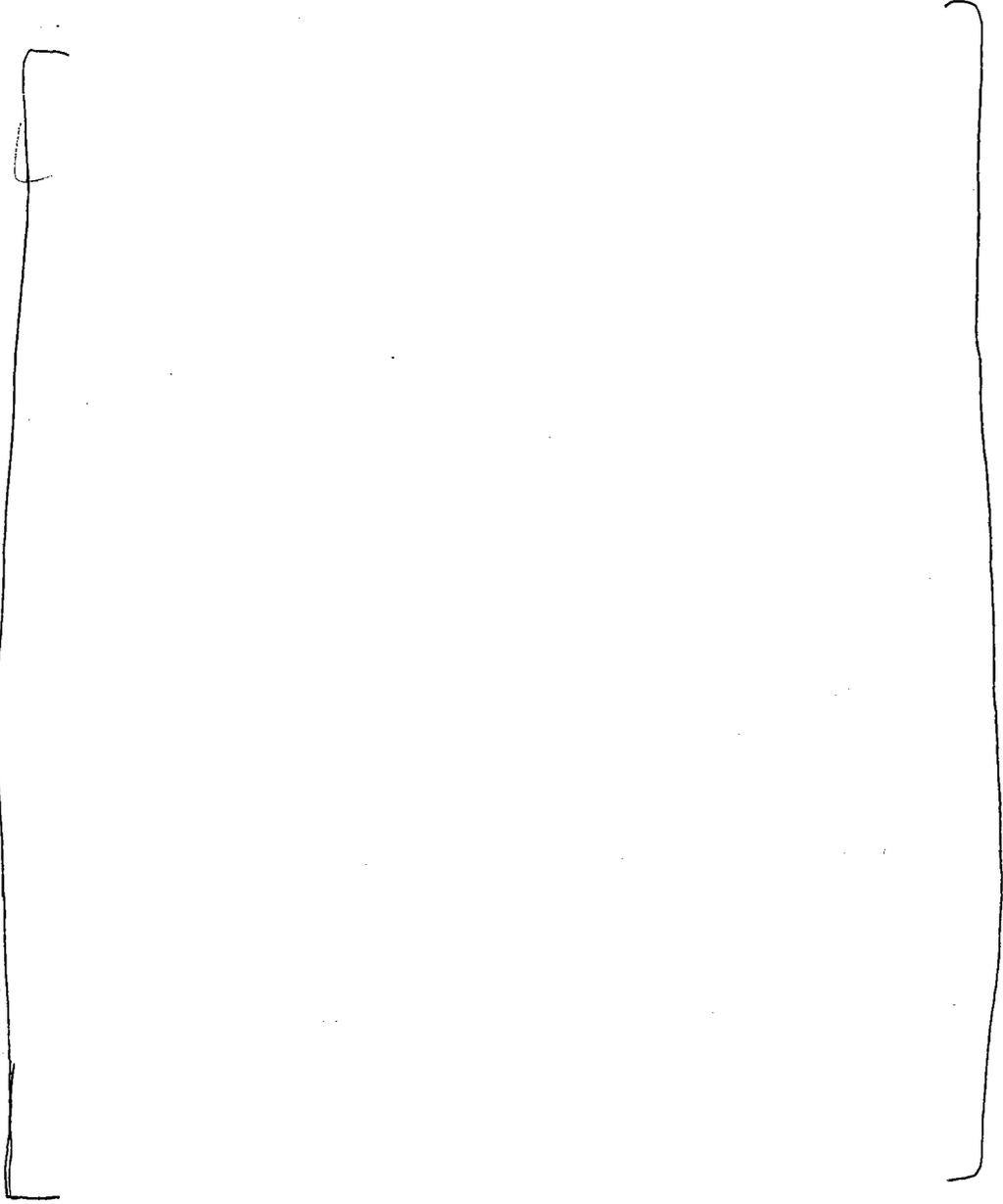
1.1 Recommendation on Regulatory Action

Based on the information provided in this submission, the application is being recommended for approval with labeling changes that update safety information of the abacavir component. Labeling changes are needed to bring consistency across the three package inserts that contain abacavir sulfate, namely Ziagen®, Epzicom®, and now TRIZIVIR®. There was no new clinical data specific to TRIZIVIR provided for this review. Clarifications to the clinical studies section of the label have been added regarding the use of TRIZIVIR alone in patients with high baseline viral load. TRIZIVIR is now being recommended for traditional approval because all three components (zidovudine, lamivudine, and abacavir sulfate) have now undergone traditional approval. The last approval was for abacavir sulfate in April 2004. TRIZIVIR was initially approved November 14, 2000 under accelerated approval based on bioequivalence data from comparison of individual components against the fixed-dose combination product –TRIZIVIR. TRIZIVIR's traditional approval is now being recommended with the same bioequivalence data with all three individual components now having traditional approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The following Phase 4 commitments (from the EPZICOM® (lamivudine/abacavir sulfate) approval in 2004) are underway by GSK as part of the risk management activity for hypersensitivity reactions related to abacavir containing products. These risk management activities are also applicable to the current TRIZIVIR® traditional approval application.



1.2.2 Required Phase 4 Commitments

GSK committed to two Phase 4 requests for TRIZIVIR with the accelerated approval in 2000. The first was the TRIZIVIR Epidemiologic Program which was designed to compare the rates of hypersensitivity (HSR), HSR-associated rechallenge, HSR-associated hospitalization and HSR-associated death in patients receiving TRIZIVIR tablets compared to Ziagen products. This

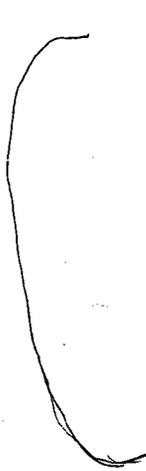
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study has been completed. A final study report was submitted and is being reviewed by the Office of Drug Safety. The second post-marketing commitment was to incorporate an additional database into the epidemiologic program to capture health care data on prescribers. This study has also been completed.

MO Comment: GSK has fulfilled their Phase 4 commitments from the accelerated approval of TRIZIVIR.

For Phase IV commitments for the current TRIZIVIR application for traditional approval, the following new activities are applicable.

There is now some information available (see reference literature articles below) about a possible predisposing factor to abacavir hypersensitivity. The following are the agreed upon Phase IV Commitments.



1.2.3 Other Phase 4 Requests

In addition to



1.3 Summary of Clinical Findings

There was no new clinical data included in this submission. Study 3005 was a 48-week, multi-center, double blind, randomized trial in treatment-naïve HIV-infected subjects. This study compared the safety and efficacy of twice daily abacavir 300 mg with indinavir 800 mg eight hourly. Each was given in combination with twice daily Combivir™. The results of this study demonstrated that the proportion of subjects treated with ABC/3TC/ZDV who achieved plasma HIV-1 RNA < 400 copies/mL at Week 48 was similar to those treated with IDV/3TC/ZDV.

Similar increases in CD4+ cell counts at Week 48 were observed for the two treatment groups. Based upon the agreed non-inferiority margin of 12%, the study arm was non-inferior to the control arm in the primary efficacy analysis. Since the overall result was non-inferior, it is hard to draw definitive conclusions about the subgroup analysis (>100,000 baseline viral load stratum) even though the lower bound of this CI is much lower at -23%. When one examines the secondary endpoint of <50 copies/mL however, the overall response rate in the triple-nucleoside arm containing the test drug ZIAGEN was inferior to the PI-containing control arm since the lower bound of the CI crosses -12%. The subgroup that is impacting on this overall inferior result is the >100,00 baseline viral load stratum where the confidence intervals are -27% to -1.2% with a significant p-value of 0.03. (Staszewski S et al. Abacavir-lamivudine-zidovudine vs. indinavir-lamivudine-zidovudine in antiretroviral-naïve HIV-infected adults: A randomized equivalence trial. JAMA 2001 Mar 7; 285 (9): 1155-63). For the subgroup of patients with baseline viral load of >100,000 copies/mL, the test arm of triple-nucleoside therapy showed an inferior result as compared to the control arm with PI-based regimen.

In addition, the conclusion drawn from the recent ACTG Study 5095 was "the triple-nucleoside combination of abacavir, zidovudine, and lamivudine was virologically inferior to a regimen containing efavirenz and two or three nucleosides" (NEJM 2004; 350(18): 1850-1861).

1.3.1 Brief Overview of Clinical Program

N/A

1.3.2 Efficacy

N/A

1.3.3 Safety

N/A

1.3.4 Dosing Regimen and Administration

N/A

1.3.5 Drug-Drug Interactions

N/A

1.3.6 Special Populations

N/A

2 Introduction and Background

2.1 Product Information

This application is submitted for traditional approval of TRIZIVIR[®]. TRIZIVIR[®] was granted an accelerated approval in 2000 based on bioequivalence data. TRIZIVIR[®] is a fixed dose combination of three nucleoside analogs. It contains abacavir 300mg (Ziagen[®]), lamivudine 150mg (Epivir[®]), and zidovudine 300mg (Retrovir[®]). All three components have been previously approved individually.

Abacavir sulfate (ABC, ZIAGEN[®]) is a synthetic carbocyclic nucleoside analogue. Based upon pharmacologic characteristics, the compound is classified as an inhibitor of the HIV-1 reverse transcriptase (RT) enzyme. As with other nucleoside RT inhibitors (NRTIs), ABC acts as a chain terminator of HIV-1 replication, thereby preventing conversion of viral ribonucleic acid (RNA) into proviral deoxyribonucleic acid (DNA). ABC has been developed by Glaxo-Smith-Kline (GSK) for the treatment of HIV-1 infection. Accelerated approval of ABC was granted on December 17, 1998 based upon 16 and 24 week results from studies CNAB3003, CNAA3006 and CNAB3005. Traditional approval was granted on April 16, 2004.

Lamivudine (3TC, Epivir[®]) is synthetic nucleoside analogue classified as an inhibitor of the HIV-1 RT enzyme. 3TC acts as a chain terminator after being incorporated into viral DNA. 3TC was granted accelerated approval on November 17, 1995. Traditional approval was granted on April 11, 1997.

Zidovudine (ZDV, AZT, Retrovir[®]) is a synthetic nucleoside analogue of the naturally occurring nucleoside thymidine. ZDV inhibits the activity of the HIV-1 RT both by competing for utilization with the natural substrate and by its incorporation into viral DNA. ZDV was approved on March 19, 1987.

2.2 Currently Available Treatment for Indications

There are now 20 drugs (not including fixed-dose combinations) approved for the treatment of HIV-1 infection. These drugs fall into four classes based on mechanism of action in the HIV life cycle: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and fusion/entry inhibitors.

2.5 Presubmission Regulatory Activity

TRIZIVIR was granted accelerated approval on November 14, 2000 with the above mentioned post-marketing commitments. It was approved based on bioequivalence data. As all three components of the drug now have traditional approval status, TRIZIVIR has been submitted for traditional approval.

Abacavir was granted accelerated approval on December 17, 1998. Traditional approval was granted on April 16, 2004. Abacavir has recently been approved for once daily dosing. There are still a number of post-marketing and pediatric study requirements to be met.

Lamivudine was granted accelerated approval on November 17, 1995. Traditional approval was granted on April 11, 1997. Lamivudine has approval for once daily dosing.

Zidovudine was approved on March 19, 1987. The last label revision was in October, 2003.

2.6 Other Relevant Background Information

3 Significant Findings from Other Review Disciplines

There was no new CMC, pharmacology, or toxicology data submitted.

4 Data Sources, Review Strategy, and Data Integrity

There was no new clinical data submitted.

5 Clinical Pharmacology

5.1 Pharmacokinetics

There was no new pharmacokinetic data submitted. In the original submission a study to establish bioequivalence was done. The study title was "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 Table Administered Concurrently and the Effect of Food on Absorption in Healthy Volunteers". The conclusions of the study from Prabhu Rajagopalan, Ph.D. were:

1. The combination tablet containing abacavir, lamivudine, and zidovudine is bioequivalent to individual tablets of these nucleoside analogs.
2. Administration of the combination table 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).

6 Integrated Review of Efficacy

6.1 Indication

The proposed indication from the applicant is "TRIZIVIR is indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection".

MO Comment: The current treatment recommendations for initial antiviral therapy is to use triple NRTI regimen only when a NNRTI based or PI based regimen cannot be used or tolerated. There is still some question as to the use of a triple NRTI regimen in subjects with a viral load > 100,000. There is evidence in a published study that subjects on triple a NRTI were more likely to have virologic failure at 48 weeks than subjects on a NNRTI based regimen (NEJM 2004; 350:1850-61). In a graphic representation of "Probability of Not Having Virologic Failure" separated by subjects with VL < 100,000 and subjects with VL ≥ 100,000, every time point after 16 weeks shows the subjects with higher viral loads having a smaller probability of not having virologic failure.

6.1.1 Methods

There was no clinical data used to support the proposed indication. This submission was based on bioequivalence data.

7 Integrated Review of Safety

There was no new safety data submitted with this submission. Based on information from studies APV30001, APV30002, APV30003, CNA30024, ESS40001, ESS40002, ESS40003, ESS40006, and ESS40009 the most recent abacavir label has been modified to include abacavir HSR as an AE in the label. The new label will report a rate of _____ As abacavir is a component of both Epzicom and TRIZIVIR, the appropriate sections are to be changed on these labels as well. (from poster presented at Conference on Retrovirus and Opportunistic Infections 2005 by Andrea James, MD)

There have been a number of changes in the label regarding safety. The warning box information regarding exacerbation of hepatitis B and abacavir HSR has been updated. The updated HSR information (including the new overall HSR rate of _____ from prospective clinical trials; see abacavir sulfate labeling supplement 4/2004) was also added to the WARNING, ADVERSE REACTIONS, and Information for Patients sections of the label.

The HSR rate reported in study CNA3005 (reviewed in 2000) was 7%. This 7% HSR adverse reaction has been added to the Adverse Events table for the current TRIZIVIR label. Wording regarding the use of TRIZIVIR in patients with viral load >100,000 copies/ml was added to the INDICATIONS and USAGE section. A table showing the information was added as well.

8 Additional Clinical Issues

8.1 Dosing Regimen and Administration

The applicant did not submit new dosing evaluation with this supplement.

8.2 Drug-Drug Interactions

8.3 Special Populations

As this is a fixed-dose product, this product should not be used in patients with hepatic impairment or in patients with creatinine clearance <50mL/min.

8.4 Pediatrics

As this is a fixed-dose combination product this product should not be used in the pediatric population or in adolescents less than 40 kg.

8.5 Advisory Committee Meeting

There was no Advisory Committee Meeting held for this application.

8.6 Literature Review

A medline search was performed to look for any new information in the literature on TRIZIVIR. A number of articles were found regarding the use of HLA-B*5701 to predict the occurrence of HSR. The population was largely white and male, and from the Western Australian HIV Cohort Study. In one report (Martin 2004), the presence of HLA-B*5701 provided a 94.4% sensitivity, and a NPV of 99.4%. In combination with other marker, these numbers may improve in sensitivity, positive predictive value, and negative predictive value.

The following references are used in this review.

Gulick Roy, Ribaldo Heater, Shikuma Cecilia, et al. "Triple-Nucleoside Regimens versus Efavirenz-Containing Regimens for the Initial Treatment of HIV-1 Infection." NEJM 2004; 350:1850-61

Staszewski S et al. "Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naïve HIV-infected adults: A randomized equivalence trial." JAMA 2001 Mar 7; 285 (9): 1155-63).

Hetherington Seth, Hughes Arlene, Mosteller Michael, et al. "Genetic variations in HLA-B region and hypersensitivity reactions to abacavir." The Lancet 359:1121-1122, 2002.

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Hughes Arlene, Mosteller Michael, Bansal Aruna et al. "Association of genetic variations in HLA-B region with hypersensitivity to abacavir in some, but not all, populations." *Pharmacogenomics* 5(2): 203-211, 2004.

Mallal S, Nolan D, Witt c, et al. "Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir." *The Lancet* 359:727-732, 2002.

Martin Annalise, Nolan David, Gaudieri Silvana et al. "Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and haplotypic Hsp70-Hom variant." *PNAS* 101(12):4180-4185, 2004.

8.7 Postmarketing Risk Management Plan

GSK had committed to 2 phase 4 activities for TRIZIVIR at the time of its accelerated approval in 2000. The first was the TRIZIVIR Epidemiologic Program which was designed to compare the rates of hypersensitivity (HSR), HSR-associated rechallenge, HSR-associated hospitalization and HSR-associated death in patients receiving TRIZIVIR tablets compared to Ziagen products. At a meeting on March 22, 2004 it was agreed that the program would end on December 31, 2003. A final study report has been submitted, and is currently under review by the Office of Drug Safety and DAVDP.

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prescribing. These point estimates suggest that the rate of re-prescribing abacavir is more common. However, the conclusions of the study were limited by a number of factors including, limited size of the dataset, and no validation of the codes used to define patients with hypersensitivity reaction and nevirapine rash. Thus, the results were considered non-interpretable. Concerns regarding inadvertent re-introduction of abacavir-related products are on-going. The following measures have been taken to minimize this important safety issue.

- 1) Usage statement in regards to the multiple abacavir containing products has been added to all the labels.
- 2) As part of the Epzicom® (third product to be approved that contains abacavir) approval, numerous phase IV steps have been committed by the applicant as follows:
 - Draft a "Dear Healthcare Provider" letter for submission to DAVDP for review and comment, followed by distribution of this letter soon after approval of this product. As in previous letters to healthcare providers, the draft letter should encourage providers to report hypersensitivity reactions and provide telephone numbers and other contact information for reporting reactions to GlaxoSmithKline and MedWatch.
 - Evaluate practical aspects of use of the Medication Guide and Warning Card in order to obtain information on the utility of these sources of information for patients. Specific questions to be addressed in a study are (a) Do patients receive the Medication Guide and Warning Card? (b) Do patients read the Medication Guide and Warning Card? (c) Do patients understand why they receive a Medication Guide and Warning Card? (d) Do patients take action (e.g., ask their doctor or pharmacist follow-up questions) based on the Medication Guide and Warning Card?
 - Conduct a multifaceted educational program to communicate the important risk information about potential hypersensitivity reactions to abacavir. Specific activities within this multifaceted educational program are listed below.
 - a. Introduce EPZICOM™ (abacavir/lamivudine) Tablet with the following activities directed to clinical investigators in future GSK-sponsored clinical studies on the abacavir/lamivudine tablet:
 - i. Protocols will include language describing the diagnosis and management of abacavir-related hypersensitivity reactions, consistent with information in FDA-approved labeling.
 - ii. Studies will continue to use a standard Case Report Form Module to facilitate collection of standardized information on cases of HSR.
 - iii. All pre-study meetings with clinical investigators will include a discussion on reporting of adverse events, including

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MO Comment: The above risk management Phase 4 activities are also applicable to the current TRIZIVIR traditional approval application.

Specifically to the current TRIZIVIR traditional approval application, GSK has agreed to the following additional Phase IV Commitments.



markers previously identified from among the 1.7 million SNPs assayed in pooled samples of "hypersensitivity cases" and "controls" are being genotyped in individual subjects to identify genetic markers that may be associated with hypersensitivity in a subset of patients. The goal of these work streams is to assess the prognostic utility of various genetic markers for hypersensitivity to abacavir.

- Start: ongoing
 - Final report submission: within 12 months post-approval
2. Supplement the previously completed work to identify genetic markers associated with hypersensitivity to abacavir in additional patient subpopulations. It is important to emphasize the breadth of GSK's ongoing pharmacogenetic investigation that is being undertaken in Caucasians, Blacks, Hispanics, males and females. This pharmacogenetics investigation will be extended to include Asian patients from study EPV40001 which was conducted in Thailand. GSK will investigate genetic associations in the HLA chromosomal region (including HLA-B*5701), statistically significant genetic markers previously identified in White analysis populations and additional markers outside the HLA-B chromosomal region included in Commitment #1.

- Start: ongoing
- Final report submission: within 12 months post-approval

Note: Our intent is to provide DAVDP with the results of work from commitments #1 and #2 in a single Summary Report.

3. Prepare and submit a summary of GSK's cumulative research on possible genetic correlates of hypersensitivity to abacavir, where evidence-based conclusions are stated and annotated to specific reports and publications previously submitted to the Agency and/or placed in the public domain.
- Start: ongoing
 - Final report submission: within 12 months post-approval
4. Provide 96 week virology results from study CNA3005 to respond to DAVDP's request. The virology data from CNA3005 provides a robust dataset of twice daily dosing in a therapy naïve patient population using the components of Trizivir, (abacavir, lamivudine and zidovudine provided as single entity abacavir and Combivir tablets) in the absence of other antiretroviral drugs.

Data are available for subjects who experienced virologic failure while receiving abacavir + Combivir twice daily therapy, as well as for subjects on the indinavir + Combivir regimen. The dataset contains data on 86 subjects (43 abacavir + Combivir, 43 indinavir + Combivir) with any data and 71 subjects (36 abacavir + Combivir, 40 indinavir + Combivir) having both baseline and at least one post baseline measure. Data include baseline and on-study genotype and phenotype information as well as corresponding plasma HIV-1 RNA levels.

8.8 Other Relevant Materials

N/A

9 Overall Assessment

9.1 Conclusions

The review team concurs that the bioequivalence data presented in this supplement support GSK's application for the Traditional Approval of TRIZIVIR.

Based on the information provided in this submission, the application is being recommended for approval with labeling changes that update safety information of the abacavir component. Labeling changes are needed to bring consistency across the three package inserts that contain abacavir sulfate, namely Ziagen®, Epzicom®, and now TRIZIVIR®. There was no new clinical data specific to TRIZIVIR provided for this review. Clarifications to the clinical studies section of the label have been added regarding the use of TRIZIVIR alone in patients with high baseline viral load. TRIZIVIR is now being recommended for traditional approval because all three components (zidovudine, lamivudine, and abacavir sulfate) have now undergone traditional approval. The last approval was for abacavir sulfate in April 2004. TRIZIVIR was initially approved November 14, 2000 under accelerated approval based on bioequivalence data (comparison of individual components against the fixed-dose combination product -TRIZIVIR) and now, TRIZIVIR's traditional approval is being recommended with the same bioequivalence data (with all three individual components now having traditional approval).

9.2 Recommendation on Regulatory Action

From a clinical perspective this sNDA should be approved.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

See Phase 4 requirements below.

9.3.2 Required Phase 4 Commitments

TRIZIVIR has fulfilled the Phase 4 Post-marketing commitments from their accelerated approval of 2000.

DAVDP has made the following Phase 4 commitment requests to GSK from the current traditional approval of TRIZIVIR.

[]

9.3.3 Other Phase 4 Requests

N/A

9.4 Labeling Review

The DVADP has a number of proposed revisions to the current label, all of which were accepted by the applicant.

- All references to study CNA3003 are to be removed from the label as this was only 16 week data.
- All references to study CAN 3006 are to be removed from the label as this was a pediatric study. As a fixed-dose combination TRIZIVIR is not indicated for the pediatric population.
- The MICROBIOLOGY section was changed to reflect the current versions of the individual product labels (including other applicable fixed dose combination products).
- The CLINICAL PHARMACOLOGY section was changed to reflect the current versions of the individual product labels (including other applicable fixed dose combination products).
- The INDICATIONS AND USAGE section was rearranged to reflect the most recent HIV treatment recommendations, namely that a triple nucleoside regimen is not considered first line therapy. And TRIZIVIR is one of multiple products containing abacavir. Before starting TRIZIVIR, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.
- Emtricitabine, and Truvada should be added to the label as they should not be used in combination with lamivudine or lamivudine containing products.
- Hypersensitivity reaction should be added to the adverse events table. The rate is to be increased from 5% to 8% for consistency across the abacavir labels.
- Wording regarding immune reconstitution syndrome was added to the label.

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- There are also a number of additions to the Medication Guide with input from ODS.

9.5 Comments to Applicant

The above labeling changes have been discussed with the applicant. All recommended label changes have been accepted by the applicant.

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References

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NDA 20-977/20-978

James A, Johann-Liang R. Increased Rate and Severity of Abacavir (ABC) Associated Hypersensitivity Reaction (HSR) in Controlled Clinical Trials. Conference on Retrovirus and Opportunistic Infections 2005, Boston, MA.

Gulick Roy, Ribaldo Heater, Shikuma Cecilia; et al. "Triple-Nucleoside Regimens versus Efavirenz-Containing Regimens for the Initial Treatment of HIV-1 Infection." NEJM 2004; 350:1850-61

Staszewski S et al. "Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naïve HIV-infected adults: A randomized equivalence trial." JAMA 2001 Mar 7; 285 (9): 1155-63).

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Mallal S, Nolan D, Witt c, et al. "Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir." The Lancet 359:727-732, 2002.

Martin Annalise, Nolan David, Gaudieri Silvana et al. "Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and haplotypic Hsp70-Hom variant." PNAS 101(12):4180-4185, 2004.

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Debra Birnkrant
5/11/05 02:58:53 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-205 / S-011

CHEMISTRY REVIEW(S)

EFFICACY SUPPLEMENTAL NDA CHEMIST'S REVIEW		DUE DATE 5/16/05	1. ORGANIZATION HFD-530	2. NDA NUMBER 21-205
3. NAME AND ADDRESS OF APPLICANT SmithKline Beecham Corporation d/b/a Glaxo SmithKline One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101 Phone: 919-483-9347		4. TYPE OF SUPPLEMENT PA		
		5. DOCUMENT(S)		
		NUMBER SE7-011 Amendment BL	DATED 7/14/04 10/19/04	RECEIVED 7/16/04 10/20/04
6. NAME OF DRUG Trizivir®		7. NONPROPRIETARY NAME Abacavir sulfate+lamivudine+zidovudine		
8. SUPPLEMENT PROVIDES FOR: traditional approval for Trizivir Tablets in accordance with 21CFR 314.105.		9. AMENDMENTS/DATES		
10. PHARMACOLOGICAL CATEGORY Antiviral	11. HOW DISPENSED <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> OTC	12. RELATED IND/NDA/DMF(s) NDA 20-977 NDA 20-978 — ibacavir sulfate tablets and oral solution)		
13. DOSAGE FORM(S) Tablet		14. POTENCY (CIES) 300 mg of abacavir as abacavir sulfate, 150 mg of lamivudine, and 300 mg of zidovudine per tablet		
15. CHEMICAL NAME 1) Abacavir sulfate: (1 <i>S</i> , <i>cis</i>)-4-[2-Amino-6-(cyclopropylamino)-9 <i>H</i> - purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1) 2) Lamivudine: (2 <i>R</i> , <i>cis</i>)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan- 5-yl)-(1 <i>H</i>)-pyrimidin-2-one 3) Zidovudine: 3'-Azido-3'-deoxythymidine		16. MEMORANDA		
17. COMMENTS This is an efficacy supplement for seeking traditional approval of Trizivir Tablets for the treatment of HIV-1 infection in accordance with 21CFR 314.105. In the initial submission, applicant did not provide the updated container and carton labels. However, upon request these labels were provided in the 10/19/04 amendment. These labels (see Appendix 1) contained all the required information and they are acceptable. The supplement is recommended for approval.				
18. CONCLUSIONS AND RECOMMENDATIONS The efficacy supplement #SE7-011 to the NDA #21-205 is recommended for approval.				
19. REVIEWER				
NAME Rao V. Kambhampati, Ph.D. Senior Regulatory Review Scientist		SIGNATURE <i>[signed electronically in DFS]</i>		DATE OF DRAFT REVIEW 3/22/05
20. CONCURRENCE: HFD-530/ChemTL/SMiller <i>[signed electronically in DFS]</i>				

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Stephen Paul Miller
3/23/05 04:02:17 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-205 / S-011

MICROBIOLOGY REVIEW

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
NDA 21-205/S-011

Reviewer: LALJI MISHRA, Ph.D. Review Completed: 02/07/05

Date Submitted: 07/14/04

Date Received: 07/14/04

Assigned Date: 08/08/04/

Sponsor: GlaxoSmithKline

Five Moore Drive

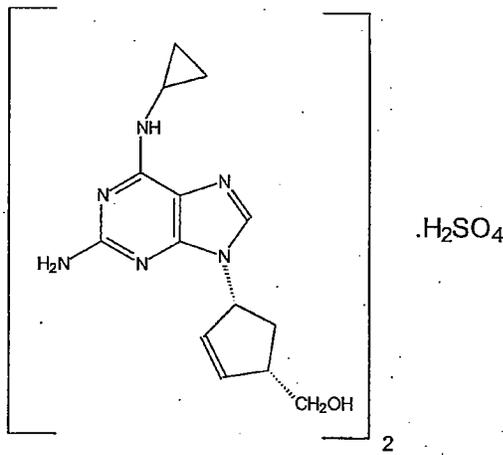
Research Triangle Park, NC 27709

(919) 483-2100

Product Names:

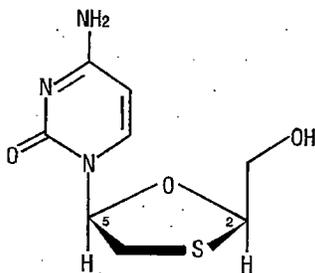
- a. **Proprietary:** Trizivir™
- b. **Non-proprietary:** Abacavir sulfate/lamivudine/zidovudine
- c. **Chemical:** (1*S*,4*R*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol; (2*R*,*cis*)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one. 3'-azido-3'-deoxythymidine

Structure:

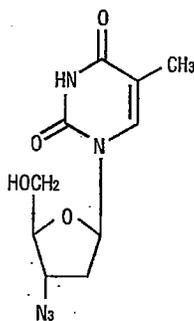


ABACAVIR

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
NDA 21-205/S-011
Reviewer: LALJI MISHRA, Ph.D. Review Completed: 02/07/05



LAMIVUDINE



ZIDOVUDINE

Route of Administration/Dosage form: Oral/Tablet
Indication: Treatment of HIV-1 infection

BACKGROUND

GlaxoSmithKline (GSK) Inc. has submitted a supplemental NDA # 21-205/S-011, and seeks traditional approval of Trizivir™ tablets for the treatment of human immunodeficiency virus (HIV-1) infection in adults and pediatric (≥3 months) patients. Trizivir™ tablets each contain 3 nucleoside reverse transcriptase inhibitors (NRTIs): abacavir sulfate (ABC), lamivudine (3TC) and zidovudine (ZDV). ABC, 3TC and ZDV are each FDA approved for the treatment of HIV-1 infection. Trizivir™ received accelerated approval on June 6, 2000 based upon human bioequivalence of the ABC, 3TC and ZDV (Trizivir™) tablet dosage form to each of the commercially available products: Ziagen® tablet 300 mg, Epivir® tablet 150 mg, and Retrovir® tablet 300 mg. The sponsor cross-referred to the original NDAs # 20-977 (abacavir), # 20-564 (lamivudine) and # 19-655 (zidovudine) for chemistry, microbiology and pharmacology/toxicology information. At the time of accelerated approval of Trizivir™, ABC had not received traditional approval. However, 3TC and ZDV had traditional approval status. ABC received traditional approval on April 15, 2004. All supportive microbiology data for each

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
NDA 21-205/S-011

Reviewer: LALJI MISHRA, Ph.D. Review Completed: 02/07/05

compound submitted to the Division for their respective NDAs were previously reviewed. Therefore, the microbiology review of these previously submitted reports can be found in the reviews of the original and supplemental NDAs for ABC, 3TC and ZDV. In the current submission, the sponsor has revised the package insert. Data recently submitted to NDA # 20-977/S012 and NDA # 20-978/S014 on the antiviral activity of 3TC and ZDV against different clades of HIV-1 and HIV-2 are reviewed here. Similarly, data on the effect of ribavirin (RBV), approved for the treatment of HCV in combination with pegylated interferon- α , on the antiviral activity of 3TC are reviewed here. Data on the antiviral activity of ABC against different HIV-1 clades and HIV-2 and the effect of RBV on the anti-HIV-1 activity of ABC were previously reviewed (microbiology review of NDA 20-977/SE2-012; 20978/SE2-014 dated July 8, 2004) and are reproduced here for reference. Data on the antiviral activity of ABC, 3TC and ZDV against different HIV-1 clades and HIV-2 and effect of RBV on the anti-HIV-1 activity of ABC and 3TC are reviewed here.

SUMMARY

- I. Antiviral activity in vitro of ABC, against a panel of HIV-1 isolates representing clades A, B, C, D, E, F, and G, and group O (GSK report RH2004/0089/00; Source: sNDA 20-977/SE2-012, and sNDA 20-978/SE2-014)**

The purpose of this study was to determine the anti-HIV-1 activity *in vitro* of ABC, against a panel of twenty-four HIV-1 isolates representing clades A, B, C, D, E, F, and G (HIV-1 group M), and three isolates from HIV-1 group O. All virus isolates were obtained from NIH AIDS Research and Reference Reagent Program. PHA-stimulated PBMCs were plated in a 96 well round bottom microplate at a concentration of 5×10^4 cells/well (50 μ L/well). Each plate contained virus/cell control wells (cell plus virus), experimental wells (drug plus cells plus virus), and compound control wells (drug plus media without cells). Test drug concentrations were prepared at a 2X concentration in microtiter tubes and 100 μ L of each concentration were placed in the appropriate well using the standard format. Fifty μ L of a HIV-1 stock was placed in each test well (m.o.i.= 0.1). The PBMC cultures were maintained at 37^oC (5% CO₂) for 7 days following infection. After 7 days, cell-free supernatant samples were collected and RT activity determined using a microtiter plate-based RT assay as described (Buckheit et al., 1991). For the determination of cell viability and cytotoxicity, 20 μ L tetrazolium-based dye MTS (Cell Titer 96 Reagent, Promega) were added per well. The microtiter plates were then incubated 4-6 hrs at 37^o C. Plates were read spectrophotometrically at 490/650 nm with a Molecular Devices V_{max} or SpectraMaxPlus plate reader. The anti-HIV-1 activity of ABC against HIV-1 isolates from different clades are shown in Table 1 (Reproduced from Table 13, Microbiology review of sNDA 20-977/SE2-012 and s NDA 20-978/SE2-014; source NDA20-977/SE2-012, electronic submission, GSK report RH2004/0089/00, Pages 9-11, Table 1).

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DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
NDA 21-205/S-011
Reviewer: LALJI MISHRA, Ph.D. Review Completed: 02/07/05

Table 1. Anti-HIV-1 activity in vitro of ABC against isolates from different clades

HIV-1 Isolate	Subtype	IC ₅₀ (nM)	TC ₅₀ (nM)	TI TC ₅₀ /IC ₅₀
RW/92/009	A	14.8	>10,000.0	>676
UG/92/029	A	676.0	>10,000.0	>14.8
UG/92/037	A	344.3	>10,000.0	>29
Br/92/014	B	1056.9	>10,000.0	>9.46
Jr-CSF	B	27.9	>10,000.0	>358.4
TH/92/026	B	5.86	>10,000.0	>1706.5
Br/92/025	C	16.7	>10,000.0	>598.8
IN/93/101	C	1.47	>10,000.0	>6802.7
MW/93/959	C	8.09	>10,000.0	>1236.1
UG/92/001	D	35.7	>10,000.0	>280.1
UG/92/024	D	396.3	>10,000.0	>25.2
UG/92/046	D	356.5	>10,000.0	>28.1
CMU 06	E	105.3	>10,000.0	>95.0
CMU 08	E	168.4	>10,000.0	>59.4
TH/93/073	E	28.1	>10,000.0	>355.9
BR/93/029	F	47.6	>10,000.0	>210.1
BR/93/019	F	5.19	>10,000.0	>1926.8
BR/93/020	F	199.7	>10,000.0	>50.1
G3	G	7.07	>10,000.0	>1414.4
JV1083	G	176.6	>10,000.0	>56.6
RU132	G	51.4	>10,000.0	>194.6
BCF01	O	22.4	>10,000.0	>446.4
BCF02	O	281.9	>10,000.0	>35.5
BCF03	O	598.3	>10,000.0	>16.7

Table 1 shows that the median and average IC₅₀ values of ABC against HIV-1 isolates representing different clades (A-G) were 49.5 μM and 0.193 ± 0.267 μM (range=0.0015-1.05 μM), respectively. The median values for the three clade A and D isolates were about 7 fold higher. These values are in agreement with the IC₅₀ value of ABC reported for clinical isolates (0.26 ± 0.18 μM).

II. Antiviral activity in vitro of 3TC against a panel of HIV-1 isolates representing clades A, B, C, D, E, F, and G (GSK report RH2004/0089/00; Pages 9-10, Table 1)

The antiviral activity in vitro of 3TC against different HIV-1 clades was measured as described for ABC. The IC₅₀ values of 3TC against different HIV-1 clades (A-G) are shown in Table 2 (GSK report RH2004/0089/00, Pages 9-11, Table 1). The median and

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
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average IC₅₀ values were 0.03 μM and 0.04 ± 0.031 μM, respectively. The IC₅₀ values of 3TC against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM.

Table 2: Anti-HIV-1 activity in vitro of 3TC against isolates from different clades

HIV-1 Isolate	Subtype	IC ₅₀ (nM)	TC ₅₀ (nM)	TI TC ₅₀ /IC ₅₀
RW/92/009	A	60.0	>10,000.0	>166.7
UG/92/029	A	20.0	>10,000.0	>500.0
UG/92/037	A	70.0	>10,000.0	>142.7
96USHIPS7	B	120.0	>10,000	>83.3
Jr-CSF	B	30.0	>10,000.0	>333.3
TH/92/026	B	40.0	>10,000.0	>250.0
BR/93/021	B	8.0	>10,000	>1250.0
Br/92/025	C	90.0	>10,000.0	>111.1
IN/93/101	C	20.0	>10,000.0	>500.0
MW/93/959	C	30.0	>10,000.0	>333.3
UG/92/001	D	20.0	>10,000.0	>500.0
UG/92/024	D	40.0	>10,000.0	>250.0
UG/92/046	D	3.0	>10,000.0	>3333.3
CMU 06	E	1.0	>10,000.0	>10,000
CMU 08	E	30.0	>10,000.0	>333.3
TH/93/073	E	60.0	>10,000.0	>166.7
BR/93/029	F	30.0	>10,000.0	>333.3
BR/93/019	F	70.0	>10,000.0	>142.9
BR/93/020	F	20.0	>10,000.0	>500.0
G3	G	70.0	>10,000.0	>142.0
JV1083	G	30.0	>10,000.0	>333.3
RU132	G	3.00	>10,000.0	>3333.3
BCF01	O	20.0	>10,000.0	>500.0
BCF02	O	90.0	>10,000.0	>111.1
BCF03	O	30.0	>10,000.0	>333.3

III. Antiviral activity in vitro of ZDV against a panel of HIV-1 isolates representing clades A, B, C, D, E, F, and G (GSK report RH2004/0089/00)

The antiviral activity in vitro of ZDV against different HIV-1 clades was determined as described for ABC. Table 3 (GSK report RH2004/0089/00, Pages 9-11, Table 1) shows that the IC₅₀ values of ZDV against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 μM. The median and average IC₅₀ values were 0.004 μM and 0.0057 ± 0.0053 μM, respectively.

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Table 3. Anti-HIV-1 activity of ZDV against isolates from different clades

HIV-1 Isolate	Subtype	IC ₅₀ (nM)	TC ₅₀ (nM)	TI TC ₅₀ /IC ₅₀
RW/92/009	A	5.83	>10,00.0	>171.5
RW/92/009	A	0.18	>1000.0	>5555.6
UG/92/029	A	6.65	>1000.0	>150.4
UG/92/029	A	12.1	>1000.0	>82.64
UG/92/037	A	14.6	>1000.0	>68.5
UG/92/037	A	3.87	>1000.0	>258.4
96USHIPS7	B	3.87	>1000.0	>258.4
Br/92/014	B	6.39	>1000.0	>156.5
Jr-CSF	B	4.31	>1000.0	>232.0
Jr-CSF	B	0.80	>1000.0	>1250.0
TH/92/026	B	3.82	>1000.0	>261.8
TH/92/026	B	0.18	>1000.0	>5555.6
BR/93/021	B	8.0	>1000.0	>125.0
BR/92/025	C	10.7	>1000.0	>93.5
BR/92/025	C	5.04	>1000.0	>198.4
IN/93/101	C	1.61	>1000.0	>621.1
IN/93/101	C	3.95	>1000.0	>253.2
MW/93/959	C	10.4	>1000.0	>96.15
MW/93/959	C	4.83	>1000.0	>207.0
UG/92/001	D	11.3	>1000.0	>88.50
UG/92/001	D	3.04	>1000.0	>329.0
UG/92/024	D	6.07	>1000.0	>164.7
UG/92/024	D	3.90	>1000.0	>256.4
UG/92/046	D	0.53	>1000.0	>1886.8
UG/92/046	D	11.0	>1000.0	>90.9
CMU 06	E	0.87	>1000.0	>1149.4
CMU 06	E	23.3	>1000.0	>42.9
CMU 08	E	0.82	>1000.0	>1219.51
CMU 08	E	19.9	>1000.0	>50.3
TH/93/073	E	3.82	>1000.0	>261.8
TH/93/073	E	0.69	>1000.0	>1449.3
BR/93/029	F	1.49	>1000.0	>671.1
BR/93/029	F	0.45	>1000.0	>2222.2
BR/93/019	F	1.69	>1000.0	>591.7
BR/93/019	F	3.47	>1000.0	>288.18
BR/93/020	F	10.9	>1000.0	>91.7
BR/93/020	F	16.0	>1000.0	>62.5

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G3	G	8.86	>1000.0	>112.9
G3	G	6.23	>1000.0	>160.5
JV1083	G	4.74	>1000.0	>>211.0
JV1083	G	1.24	>1000.0	>806.5
RU132	G	0.28	>1000.0	>3571.4
RU132	G	8.16	>1000.0	>122.6
BCF01	O	11.9	>1000.0	>84.0
BCF01	O	2.81	>1000.0	>355.9
BCF02	O	1.94	>1000.0	>515.7
BCF02	O	0.57	>1000.0	>1754.4
BCF03	O	1.87	>1000.0	>534.8
BCF03	O	4.68	>1000.0	>213.7

IV. Anti-viral activity in vitro of ABC against HIV-2 isolates

Table 4 shows that the IC₅₀ values of ABC against HIV-2 isolates ranged from 0.024 to 0.49 µM (electronic submission NDA20-9777/SE2-012/BI, dated June 16, 2004, GSK report RH2004/0089/00, Pages 11, Table 2). ABC exhibited similar antiviral activity against HIV-1 and HIV-2 isolates.

Table 4. Anti-viral activity of ABC against HIV-2 isolates

HIV-2 Isolate	IC ₅₀ (nM)	TC ₅₀ (nM)	TI TC ₅₀ /IC ₅₀
CDC 310319	171.0	>10,000	>58.5
CDC 310342	23.7	>10,000	>421.9
CBL-20	489.6	>10,000	>20.4

V. Anti-viral activity in vitro of 3TC against HIV-2 isolates

Table 5 (GSK report RH2004/0089/00, Pages 11, Table 2) shows that antiviral activity in vitro of 3TC against HIV-2 isolates ranged from 0.002 to 0.120 µM.

Table 5. Anti-viral activity of 3TC against HIV-2 isolates

HIV-2 Isolate	IC ₅₀ (nM)	TC ₅₀ (nM)	TI TC ₅₀ /IC ₅₀
CDC 310319	3.00	>10,000	>3333.3
CDC 310342	2.00	>10,000	>5000.0
CBL-20	120.0	>10,000	>83.3

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VI. Anti-viral activity in vitro of ZDV against HIV-2 isolates

Table 6 (GSK report RH2004/0089/00, Pages 11, Table 2) shows that antiviral activity of ZDV against HIV-2 isolates ranged from 0.00049 to 0.0042 μM . The median and average IC_{50} values were 0.0012 μM and $0.0016 \pm 0.0015 \mu\text{M}$, respectively.

Table 6. Anti-viral activity of ZDV against HIV-2 isolates

HIV-2 Isolate	IC_{50} (nM)	TC_{50} (nM)	TI $\text{TC}_{50}/\text{IC}_{50}$
CDC 310319	1.21	>1000.0	>826.5
CDC 310319	0.75	>1000.0	>1333.3
CDC 310342	0.49	>1000.0	>2040.8
CDC 310342	1.39	>1000.0	>719.0
CBL-20	4.25	>1000.0	>235.3
CBL-20	0.94	>1000.0	>1063.8

VII. Effect of ribavirin (RBV) on the anti-HIV-1 activity in vitro of ABC or 3TC
(GSK research report RH2004/00092/00)

The objective of this study was to determine the effect of RBV on the antiviral activity of ABC or 3TC in MT4 cells. The *in vitro* combination antiviral activity was determined by a checkerboard style experimental design as described (GSK research report RH2004/00092/00, Page 8). In these experiments, drug A was always RBV and drug B was either ABC, or 3TC alone. Dilutions were arranged so that every concentration of each drug was tested in the presence and absence of every concentration of the other. Aliquots of ABC or 3TC were serially diluted vertically in a deep-well master assay plate in RPMI 1640 medium containing 10% FBS at concentrations that were 40-fold higher than the final assay concentration. RBV was diluted horizontally across a separate master plate in RPMI 1640 containing 10% FBS at concentration that were 40-fold higher than the final assay concentration. Test concentration range for either ABC or 3TC was 25 μM to 25 nM and for RBV 50 μM to 50 nM. Anti-HIV-1 activity assays were performed in triplicate for each combination and direct cytotoxicity test as a single read out for each combination. Exponentially growing MT-4 cells were harvested and suspended in cell culture medium (RPMI 1640, 20% FBS and 20% IL-2) to a density of 1.25×10^6 cells/mL. MT-4 cell aliquots were infected with HIV-1_{MB} at an m.o.i. of 73 pfu per 1×10^4 cells. After 1 hour incubation the virus/cell suspensions were added to each well of the plates containing prediluted compounds. Plates were then placed in a tissue culture incubator for 5 days. After 5 days of incubation, the infected cells were treated with 20 μL of Cell titer 96 MTS reagent and processed as described before. The OD was measured at 492 nm using a microplate absorbance reader. IC_{50} values were calculated as

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described earlier. The IC_{50} value of RBV against HIV-1 was $>40 \mu M$ (GSK Document Number RH 2004/00015/00, electronic submission, NDA20-977/SE2-012 & NDA 20-978/SE2-014, dated 06/14/2004,). The IC_{50} values of ABC in the absence and presence of $50 \mu M$ RBV were 15.5 and $15 \mu M$, respectively (GSK report RH2004/00092/00, Page 19, Table 1). On the other hand, the IC_{50} of 3TC in the absence and presence of ribavirin ($50 \mu M$) were 14.4 and $50.4 \mu M$, respectively. Thus, RBV increased the IC_{50} of 3TC by 3.5 fold, but had no effect on the IC_{50} values of ABC. Thus, the results from this study confirmed previous findings that RBV was not antagonistic to the anti-HIV-1 activity of ABC.

MICROBIOLOGY LABEL (03/30/05)

Mechanism of Action:

Abacavir: Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5'-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleotide analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA polymerases α , β , and γ .

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. 3TC-TP is a weak inhibitor of cellular DNA polymerases α , β , and γ .

Zidovudine: Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is phosphorylated to its active 5'-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerases α and γ and has been reported to be incorporated into the DNA of cells in culture.

Antiviral Activity:

Abacavir: The in vitro anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1_{MB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BAL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50 percent (IC_{50}) ranged from 3.7 to $5.8 \mu M$ ($1 \mu M = 0.28 \text{ mcg/mL}$) and 0.07 to $1.05 \mu M$ against HIV-1_{MB} and HIV-1_{BAL}, respectively, and was $0.26 \pm 0.18 \mu M$ against 8 clinical isolates. The IC_{50} values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to $1.05 \mu M$, and against HIV-2 isolates, from 0.024 to $0.49 \mu M$.

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Abacavir had synergistic activity in vitro in combination with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the protease inhibitor (PI) amprenavir, and additive activity in combination with the NRTIs didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50 μ M) had no effect on the in vitro anti-HIV-1 activity of abacavir.

Lamivudine: The in vitro activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. IC₅₀ values (50% inhibitory concentrations) were in the range of 0.003 to 15 μ M (1 μ M = 0.23 mcg/mL). The IC₅₀ values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μ M, and against HIV-2 isolates from 0.003 to 0.120 μ M. In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity. Ribavirin (50 μ M) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold.

Zidovudine: In vitro activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The IC₅₀ and IC₉₀ values for zidovudine were 0.01 to 0.49 μ M (1 μ M = 0.27 mcg/mL) and 0.1 to 9 μ M, respectively. Zidovudine had anti-HIV-1 activity in all acute virus-cell infections tested. However, zidovudine activity was substantially less in chronically infected cell lines. The IC₅₀ values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 μ M, and against HIV-2 isolates from 0.00049 to 0.004 μ M. In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the NRTIs abacavir, didanosine, lamivudine, and zalcitabine, the NNRTIs delavirdine, and nevirapine, and the PIs indinavir, nelfinavir, ritonavir, and saquinavir and additive activity with interferon-alpha. Ribavirin has been found to inhibit the phosphorylation of zidovudine in vitro.

Resistance:

HIV-1 isolates with reduced sensitivity to abacavir, lamivudine, or zidovudine have been selected in vitro and were also obtained from patients treated with abacavir, lamivudine, and zidovudine, or the combination of lamivudine and zidovudine.

Abacavir: Genotypic analysis of isolates selected in vitro and recovered from abacavir-treated patients demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in RT contributed to abacavir resistance. In a study of subjects receiving abacavir once or twice daily in combination with lamivudine and efavirenz once daily, 39% (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7 to 13).

Lamivudine: Genotypic analysis of isolates selected in vitro and recovered from lamivudine-treated patients showed that the resistance was due to a specific amino acid

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substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine.

Zidovudine: Genotypic analyses of the isolates selected in vitro and recovered from zidovudine-treated patients identified mutations in the HIV-1 RT gene resulting in amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of mutations. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Cross-Resistance:

Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors.

Abacavir: Isolates containing abacavir resistance-associated mutations, namely, K65R, L74V, Y115F and M184V exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in vitro and in patients. The K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

Lamivudine: Cross-resistance to abacavir, didanosine, tenofovir, and zalcitabine has been observed in some patients harboring lamivudine-resistant HIV-1 isolates. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including lamivudine, have emerged (see under Zidovudine below). Cross-resistance between lamivudine and zidovudine has not been reported.

Zidovudine: In a study of 167 HIV-infected patients, isolates (n = 2) with multidrug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from patients treated for ≥ 1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of resistance-associated mutations with such combination therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the Q151M mutation being most commonly associated with multidrug resistance. The mutation at codon 151 in combination with mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine. TAMs are selected by zidovudine and confer cross-resistance to abacavir, didanosine, stavudine, tenofovir, and zalcitabine.

CONCLUSIONS

Data on the antiviral activity in vitro of ABC, 3TC and ZDV against different HIV-1 clades and HIV-2 and effect of RBV on the anti-HIV-1 activity of ABC and 3TC are

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