PRESCRIBING INFORMATION

COMBIVIR®

(lamivudine/zidovudine)

Tablets

WARNING

ZIDOVUDINE, ONE OF THE TWO ACTIVE INGREDIENTS IN COMBIVIR, HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS). PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

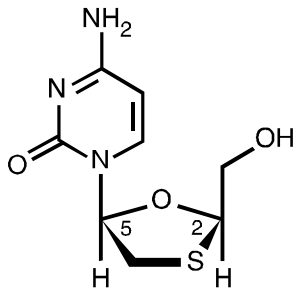
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE, ZIDOVUDINE, AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

COMBIVIR: COMBIVIR Tablets are combination tablets containing lamivudine and zidovudine. Lamivudine (EPIVIR®, 3TC®) and zidovudine (RETROVIR®, azidothymidine, AZT, or ZDV) are synthetic nucleoside analogues with activity against human immunodeficiency virus (HIV).

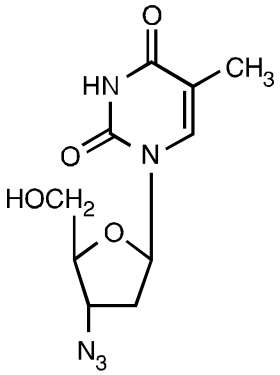
COMBIVIR Tablets are for oral administration. Each film-coated tablet contains 150 mg of lamivudine, 300 mg of zidovudine, and the inactive ingredients colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

Lamivudine: The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-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. 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. It has the following structural formula:



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

MICROBIOLOGY

Mechanism of Action: *Lamivudine:* Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (L-TP). The principal mode of action of L-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue. L-TP is a weak inhibitor of mammalian DNA polymerases α and β, and mitochondrial DNA polymerase-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 nucleoside analogue. ZDV-TP is a weak inhibitor of the mammalian DNA polymerase-α and mitochondrial DNA polymerase-γ and has been reported to be incorporated into the DNA of cells in

culture.

Antiviral Activity In Vitro: The relationship between in vitro susceptibility of HIV to lamivudine or zidovudine and the inhibition of HIV replication in humans has not been established.

Lamivudine Plus Zidovudine: In HIV-1–infected MT-4 cells, lamivudine in combination with zidovudine had synergistic antiretroviral activity. Synergistic activity of lamivudine and zidovudine was also shown in a variable-ratio study.

Lamivudine: In vitro activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) for lamivudine were 0.0006 mcg/mL to 0.034 mcg/mL and 0.015 to 0.321 mcg/mL, respectively. Lamivudine had anti–HIV-1 activity in all acute virus-cell infections tested.

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 0.003 to 0.013 mcg/mL and 0.03 to 0.13 mcg/mL, 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. In cell culture drug combination studies with zidovudine, interferon-alpha demonstrated additive activity and zalcitabine, didanosine, saquinavir, indinavir, ritonavir, nelfinavir, nevirapine, and delavirdine demonstrated synergistic activity.

Drug Resistance: Lamivudine Plus Zidovudine Administered As Separate Formulations: In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. 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.

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged lamivudine/zidovudine therapy. Dual resistance required the presence of multiple mutations, the most essential of which may be at codon 333 (Gly→Glu). The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.

Lamivudine: Lamivudine-resistant isolates of HIV-1 have been selected in vitro and have also been recovered from patients treated with lamivudine or lamivudine plus zidovudine. Genotypic analysis of the resistant isolates showed that the resistance was due to mutations in the HIV-1 reverse transcriptase gene at codon 184 from methionine to either isoleucine or valine.

Zidovudine: HIV isolates with reduced susceptibility to zidovudine have been selected in vitro and were also recovered from patients treated with zidovudine. Genotypic analyses of the isolates showed mutations which result in 5 amino acid substitutions (Met41→Leu, Asp67→Asn, Lys70→Arg, Thr215→Tyr or Phe, and Lys219→Gln) in the HIV-1 reverse transcriptase gene. In general, higher levels of resistance were associated with greater number of mutations.

Cross-Resistance: Cross-resistance among certain reverse transcriptase inhibitors has been recognized.

Lamivudine Plus Zidovudine: Cross-resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a mutation at codon 184, which confers resistance to lamivudine. In the presence of the 184 mutation, cross-resistance to didanosine and zalcitabine has been seen in some patients; the clinical significance is unknown. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including lamivudine, have emerged (see under Zidovudine below).

Lamivudine: See Lamivudine Plus Zidovudine (above).

Zidovudine: HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for ≥1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of genotypic resistant mutations with such combination therapies was different (Ala62→Val, Val75→Ile, Phe77→Leu, Phe116→Tyr, and Gln151→Met) from the pattern with zidovudine monotherapy, with the 151 mutation being most commonly associated with multidrug resistance. The mutation at codon 151 in combination with the mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine.

Multiple-drug resistance has been observed in 2 of 39 (5%) patients receiving zidovudine and didanosine combination therapy for 2 years.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: ***COMBIVIR:*** One COMBIVIR Tablet was bioequivalent to one EPIVIR Tablet (150 mg) plus one RETROVIR Tablet (300 mg) following single-dose administration to fasting healthy subjects (n = 24).

Lamivudine: The pharmacokinetic properties of lamivudine in fasting patients are summarized in Table 1. 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: The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 1. 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.

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

Parameter	Lamivudine		Zidovudine	
Oral bioavailability (%)	86 ± 16	n = 12	64 ± 10	n = 5
Apparent volume of distribution (L/kg)	1.3 ± 0.4	n = 20	1.6 ± 0.6	n = 8
Plasma protein binding (%)	<36		<38	
CSF:plasma ratio[†]	0.12 [0.04 to 0.47]	n = 38[‡]	0.60 [0.04 to 2.62]	n = 39[§]
Systemic clearance (L/hr/kg)	0.33 ± 0.06	n = 20	1.6 ± 0.6	n = 6
Renal clearance (L/hr/kg)	0.22 ± 0.06	n = 20	0.34 ± 0.05	n = 9
Elimination half-life (hr)[‖]	5 to 7		0.5 to 3	

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

[†]Median [range].

[‡] Children.

[§] Adults.

[‖] Approximate range.

Effect of Food on Absorption of COMBIVIR: COMBIVIR may be administered with or without food. The extent of lamivudine and zidovudine absorption (AUC) following administration of COMBIVIR with food was similar when compared to fasting healthy subjects (n = 24).

Special Populations: ***Impaired Renal Function: COMBIVIR:*** Because lamivudine and zidovudine require dose adjustment in the presence of renal insufficiency, COMBIVIR is not recommended for patients with impaired renal function (see PRECAUTIONS).

Impaired Hepatic Function: COMBIVIR: A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Because COMBIVIR is a fixed-dose combination that cannot be adjusted for this patient population, COMBIVIR is not recommended for patients with impaired hepatic function.

Pregnancy: See PRECAUTIONS: Pregnancy.

COMBIVIR: No data are available.

Zidovudine: Zidovudine pharmacokinetics has 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 was 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.

COMBIVIR: No data are available.

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: COMBIVIR: COMBIVIR should not be administered to pediatric patients less than 12 years of age because it is a fixed-dose combination that cannot be adjusted for this patient population.

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

Drug Interactions: See PRECAUTIONS: Drug Interactions.

COMBIVIR: No drug interaction studies have been conducted using COMBIVIR Tablets.

Lamivudine Plus 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 Lamivudine and Zidovudine AUC*

Note:ROUTINE DOSE MODIFICATION OF 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	↑ AUC 10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	single 300 mg	14	↑ AUC 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	↑ AUC 31%	Range 23% to 78%†	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑ AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑ AUC 43%	Range 16% to 64%†	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓ AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑ AUC 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	↓ AUC 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	↑ AUC 80%	Range 64% to 130%†	Not Assessed

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

* This table is not all inclusive.

†Estimated range of percent difference.

INDICATIONS AND USAGE

COMBIVIR in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

Description of Clinical Studies: *COMBIVIR:* There have been no clinical trials conducted with COMBIVIR. See CLINICAL PHARMACOLOGY for information about bioequivalence. One COMBIVIR Tablet given twice a day is an alternative regimen to EPIVIR Tablets 150 mg twice a day plus RETROVIR 600 mg per day in divided doses.

Lamivudine Plus Zidovudine: The NUCB3007 (CAESAR) study was conducted using EPIVIR 150-mg Tablets (150 mg b.i.d.) and RETROVIR 100-mg Capsules (2 x 100 mg t.i.d.). CAESAR was a multicenter, double-blind, placebo-controlled study comparing continued current therapy [zidovudine alone (62% of patients) or zidovudine with didanosine or zalcitabine (38% of patients)] to the addition of EPIVIR or EPIVIR plus an investigational non-nucleoside reverse transcriptase inhibitor, randomized 1:2:1. A total of 1,816 HIV-infected adults with 25 to 250 (median 122) CD4 cells/mm^3 at baseline were enrolled: median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median duration on study was 12 months. Results are summarized in Table 3.

Table 3. Number of Patients (%) With At Least 1 HIV Disease-Progression Event or Death

Endpoint	Current Therapy (n = 460)	EPIVIR plus Current Therapy (n = 896)	EPIVIR plus a NNRTI* plus Current Therapy (n = 460)
HIV progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

*An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United States.

CONTRAINDICATIONS

COMBIVIR Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product.

WARNINGS

COMBIVIR is a fixed-dose combination of lamivudine and zidovudine. Ordinarily, COMBIVIR should not be administered concomitantly with lamivudine, zidovudine, or TRIZIVIR®, a fixed-dose combination of abacavir, lamivudine, and zidovudine.

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

Bone Marrow Suppression: COMBIVIR should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm^3 or hemoglobin <9.5 g/dL (see ADVERSE REACTIONS).

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with COMBIVIR. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended.

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 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 COMBIVIR 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 COMBIVIR 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).

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 COMBIVIR.

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B, 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 hepatitis B viral DNA (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.

PRECAUTIONS

Patients with HIV and Hepatitis B Virus Coinfection: 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. Posttreatment exacerbations of hepatitis have also been reported (see WARNINGS).

Patients with Impaired Renal Function: Reduction of the dosages of lamivudine and zidovudine is recommended for patients with impaired renal function. Patients with creatinine clearance <50 mL/min should not receive COMBIVIR.

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: COMBIVIR is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should be advised that the use of COMBIVIR has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be informed that the major toxicities of COMBIVIR 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. Patients should be advised of the importance of taking COMBIVIR as it is prescribed.

Patients should be informed 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.

Drug Interactions: ***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). No data are available regarding the potential for interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

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

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

Concomitant use of COMBIVIR with stavudine should be avoided since an antagonistic relationship with zidovudine has been demonstrated in vitro. In addition, concomitant use of zidovudine with doxorubicin or ribavirin should be avoided because an antagonistic relationship has been demonstrated in vitro.

See CLINICAL PHARMACOLOGY for additional drug interactions.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: ***Carcinogenicity:***

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/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. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months at the highest 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: Lamivudine: Lamivudine was negative in a microbial mutagenicity screen, 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. It was mutagenic in a L5178Y/TK$^{+/-}$ mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes.

Zidovudine: Zidovudine was mutagenic in a 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: 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.

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

Lamivudine: 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 embryolethality 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. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

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 3,683 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, Impairment of Fertility).

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to COMBIVIR and 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. No specific studies of lamivudine and zidovudine excretion in breast milk after dosing with COMBIVIR have been performed, although zidovudine is excreted in breast milk after dosing with RETROVIR (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Nursing Mothers). Although it is not known if lamivudine is excreted in human milk, a study in which lactating rats were administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma.

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 COMBIVIR.**

Pediatric Use: COMBIVIR should not be administered to pediatric patients less than 12 years of age because it is a fixed-dose combination that cannot be adjusted for this patient population.

Geriatric Use: Clinical studies of COMBIVIR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. 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. COMBIVIR 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

Lamivudine Plus Zidovudine Administered As Separate Formulations: In 4 randomized, controlled trials of EPIVIR 300 mg per day plus RETROVIR 600 mg per day, the following selected clinical and laboratory adverse events were observed (see Tables 4 and 5).

Table 4. Selected Clinical Adverse Events (≥5% Frequency) in 4 Controlled Clinical Trials With EPIVIR 300 mg/day and RETROVIR 600 mg/day

Adverse Event	EPIVIR plus RETROVIR (n = 251)
Body as a whole	
Headache	35%
Malaise & fatigue	27%
Fever or chills	10%
Digestive	
Nausea	33%
Diarrhea	18%
Nausea & vomiting	13%
Anorexia and/or decreased appetite	10%
Abdominal pain	9%
Abdominal cramps	6%
Dyspepsia	5%
Nervous system	
Neuropathy	12%
Insomnia & other sleep disorders	11%
Dizziness	10%
Depressive disorders	9%
Respiratory	
Nasal signs & symptoms	20%
Cough	18%
Skin	
Skin rashes	9%
Musculoskeletal	
Musculoskeletal pain	12%
Myalgia	8%
Arthralgia	5%

Pancreatitis was observed in 3 of the 656 adult patients (<0.5%) who received EPIVIR in controlled

clinical trials.

Selected laboratory abnormalities observed during therapy are listed in Table 5.

Table 5. Frequencies of Selected Laboratory Abnormalities Among Adults in 4 Controlled Clinical Trials of EPIVIR 300 mg/day plus RETROVIR 600 mg/day*

Test (Abnormal Level)	EPIVIR plus RETROVIR % (n)
Neutropenia (ANC<750/mm^3)	7.2% (237)
Anemia (Hgb<8.0 g/dL)	2.9% (241)
Thrombocytopenia (platelets<50,000/mm^3)	0.4% (240)
ALT (>5.0 x ULN)	3.7% (241)
AST (>5.0 x ULN)	1.7% (241)
Bilirubin (>2.5 x ULN)	0.8% (241)
Amylase (>2.0 x ULN)	4.2% (72)

ULN = Upper limit of normal.

ANC = Absolute neutrophil count.

n = Number of patients assessed.

* Frequencies of these laboratory abnormalities were higher in patients with mild laboratory abnormalities at baseline.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of EPIVIR, RETROVIR, and/or COMBIVIR. 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 EPIVIR, RETROVIR, and/or COMBIVIR.

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

Digestive: Stomatitis.

Endocrine and Metabolic: Gynecomastia, hyperglycemia.

Gastrointestinal: Oral mucosal pigmentation, stomatitis.

General: Vasculitis, weakness.

Hemic and Lymphatic: Aplastic anemia, anemia, lymphadenopathy, pure red cell aplasia,

splenomegaly.

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

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

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

OVERDOSAGE

COMBIVIR: There is no known antidote for COMBIVIR.

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. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

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, confusion, and 1 report of a grand mal seizure. 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

The recommended oral dose of COMBIVIR for adults and adolescents (at least 12 years of age) is 1 tablet (containing 150 mg of lamivudine and 300 mg of zidovudine) twice daily.

Dose Adjustment: Because it is a fixed-dose combination, COMBIVIR should not be prescribed for patients requiring dosage adjustment such as those with reduced renal function (creatinine clearance <50 mL/min) or those experiencing dose-limiting adverse events.

A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Because COMBIVIR is a fixed-dose combination that cannot be adjusted for this patient population, COMBIVIR is not recommended for patients with impaired hepatic function.

HOW SUPPLIED

COMBIVIR Tablets, containing 150 mg lamivudine and 300 mg zidovudine, are white, film-coated, modified-capsule-shaped tablets engraved with "GXFC3" on one side. They are available as follows:

60 Tablets/Bottle (NDC 0173-0595-00)

Store between 2° and 30°C (36° and 86°F).

Unit Dose Pack of 120 (NDC 0173-0595-02)

Store between 2° and 30°C (36° and 86°F).

GlaxoSmithKline

Research Triangle Park, NC 27709

Lamivudine is manufactured under agreement from

Shire Pharmaceuticals Group plc

Basingstoke, UK

August 2002 RL-1138

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/s/

Debra Birnkrant
10/8/02 12:51:59 PM
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