

PRODUCT MONOGRAPH

Pr **COMBIVIR**[®]

lamivudine and zidovudine

150 mg of lamivudine and 300 mg zidovudine tablets

Antiretroviral Agent

ViiV Healthcare Shire Canada
7333 Mississauga Road
Mississauga, Ontario
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Pr COMBIVIR®

lamivudine and zidovudine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets/ 150 mg lamivudine and 300 mg zidovudine	None. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

COMBIVIR® (lamivudine and zidovudine) is indicated for:

- the treatment of HIV infection when therapy is warranted.

The clinical trial data obtained with COMBIVIR® is limited. (See ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics section for information on bioequivalence).

CONTRAINDICATIONS

- COMBIVIR® (lamivudine and zidovudine) is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product. For a complete listing see Dosage Forms, Composition and Packaging section. The coadministration of COMBIVIR® with 3TC® or RETROVIR® (AZT) is not recommended.
- Due to the active ingredient zidovudine, COMBIVIR® is contraindicated in patients with abnormally low neutrophil counts ($< 0.75 \times 10^9/L$) or abnormally low haemoglobin levels ($< 7.5 \text{ g/dL}$ or 4.65 mmol/L)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Lactic Acidosis and 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 COMBIVIR[®] and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. 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).

- **Post-Treatment Exacerbation of Hepatitis**

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. COMBIVIR[®] is not indicated for the treatment of chronic HBV infection and the safety and efficacy of COMBIVIR[®] have not been established in patients coinfecting with HBV and HIV. Exacerbations of hepatitis B have been reported in patients after the discontinuation of antiretroviral therapy. Patients coinfecting with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with COMBIVIR[®].

- **Pancreatitis in Pediatric Patients**

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, COMBIVIR[®] should be used with caution. Treatment with COMBIVIR[®] should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS section).

General

The incidence of adverse reactions appears to increase with disease progression and patients should be monitored carefully, especially as disease progression occurs.

The complete prescribing information for all agents being considered for use with COMBIVIR[®] (lamivudine and zidovudine) should be consulted before combination therapy with COMBIVIR[®] is initiated.

Patients should be cautioned about the concomitant use of self-administered medications.

Serious Adverse Reactions

Zidovudine

Several serious adverse events have been reported with use of zidovudine in clinical practice. Reports of pancreatitis, sensitization reactions (including anaphylaxis in one patient), vasculitis, and seizures have been rare. These adverse events, except for sensitization, have also been associated with HIV disease. Changes in skin and nail pigmentation have been associated with the use of zidovudine.

Lamivudine

Several serious adverse events have been reported with use of lamivudine in clinical practice. Reports of anaphylaxis, rhabdomyolysis and peripheral neuropathy have been rare (< 1 in 1000) (see DRUG INTERACTIONS section).

Patients receiving COMBIVIR[®] or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close observation by physicians experienced in the treatment of patients with HIV-associated diseases.

Patients should be advised that current antiretroviral therapy, including COMBIVIR[®], has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

It is recommended that the dose of lamivudine be reduced for adults with body weight below 50 kg (110 lb.) therefore; a patient may be on a reduced dose of lamivudine and a standard dose of zidovudine and would not be a candidate for the use of COMBIVIR[®] tablets. See complete prescribing information for 3TC[®] and RETROVIR[®] (AZT) for dosage adjustment.

Endocrine and Metabolism

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.

Hematologic

Very rare occurrences of pure red cell aplasia have been reported with lamivudine or zidovudine use. Discontinuation of lamivudine and/or zidovudine has resulted in normalization of hematologic parameters in patients with suspected lamivudine- or zidovudine-induced pure red cell aplasia.

Anemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients receiving zidovudine. These occurred more frequently at higher zidovudine dosages (1200 to 1500 mg/day), in patients with advanced HIV disease and in those who had poor marrow reserve prior to treatment (see ADVERSE REACTIONS). Hematological parameters should therefore be carefully monitored (see CONTRAINDICATIONS) in patients receiving COMBIVIR[®].

These hematological effects are not usually observed before four to six weeks therapy. For patients with advanced symptomatic HIV disease, it is generally recommended that blood tests are performed at least every two weeks for the first three months of therapy and at least monthly thereafter. In patients with early HIV disease hematological adverse reactions are infrequent. Depending on the overall condition of the patient, blood tests may be performed less often, for example every one to three months.

Bone Marrow Suppression

COMBIVIR[®] should be used with extreme caution in patients who have bone marrow compromise evidenced by granulocyte count < 1000 cells/mm³ or haemoglobin < 9.5 g/dL. In patients with advanced symptomatic disease, anemia and granulocytopenia were the most significant adverse events observed (see ADVERSE REACTIONS section). There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuation of the drug.

Additionally dosage adjustment of zidovudine may be required if severe anemia or myelosuppression occurs during treatment with COMBIVIR[®], or in patients with pre-existing bone marrow compromise for example haemoglobin less than 9 g/dl (5.59 mmol/l) or neutrophil count less than $1.0 \times 10^9/l$. As dosage adjustment of COMBIVIR[®] is not possible separate preparations of zidovudine and lamivudine should be used (see CONTRAINDICATIONS).

Hepatic/Biliary/Pancreatic

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including lamivudine and zidovudine. A majority of these cases have been in women.

Clinical features which may be indicative of the development of lactic acidosis include generalized weakness, anorexia and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnea and tachypnea).

Caution should be exercised when administering COMBIVIR[®] to any patient, and particularly to those with known risk factors for liver disease. Treatment with COMBIVIR[®] should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Cases of pancreatitis have occurred rarely in patients treated with lamivudine and zidovudine. However it is not clear whether these cases were due to treatment with the medicinal products or to the underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of COMBIVIR[®] until diagnosis of pancreatitis is excluded.

Coadministration of zidovudine with other drugs metabolized by glucuronidation should be avoided because the toxicity of either drug may be potentiated (see DRUG INTERACTIONS section).

Patients Coinfected with Hepatitis B virus

Clinical trials and marketed use of lamivudine, have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with decompensated liver disease. If COMBIVIR[®] is discontinued in a patient with HIV and HBV coinfection, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Patients co-infected with hepatitis C virus

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. Therefore, the co-administration of ribavirin and zidovudine is not advised and consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

Use With Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine or zidovudine in HIV/HCV co-infected patients, **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin.** Patients receiving interferon alfa with or without ribavirin and COMBIVIR[®] should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of COMBIVIR[®] should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child Pugh >6) (see the complete prescribing information for interferon and ribavirin).

Immune

Immune Reconstitution

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP, and TB), which may necessitate further evaluation and treatment.

Ophthalmologic

Myopathy

Myopathy and myositis with pathological changes similar to those produced by HIV disease have been associated with prolonged use of zidovudine and may occur with COMBIVIR[®] therapy.

Renal

Patients with impaired renal function may be at a greater risk of toxicity from COMBIVIR[®] due to decreased renal clearance of the drug. Therefore a dosage adjustment of lamivudine and zidovudine may be necessary. It is recommended that COMBIVIR[®] not be used in patients with reduced renal function (creatinine clearance ≤ 50 mL/min). For these patients, it is recommended that 3TC[®] (lamivudine) and RETROVIR[®] (AZT) (zidovudine) be administered. The individual Product Monographs for 3TC[®] (lamivudine) and RETROVIR[®] (AZT) (zidovudine) should be consulted for appropriate dosage adjustments.

Special Populations

Pregnant Women

There are no adequate and well-controlled studies of COMBIVIR[®] in pregnant women.

Consistent with passive transmission of the drug across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum.

A randomized, double-blind, placebo-controlled trial was conducted in HIV-infected pregnant women to determine the utility of zidovudine for the prevention of maternal-fetal HIV transmission. Congenital abnormalities occurred with similar frequency between infants born to mothers who received zidovudine and infants born to mothers who received placebo.

Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

The long-term consequences of *in utero* and infant exposure to zidovudine are unknown. The long-term effects of early or short-term use of zidovudine in pregnant women are also unknown.

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or peripartum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure *in utero* or peripartum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV. Reproductive studies with lamivudine in animals have not shown evidence of teratogenicity, and showed no effect on male or female fertility. Lamivudine induced early embryoletality when lamivudine was administered to pregnant rabbits at exposure levels comparable to those achieved in man.

Because animal reproduction studies are not always predictive of the human response, COMBIVIR[®] should be used during pregnancy only if the potential benefit outweighs any possible risk. Administration of COMBIVIR[®] during the first three months of pregnancy is not recommended unless the benefit outweighs the risk.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to COMBIVIR[®], an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling ViiV Healthcare Shire Canada's Drug Safety Department (1-877-393-8448).

Nursing Women

It is recommended that HIV-infected women do not breastfeed their infants in order to avoid transmission of HIV. Both lamivudine and zidovudine are excreted in human milk at similar concentrations to those found in serum. Since lamivudine, zidovudine and HIV virus pass into breast milk it is recommended that mothers taking COMBIVIR[®] do not breastfeed their infants.

Following oral administration, lamivudine was excreted in breast milk at similar concentrations to those found in serum. It is recommended that mothers taking lamivudine do not breastfeed to avoid risking postnatal transmission of HIV infection and potential adverse effects from lamivudine in nursing infants.

Zidovudine is excreted in human milk. 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. Mothers should be instructed to discontinue nursing if they are receiving COMBIVIR[®].

Pediatrics

There are no data on the use of COMBIVIR[®] in pediatric patients (see DETAILED PHARMACOLOGY: Pharmacokinetics section).

COMBIVIR[®] is not recommended in children less than 12 years of age, as appropriate dose reduction for the weight of the child cannot be made. (see DOSAGE AND ADMINISTRATION section).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In a human bioequivalence trial, the clinical adverse events associated with COMBIVIR[®] (lamivudine and zidovudine) in 24 subjects were similar when compared to 3TC[®] 150 mg plus RETROVIR[®] (AZT) 300 mg administered as separate tablets. All reported adverse events were mild in intensity. The most frequently reported adverse events after single-dose administration were headache or dizziness (seven events in six subjects) and nausea (four events in four subjects). Other reported adverse events included pruritus, skin lesion, visual disturbance, rhinorrhea, and phlebitis (one event in one subject, each). Ten events in seven subjects were assessed by the investigator as possibly or probably drug related and included headache, nausea, phlebitis, and disturbance of vision.

The safety of chronic dosing with COMBIVIR[®] has not been assessed but is not expected to be different from the safety profiles of 3TC[®] and RETROVIR[®] (AZT) administered concurrently as separate formulations. In four randomized, controlled trials of 3TC[®] 300 mg per day plus RETROVIR[®] (AZT) 600 mg per day, the following selected clinical adverse events were observed (see Table 1).

Table 1: Selected clinical adverse events ($\geq 5\%$ frequency) in four controlled clinical trials with 3TC[®] 300 mg/day and RETROVIR[®] (AZT) 600 mg/day

Adverse Event	3TC [®] plus RETROVIR [®] (AZT) (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%

Other clinical adverse events reported in controlled clinical trials in association with 3TC[®] (lamivudine) 150 mg b.i.d. plus zidovudine 600 mg per day in at least 1% of patients were:

Gastrointestinal: Abdominal discomfort and pain (3%), abdominal distension (3%), dyspepsia (2%), gastrointestinal discomfort and pain (3%), gastrointestinal gas (4%), hyposalivation (2%), oral ulceration (1%)

Musculoskeletal: Muscle atrophy/weakness/tiredness (1%), muscle pain (2%)

Neurological: Mood disorders (1%), sleep disorders (4%), taste disturbances (1%)

Other: Breathing disorders (2%), general signs and symptoms (1%), pain (2%), sexual function disturbances (1%), temperature regulation disturbance (1%)

Skin: Pruritis (1%), skin rashes (1%), sweating (1%)

Pancreatitis was observed in three of the 656 adult patients (< 0.5%) who received 3TC[®] in controlled clinical trials.

Selected laboratory abnormalities observed during therapy are listed in Table 2.

Table 2: Frequencies of selected laboratory abnormalities among adults in four controlled clinical trials of 3TC[®] 300 mg/day plus RETROVIR[®] (AZT) 600 mg/day*

Test (Abnormal Level)	3TC [®] plus RETROVIR [®] (AZT) %(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 ULN)	0.8% (241)
Amylase (>2.0 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

Post-Market Adverse Drug Reactions

The following events have been identified during post-approval use of 3TC[®] and/or RETROVIR[®] (AZT) alone or in combination with other antiretroviral therapy in clinical practice. 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 either their seriousness, frequency of reporting, causal connection to 3TC[®] and/or RETROVIR[®] (AZT), or a combination of these factors.

Body as a Whole:

Redistribution/accumulation of body fat (see WARNINGS AND PRECAUTIONS: Fat Redistribution section).

Cardiovascular:

Cardiac arrest, cardiac failure, cardiomegaly, cardiomyopathy, cerebrovascular accident, hypertension, hypotension, intracranial hemorrhage, orthostatic hypotension, palpitation(s), syncope, tachycardia, vasculitis, vasodilation.

Endocrine and Metabolic:	Acidosis, anorexia, dehydration, gynecomastia, hypercholesterolemia, hyperglycemia, hyperlactataemia, hyperlipidemia, hyperuricemia, hypoglycemia, hyponatremia, inappropriate antidiuretic hormone secretion, increased appetite, increased CPK, increased LDH, increased serum iron, lactic acidosis and hepatic steatosis (see WARNINGS AND PRECAUTIONS section), weight loss.
Eye:	Conjunctivitis, retinitis, visual field defect.
Gastrointestinal:	Abdominal distention, ascites, bleeding gums, constipation, diarrhea, discolouration of tongue, dyspepsia, dysphagia, edema of the tongue, esophagitis, esophageal ulcer, flatulence, gastritis, gastrointestinal hemorrhage, mouth ulcer, nausea and vomiting, oral mucosa pigmentation, peptic ulcer, rectal hemorrhage, rises in serum amylase, sialoadenitis, stomatitis.
General:	Abdominal pain, allergic reaction, anaphylaxis, back pain, <i>Candida</i> infection, chills, chest pain, death, edema of face, edema of extremities, fatigue, fever, flu syndrome, hypertonia, hypotonia, malaise, pain, pallor, sepsis, weakness.
Hemic and Lymphatic:	Abnormalities of red cells, abnormalities of white cells, agranulocytosis, anemia, aplastic anemia, bone marrow depression, eosinophilia, hemolysis, impaired red cell maturation, leukocytosis, leukopenia, lymphadenopathy, lymphocytosis, lymphoma, methemoglobinemia, neutropenia, pancytopenia, pure red cell aplasia, sarcoma, splenomegaly, thrombocytopenia, thrombotic thrombocytopenic purpura.
Hepatobiliary Tract and Pancreas:	Cholestatic jaundice, fatty liver, hepatic impairment, hepatic failure, hepatitis, hepatomegaly, hyperbilirubinemia, increased aminotransferase levels, increased amylase, jaundice, pancreatitis.
Musculoskeletal:	Amyotrophy, arthralgia, muscle disorders including rarely rhabdomyolysis, myositis, tremor, twitch, myalgia, hemarthrosis, leg cramps.

Nervous:	Aggressive behavior, agitation, amnesia, anxiety, ataxia, confusion, convulsions, delusions, dementia, depression, dizziness, dystonic movement(s), emotional lability, encephalitis, facial palsy, hallucinations, headache, hypoesthesia, insomnia, loss of mental acuity, meningitis, myasthenia, nervousness, mania, paresthesia, paranoia, peripheral neuritis, peripheral neuropathy, personality disorder, psychotic disorders, somnolence, tremor, vertigo.
Reproductive:	Amenorrhea, decreased libido, gynaecomastia impotence, intermenstrual bleeding.
Respiratory:	Apnea, cough, dyspnea, epistaxis, hyperventilation, influenza, pharyngitis, pneumonia, rhinitis, sinusitis.
Skin:	Acne, alopecia, changes in skin and nail pigmentation, dryness of skin, erythema multiforme, exfoliative dermatitis, hair colour change, hirsutism, hyperpigmentation, maculopapular lesions, nail disorders, photosensitivity, pruritus, rash, rubelliform rash, Stevens-Johnson syndrome, sweating, urticaria, vesiculobullous rash.
Special Senses:	Ageusia, amblyopia, hearing loss, photophobia, taste disturbance, speech disorder, tinnitus.
Urogenital:	Albuminuria, dysuria, hematuria, increased creatinine levels, polyuria, renal dysfunction, renal failure, urinary frequency.

DRUG INTERACTIONS

Overview

As COMBIVIR[®] contains lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur with COMBIVIR[®].

Zidovudine plasma levels are not significantly altered when coadministered with lamivudine. Zidovudine had no effect on the pharmacokinetics of lamivudine (see ACTION AND CLINICAL PHARMACOLOGY section).

The possibility of interactions with other drugs administered concurrently should be considered, particularly when the main route of elimination is renal.

Drug-Drug Interactions

Table 3: Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
Atovaquone	Zidovudine does not appear to affect the pharmacokinetics of atovaquone	Pharmacokinetic data have shown that atovaquone appears to decrease the rate of metabolism of zidovudine to its glucuronide metabolite (steady state AUC of zidovudine was increased by 33% and peak plasma concentration of the glucuronide was decreased by 19%). At zidovudine dosages of 500 or 600 mg/day it would seem unlikely that a three week, concomitant course of atovaquone for the treatment of acute PCP would result in an increased incidence of adverse reactions attributable to higher plasma concentrations of zidovudine. Extra care should be taken in monitoring patients receiving prolonged atovaquone therapy.
Bone marrow suppressive agents/cytotoxic agents	Coadministration may increase risk of hematologic toxicity.	Coadministration of zidovudine with drugs that are cytotoxic or which interfere with RBC/WBC number or function (e.g. dapsone, flucytosine, vincristine, vinblastine, or adriamycin) may increase the risk of hematologic toxicity.
Clarithromycin	Clarithromycin tablets reduce the absorption of zidovudine.	This can be avoided by separating the administration of zidovudine and clarithromycin by at least two hours.
Fluconazole	Fluconazole interferes with the oral clearance and metabolism of zidovudine.	Preliminary data suggest that fluconazole interferes with the oral clearance and metabolism of zidovudine. In a pharmacokinetic interaction study in which 12 HIV-positive men received zidovudine alone and in combination with fluconazole, increases in the mean peak serum concentration (79%), AUC (70%) and half-life (38%) were observed at steady state. The clinical significance of this interaction is unknown.
Ganciclovir	Coadministration increases the risk of hematologic toxicities in some patients with advanced HIV disease.	Use of zidovudine in combination with ganciclovir increases the risk of hematologic toxicities in some patients with advanced HIV disease. Should the use of this combination become necessary in the treatment of patients with HIV disease, dose reduction or interruption of one or both agents may be necessary to minimize hematologic toxicity. Hematologic parameters, including hemoglobin, hematocrit, and white blood cell count with differential, should be monitored frequently in all patients receiving this combination.
Interferon-alpha	Hematologic toxicities have been seen when zidovudine is used concomitantly with interferon-alpha.	As with the concomitant use of RETROVIR® (AZT) and ganciclovir, dose reduction or interruption of one or both agents may be necessary, and hematologic parameters should be monitored frequently.

Proper name	Effect	Clinical comment
Methadone	Plasma levels of zidovudine can be elevated in some patients while remaining unchanged in others.	In a pharmacokinetic study of 9 HIV-positive patients receiving methadone-maintenance (30 to 90 mg daily) concurrent with 200 mg of zidovudine every 4 hours, no changes were observed in the pharmacokinetics of methadone upon initiation of therapy with zidovudine and after 14 days of treatment with zidovudine. No adjustments in methadone-maintenance requirements were reported. However, plasma levels of zidovudine were elevated in some patients while remaining unchanged in others. The exact mechanism and clinical significance of these data are unknown.
Phenytoin	A decrease in oral zidovudine clearance.	Phenytoin plasma levels have been reported to be low in some patients receiving zidovudine, while in one case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-positive volunteers received a single 300 mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin. Phenytoin concentrations should be carefully monitored in patients receiving COMBIVIR [®] and Phenytoin.
Probenecid	May increase zidovudine levels.	Limited data suggest that probenecid may increase zidovudine levels by inhibiting glucuronidation and/or reducing renal excretion of zidovudine. Some patients who have used zidovudine concomitantly with probenecid have developed flu-like symptoms consisting of myalgia, malaise, and/or fever and maculopapular rash.
Ribavirin	Coadministration of ribavirin and zidovudine may lead to increased ribavirin levels and increased risk of anemia.	Preliminary data suggest that the use of ribavirin and zidovudine lead to increased ribavirin levels and increased risk of anemia. The use of ribavirin concomitantly with zidovudine in the treatment of HIV / Hep C co-infected patients is not advised. Consideration should be given to replacing zidovudine in a combination ART regimen if this is already established.
Stavudine	Zidovudine may inhibit intracellular phosphorylation of stavudine	Zidovudine may inhibit the intracellular phosphorylation of stavudine when the two medicinal products are used concurrently. Stavudine is therefore not recommended to be used in combination with zidovudine.
Trimethoprim, a constituent of co-trimoxazole	Administration of trimethoprim, a constituent of co-trimoxazole causes a 40% increase in lamivudine plasma levels.	However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of co-trimoxazole. Administration of co-trimoxazole with the lamivudine/zidovudine combination in patients with renal impairment should be carefully assessed.

Proper name	Effect	Clinical comment
Valproic acid	Increase in zidovudine AUC and a decrease in the plasma GZDV AUC.	The concomitant administration of valproic acid 250 mg (n=5) or 500 mg (n=1) every 8 hours and zidovudine 100 mg orally every 8 hours for 4 days to 6 HIV-infected, asymptomatic male volunteers resulted in a 79% ± 61% (mean ± SD) increase in the plasma zidovudine AUC and a 22% ± 10% decrease in the plasma GZDV AUC as compared to the administration of zidovudine in the absence of valproic acid. The GZDV/zidovudine urinary excretion ratio decreased 58% ± 12%. Because no change in the zidovudine plasma half-life occurred, these results suggest that valproic acid may increase the oral bioavailability of zidovudine through inhibition of first-pass metabolism. Although the clinical signification of this interaction is unknown, patients should be monitored more closely for a possible increase in zidovudine-related adverse effects. The effect of zidovudine on the pharmacokinetics of valproic acid was not evaluated.
Zalcitabine	Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently.	COMBIVIR [®] is therefore not recommended to be used in combination with zalcitabine.
Other agents		Preliminary data from a drug interaction study (n=10) suggest that coadministration of 200 mg RETROVIR [®] (AZT) and 600 mg rifampin decreases the area under the plasma concentration curve of zidovudine by an average of 48% ± 34%. However, the effect of once daily dosing of rifampin on multiple daily doses of RETROVIR [®] (AZT) is unknown.
Miscellaneous		<p>Other medicinal products, including but not limited to, acetylsalicylic acid, codeine, morphine, methadone, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone and isoprinosine, may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Careful thought should be given to the possibilities of interactions before using such medicinal products particularly for chronic therapy, in combination with COMBIVIR[®].</p> <p>Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicinal products (for example systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse reactions to zidovudine. If concomitant therapy with COMBIVIR[®] and any of these medicinal products is necessary then extra care should be taken in monitoring renal function and hematological parameters and, if required, the dosage of one or more agents should be reduced.</p>

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended oral dose of COMBIVIR[®] (lamivudine and zidovudine) for adults and adolescents who are at least 12 years old is one tablet (containing 150 mg of lamivudine and 300 mg zidovudine) twice daily.

Dose Adjustment

It is recommended that separate doses of lamivudine (as 3TC[®]) and zidovudine [as RETROVIR[®] (AZT)] be administered to patients with reduced renal function (see WARNINGS AND PRECAUTIONS section), pediatric patients below 12 years of age, patients with low body weights (less than 50 kg or 110 lb) or patients requiring dosing adjustments due to adverse events. See complete prescribing information for 3TC[®] and RETROVIR[®] (AZT) for dosage adjustments.

Missed Dose

If you forget to take your medicine, take it as soon as you remember. Then continue as before.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is no known antidote for COMBIVIR[®] (lamivudine and zidovudine).

If overdose occurs the patient should be monitored, and standard supportive treatment applied as required. Although no data is available, administration of activated charcoal may be used to aid in removal of unabsorbed drug. 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. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine while elimination of its primary metabolite, GZDV is enhanced.

Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patient recovered. No specific signs or symptoms have been identified following such overdose.

One case of acute overdose in an adult ingesting 6 g of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. One other adult patient in error ingested lamivudine 1,200 mg per day plus zidovudine 1,200 mg per day for approximately 2 weeks; he had a Grade 3 decrease in absolute neutrophil count that resolved upon reduction of doses of lamivudine and zidovudine. In Phase I studies, lamivudine was administered at doses up to 20 mg/kg per day (i.e., approximately five times the usual recommended dose in adults) without serious consequences.

Cases of acute overdose of zidovudine in both children and adults have been reported with doses up to 50 grams. The only consistent finding in these cases of overdose was spontaneous or induced nausea and vomiting. Hematologic changes were transient and not severe. Some patients experienced nonspecific CNS symptoms such as headache, dizziness, drowsiness, lethargy, and confusion. One report of a grand mal seizure possibly attributable to zidovudine occurred in a 35-year-old male 3 hours after ingesting 36 grams of zidovudine. No other cause could be identified. All patients recovered without permanent sequelae.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Lamivudine and zidovudine are potent, selective inhibitors of HIV-1 and HIV-2 replication *in vitro*. Lamivudine is the (-) enantiomer of a dideoxy analogue of cytidine. Zidovudine is a thymidine analogue in which the 3'-hydroxy (-OH) group is replaced by an azido (-N₃) group. Intracellularly, lamivudine and zidovudine are phosphorylated to their active 5'-triphosphate metabolites, lamivudine triphosphate (L-TP) and zidovudine triphosphate (ZDV-TP). *In vitro* L-TP has an intracellular half-life of approximately 10.5 to 15.5 hours. The principal mode of action of L-TP and ZDV-TP is inhibition of HIV reverse transcription (RT) via viral DNA chain termination. L-TP is a weak inhibitor of mammalian α , β , and γ -DNA polymerases. ZDV-TP is a weak inhibitor of the cellular DNA polymerase- α and mitochondrial polymerase- γ and has been reported to be incorporated into the DNA of cells in culture.

Pharmacokinetics

The single-dose pharmacokinetic properties of COMBIVIR[®] (lamivudine and zidovudine) have been studied in 24 healthy adult subjects in a single-centre, open label, randomized, three-way crossover study to evaluate the bioequivalence between COMBIVIR[®] and the 150 mg 3TC[®] tablet and the 300 mg RETROVIR[®] (AZT) tablet given simultaneously. COMBIVIR[®] was bioequivalent to one 3TC[®] tablet (150 mg) plus one RETROVIR[®] (AZT) tablet (300 mg) when administered to fasting subjects. A summary of the results is provided in Table 4.

Table 4 : Summary Table of Measured Comparative Bioavailability Data for COMBIVIR® (Lamivudine and Zidovudine) Tablets

	Geometric Mean and Arithmetic Mean (CV)						Ratio of Geometric Means A:B (%) (CI)		Ratio of Geometric Means C:A (%) (CI)	
	Treatment A Combined 150 mg Lamivudine and Zidovudine 300 mg Fasted		Treatment B 3TC® 150 mg Tablet + RETROVIR® (AZT) 300 mg Tablet Fasted		Treatment C Combined 150 mg Lamivudine and Zidovudine 300 mg Fed					
	ZDV	LAM	ZDV	LAM	ZDV	LAM	ZDV	LAM	ZDV	LAM
AUC _{last} (ng·h/mL)	2266.80 2365.63 (29.6)	5747.93 5896.06 (21.45)	2296.02 2357.09 (23.22)	5931.51 6131.41 (26.37)	2029.33 1810.16 (31.21)	5683.12 5167.96 (18.67)	0.99 (0.91-1.07)	0.97 (0.92-1.03)	0.90 (0.83-0.97)	0.99 (0.93-1.05)
AUC _∞ (ng·h/mL)	2299.44 2398.16 (29.43)	6004.95 6137.56 (20.11)	2329.36 2390.88 (23.13)	6185.54 6374.20 (25.22)	2061.10 2147.63 (30.95)	5932.26 6035.41 (19.23)	0.99 (0.91-1.07)	0.97 (0.92-1.02)	0.90 (0.83-0.97)	0.99 (0.94-1.04)
C _{max} (ng/mL)	1827.27 2008.27 (40.33)	1536.96 1620.28 (32.07)	1883.15 1992.64 (31.92)	1634.32 1742.22 (35.37)	1000.26 1139.24 (51.59)	1311.73 1367.59 (29.53)	0.97 (0.82-1.15)	0.94 (0.84-1.06)	0.55 (0.46-0.65)	0.85 (0.76-0.96)
T _{max} (h)	0.50* 0.57 (80.32)	0.75* 0.91 (53.16)	0.50* 0.58 (58.83)	1.00* 0.91 (40.51)	1.00* 1.07 (61.26)	1.50* 1.86 (50.81)	NA	NA	NA	NA
T _{1/2} (h)	1.48	9.66	1.43	9.52	1.48	9.80	NA	NA	NA	NA
	1.50 (15.73)	9.98 (27.85)	1.45 (16.24)	9.79 (24.71)	1.53 (26.78)	10.52 (50.61)				

ZDV = zidovudine, LAM = lamivudine

* Median

NA: not applicable

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-infected adult patients after administration of single oral, multiple oral and intravenous (IV) doses ranging from 0.25 to 10 mg/kg. After oral administration of 2 mg/kg, the peak plasma lamivudine concentration (C_{max}) was 1.5 ± 0.5 mcg/mL (mean ± SD) and half-life was 2.6 ± 0.5 hours. There were no significant differences in half-life across the range of single doses (0.25 to 8 mg/kg). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to dose over the range from 0.25 to 10 mg/kg.

Lamivudine is well absorbed from the gut, and the bioavailability of oral lamivudine in adults is normally between 80 and 85%. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour.

Pharmacokinetic studies of RETROVIR[®] (AZT) following intravenous dosing in adults indicate dose-independent kinetics over the range of 1 to 5 mg/kg with a mean zidovudine half-life of 1.1 hours. Zidovudine is rapidly metabolized in the liver to 3'-azido-3'-deoxy-5'-O-β-D- glucopyranuronosylthymidine (GZDV, formerly called GAZT), and both are rapidly eliminated by the kidney. A second metabolite, 3'-amino-3'-deoxythymidine (AMT) has been identified in the plasma following single-dose intravenous administration of zidovudine.

After oral dosing in adults, zidovudine is rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring within 0.5 to 1.5 hours, with an average oral bioavailability of 65%.

STORAGE AND STABILITY

COMBIVIR[®] (lamivudine and zidovudine) tablets should be stored between 2°C and 30°C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

COMBIVIR[®] (lamivudine and zidovudine) tablets are white to off-white, capsule-shaped, film-coated tablets containing 150 mg lamivudine and 300 mg zidovudine. The tablets are scored and embossed "GX FC3" on both sides. Available in HDPE bottles of 60 tablets.

Composition

Each COMBIVIR[®] tablet contains 150 mg of lamivudine and 300 mg of zidovudine. In addition, each tablet contains the nonmedicinal ingredients colloidal silicon dioxide, hydroxypropyl methyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

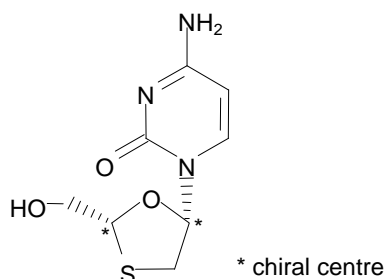
Drug Substance

Proper name: lamivudine

Chemical name: 2(1H)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-, (2R-cis)-

Molecular formula and molecular mass: $C_8H_{11}N_3O_3S$ 229.3

Structural formula:



Physicochemical properties:

Description: Lamivudine is a white to off-white crystalline solid. It has a melting point of 176°C and a solubility of approximately 70 mg/mL in water at 20°C.

pKa and pH: The pH value of a 1% w/v solution of lamivudine in water is approximately 6.9. The pKa determined by UV is 4.30.

Distribution Coefficient: The distribution coefficient of lamivudine between n-octanol and water at pH 7.4 was -0.7 ± 0.2 when measured by HPLC.

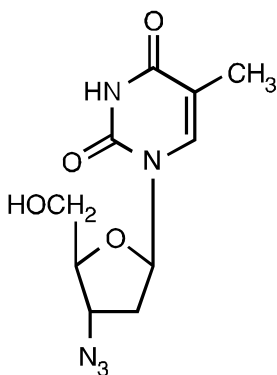
Drug Substance

Proper name: zidovudine

Chemical name: 3'-azido-3'-deoxythymidine

Molecular formula and molecular mass: $C_{10}H_{13}N_5O_4$ 267.24

Structural formula:



Physicochemical properties:

Description: Zidovudine is a white to beige, odourless, crystalline solid. It has a melting point of 122-124°C and a solubility in water of 20.1 mg/mL at 25°C.

pKa and pH: The pH value of a 10 mg/L solution of zidovudine in water is approximately 6.2. The pKa is 9.68.

Distribution Coefficient: The distribution coefficient of zidovudine between 1-octanol and distilled water at 25°C is 1.15.

CLINICAL TRIALS

Please refer to PART II: SCIENTIFIC INFORMATION, DETAILED PHARMACOLOGY section.

DETAILED PHARMACOLOGY

Pharmacokinetics in Adults

The single-dose pharmacokinetic properties of COMBIVIR[®] (lamivudine and zidovudine) have been studied in 24 healthy adult subjects in a single-center, open-label, randomized, three-way crossover study to evaluate the bioequivalence between COMBIVIR[®] and the 150 mg 3TC[®] tablet and the 300 mg RETROVIR[®] (AZT) tablet given simultaneously. The effect of food (67 grams fat, 33 grams protein, and 58 grams carbohydrate) on the rate and extent of absorption of COMBIVIR[®] was also evaluated (see Effect of Food on Absorption). COMBIVIR[®] was bioequivalent to one 3TC[®] tablet (150 mg) plus one RETROVIR[®] (AZT) tablet (300 mg) when administered to fasting subjects.

Absorption and Bioavailability

Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the tablet and 87% ± 13% for the oral solution. After oral dosing (capsules) zidovudine was rapidly absorbed from the gastrointestinal tract. As a result of first-pass metabolism, the average oral capsule bioavailability of zidovudine is 64% ± 10% (mean ± SD).

Distribution

Lamivudine's apparent volume of distribution after intravenous (IV) administration to 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight. Binding of lamivudine to human plasma proteins is low (< 36%). *In vitro* studies showed that, over the concentration range of 0.1 to 100 µg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration. Similar to lamivudine, zidovudine's apparent volume of distribution after IV administration was 1.6 L/kg and plasma protein binding is 34% to 38%.

Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF lamivudine concentrations in eight patients ranged from 5.6% to 30.9% (mean ± SD of 14.2% ± 7.9%) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.30 µg/mL. The zidovudine CSF/plasma concentration ratio was determined in 39 adult patients receiving chronic therapy with RETROVIR[®] (AZT). The median ratio measured in 50 paired samples drawn 1 to 8 hours after the last dose of RETROVIR[®] (AZT) was 0.6 (range 0.04 to 2.62).

Metabolism

Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral lamivudine dose in six HIV-infected adults, $5.2\% \pm 1.4\%$ (mean \pm SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

Zidovudine is rapidly metabolized to 3'-azido-3'-deoxy-5'-O- β -D-glucopyranuronosylthymidine (GZDV), which has an apparent elimination half-life of 1 hour (range 0.61 to 1.73 hours). Following oral administration, urinary recovery of zidovudine and GZDV accounted for 14% and 74% of the dose, respectively, and the total urinary recovery averaged 90% (range 63% to 95%), indicating a high degree of absorption. A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous administration of zidovudine. AMT area-under-the-curve (AUC) was one-fifth of the AUC of zidovudine and had a half-life of 2.7 ± 0.7 hours. In comparison, GZDV AUC was about three-fold greater than the AUC of zidovudine.

Elimination

The majority of lamivudine is eliminated unchanged in urine. In 20 patients given a single IV dose, renal clearance was 0.22 ± 0.06 L/hr/kg (mean \pm SD), representing $71\% \pm 16\%$ (mean \pm SD) of total lamivudine clearance. In most single-dose studies in HIV-infected patients with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours. Oral clearance was 0.37 ± 0.05 L/hr/kg (mean \pm SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg. Renal clearance is estimated to be 314 mL/min, indicating glomerular filtration and active tubular secretion by the kidneys.

Zidovudine pharmacokinetic data following intravenous dosing indicated dose-independent kinetics over the range of 1 to 5 mg/kg with a mean zidovudine half-life of 1.1 hours (range 0.48 to 2.86 hours). Total body clearance averaged 1.6 L/hr/kg. Renal clearance is estimated to be 0.34 L/hr/kg, indicating glomerular filtration and active tubular secretion by the kidneys.

Special Populations

Impaired Renal Function

The elimination of lamivudine and zidovudine in patients with impaired renal function is diminished. Reduction of the dosages of lamivudine and zidovudine are recommended for patients with impaired renal function (see WARNINGS AND PRECAUTIONS section).

The pharmacokinetic properties of lamivudine were determined in a small group of HIV-infected adults with impaired renal function, and are summarized in Table 5.

Table 5: Pharmacokinetic Parameters (Mean ± S.D.) After a Single 300 mg Oral Dose of Lamivudine in Three Groups of Adults with Varying Degrees of Renal Function (CrCl > 60 mL/min, CrCl = 10-30 mL/min and CrCl < 10mL/min)

Number of subjects	6	4	6
Creatinine clearance criterion	> 60 mL/min	10-30 mL/min	< 10 mL/min
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C _{max} (µg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC _∞ (µg·h/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

These results show increases in C_{max} and half-life with diminishing creatinine clearance. Apparent total clearance (Cl/F) of lamivudine decreased as creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with reduced creatinine clearance (see DOSAGE AND ADMINISTRATION section).

The pharmacokinetics of zidovudine has been evaluated in patients with impaired renal function following a single 200 mg oral dose. In 14 patients (mean creatinine clearance 18 ± 2 mL/min), the half-life of zidovudine was 1.4 hours compared to 1.0 hour for control subjects with normal renal function; AUC values were approximately twice those of controls. Additionally, GZDV half-life in these patients was 8.0 hours (vs 0.9 hours for control) and AUC was 17 times higher than for control subjects. The pharmacokinetics and tolerance were evaluated in a multiple-dose study in patients undergoing hemodialysis (n=5) or peritoneal dialysis (n=6). Patients received escalating doses of zidovudine up to 200 mg 5 times daily for 8 weeks. Daily doses of 500 mg or less were welltolerated despite significantly elevated plasma levels of GZDV. Total body clearance after oral administration of zidovudine was approximately 50% of that reported in patients with normal renal function. The plasma concentrations of AMT are not known in patients with renal insufficiency. Daily doses of 300 to 400 mg should be appropriate in HIV-infected patients with severe renal dysfunction. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, whereas GZDV elimination is enhanced.

Pregnancy

The pharmacokinetics of zidovudine have been studied in a Phase 1 study of eight women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine were similar to those of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in infant plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone-maintenance therapy in five pregnant women did not appear to alter zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has been identified (see DRUG INTERACTIONS section).

Following oral administration, lamivudine pharmacokinetics in latepregnancy were similar to nonpregnant adults.

Nursing Mothers

See WARNINGS AND PRECAUTIONS: Nursing Mothers.

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum.

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[®] has not been studied in pediatric patients. Such patients can receive 3TC[®] or RETROVIR[®] (AZT) in accordance with proper dosage and administration.

Zidovudine

The pharmacokinetics and bioavailability of zidovudine have been evaluated in 21 HIV-infected children, aged 6 months through 12 years, following intravenous doses administered over the range of 80 to 160 mg/m² every 6 hours, and following oral doses of the intravenous solution administered over the range of 90 to 240 mg/m² every 6 hours. After discontinuation of the I.V. infusion, zidovudine plasma concentrations decayed biexponentially, consistent with two-compartment pharmacokinetics. Proportional increases in AUC and in zidovudine concentrations were observed with increasing dose, consistent with dose-independent kinetics over the dose range studied. The mean terminal half-life and total body clearance across all dose levels administered were 1.5 hours and 30.9 mL/min/kg, respectively. These values compare to mean half-life and total body clearance in adults of 1.1 hours and 27.1 mL/min/kg.

The mean oral bioavailability of 65% was independent of dose. This value is the same as the bioavailability in adults. Doses of 180 mg/m² four times daily in pediatric patients produced similar systemic exposure (24 hour AUC 10.7 hr•µg/mL) as doses of 200 mg six times daily in adult patients (10.9 hr•µg/mL).

The pharmacokinetics of zidovudine have been studied in neonates from birth to 3 months of life. In one study of the pharmacokinetics of zidovudine in women during the last trimester of pregnancy, zidovudine elimination was determined immediately after birth in 8 infants who were exposed to zidovudine *in utero*. The half-life was 13.0 ± 5.8 hours. In another study, the pharmacokinetics of zidovudine were evaluated in infants (ranging in age from 1 day to 3 months) of normal birth weight for gestational age and with normal renal and hepatic function. In infants less than or equal to 14 days old, mean ± SD total body clearance was 10.9 ± 4.8 mL/min/kg (n=18) and half-life was 3.1 ± 1.2 hours (n=21). In infants greater than 14 days, total body clearance was 19.0 ± 4.0 mL/min/kg (n=16) and half-life was 1.9 ± 0.7 hours (n=18). Bioavailability was 89% ± 19% (n=15) in the younger age group and decreased to 61% ± 19% (n=17) in infants older than 14 days.

Concentrations of zidovudine in cerebrospinal fluid were measured after both intermittent oral and I.V. drug administration in 21 children during Phase I and Phase II studies. The mean zidovudine CSF/plasma concentration ratio measured at an average time of 2.2 hours post-dose at doses of 120 to 240 mg/m² was 0.52 ± 0.44 (n=28); after an I.V. infusion of doses of 80 to 160 mg/m² over 1 hour, the mean CSF/plasma concentration ratio was 0.87 ± 0.66 (n=23) at 3.2 hours after the start of the infusion. During continuous intravenous infusion the mean steady-state CSF/plasma ratio was 0.26 ± 0.17 (n=28).

As in adult patients, the major route of elimination in children was by metabolism to GZDV. After I.V. dosing, about 29% of the dose was excreted in the urine unchanged and about 45% of the dose was excreted as GZDV. Overall, the pharmacokinetics of zidovudine in pediatric patients older than 3 months of age is similar to that of zidovudine in adult patients.

Lamivudine

Pharmacokinetic properties of lamivudine have been assessed as part of a study of 97 HIV-infected patients. A subset of 57 of these patients had pharmacokinetic assessments after oral and IV administration of 1, 2, 5, 8, 12 and 20 mg/kg per day. These patients ranged in age from 4.8 months to 16 years and in weight from 5 to 66 kg. In the 9 infants and children receiving 8 mg/kg per day, absolute bioavailability was $66\% \pm 26\%$ (mean \pm S.D.), which is less than the $86\% \pm 16\%$ (mean \pm SD) observed in adolescents and adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown.

After oral administration of 8 mg/kg of lamivudine to 12 pediatric patients, C_{max} was 1.2 ± 0.5 μ g/mL and half-life was 2.1 ± 0.6 hours (In adults with similar blood sampling, the half-life was 3.7 ± 1 hours.). There were no significant differences in pharmacokinetic properties in infants compared with children. There were no significant differences in $T_{1/2}$ across the range of doses. AUC and C_{max} increased in proportion to dose over the range from 1 to 20 mg/kg. Total exposure to lamivudine, as reflected by AUC, was comparable between pediatric patients receiving an 8 mg/kg dose and adults receiving a 4 mg/kg dose.

Distribution of lamivudine into cerebrospinal fluid was assessed in 38 pediatric patients. Cerebrospinal fluid concentrations were 3% to 47% of the concentration in a simultaneous serum sample.

Geriatric Patients

Lamivudine and zidovudine pharmacokinetics have not been studied in patients over 65 years of age.

Gender

There are no significant differences in pharmacokinetic properties of lamivudine by gender.

Race

There are no significant differences in pharmacokinetic properties of lamivudine among races.

Effect of Food on Absorption

The extent of lamivudine and zidovudine absorption (AUC_{∞}) and estimates of half-life following administration of COMBIVIR[®] with food were similar when compared to fasting subjects. Therefore, COMBIVIR[®] may be administered with or without food. The rate of absorption (C_{max} , t_{max}) was slowed by food. Lamivudine C_{max} and zidovudine C_{max} were decreased by 15% (4% to 24%) and 45% (35% to 54%) (geometric mean ratio with 90% confidence interval), respectively, when administered with food. The slower rate of absorption in the presence of food resulted in a median prolongation of t_{max} , approximately 0.9 hours for lamivudine and 0.6 hours for zidovudine, when compared to fasted conditions.

MICROBIOLOGY

Virology

Lamivudine and zidovudine are potent selective inhibitors of HIV-1 and HIV-2 replication *in vitro*. Lamivudine is the (-) enantiomer of a dideoxy analogue of cytidine. Zidovudine is a thymidine analogue in which the 3'-hydroxy (-OH) group is replaced by an azido (-N₃) group. Intracellularly, lamivudine and zidovudine are phosphorylated to their active 5'-triphosphate metabolites, lamivudine triphosphate (L-TP) and zidovudine triphosphate (ZDV-TP). *In vitro* L-TP and ZDV-TP have an intracellular half-life of approximately 10.5 to 15.5 hours and 3 hours respectively. The principal mode of action of L-TP and ZDV-TP is inhibition of HIV reverse transcription (RT) via viral DNA chain termination. L-TP is a weak inhibitor of mammalian α , β , and γ -DNA polymerases. ZDV-TP is a weak inhibitor of the cellular DNA polymerase- α and mitochondrial polymerase- γ and has been reported to be incorporated into the DNA of cells in culture.

In Vitro Activity

The relationships between *in vitro* susceptibility of HIV to lamivudine and zidovudine and the inhibition of HIV replication in humans or clinical response are still being investigated. The anti-HIV activity of nucleoside analogues *in vitro* can vary depending on the viral strain, cell type, and assay used to measure such activity. To assess the activity of lamivudine and zidovudine, a number of virus/cell combinations were used, and inhibitory activity was measured in different assays by determination of IC_{50} and IC_{90} values. Lamivudine and zidovudine demonstrated anti-HIV-1 activities in all virus/cell combinations tested. However, zidovudine activity was substantially less in chronically infected cell lines.

The antiviral activity of lamivudine has been studied in combination with other antiretroviral compounds (zidovudine, zalcitabine, and didanosine) using HIV-1-infected MT-4 cells as the test system. The MTT formazan assay demonstrated synergistic antiretroviral activity between lamivudine and zidovudine, additive antiretroviral activity between lamivudine and zalcitabine, and additive antiretroviral activity between lamivudine and didanosine. The combination of lamivudine/zidovudine also showed synergistic activity in a variable-ratio study.

Resistance

In nonclinical studies, lamivudine-resistant isolates of HIV have been selected *in vitro*. A known mechanism of lamivudine resistance is the change in the 184 amino acid of RT from methionine to either isoleucine or valine. *In vitro* studies indicate that zidovudine-resistant viral isolates can become sensitive to zidovudine when they acquire the 184 mutation. The clinical relevance of such findings remains, however, not well defined.

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a < 4-fold decrease in susceptibility to didanosine and zalcitabine; the clinical significance of these findings is unknown.

Multiple drug antiretroviral therapy containing lamivudine has been shown to be effective in antiretrovirally-naïve patients as well as in patients presenting with viruses containing the M184V mutations.

In vitro resistance to zidovudine is due to the accumulation of specific mutations in the HIV reverse transcriptase coding region. Six amino acid substitutions (Met41→Leu, A67→Asn, Lys70→Arg, L210W, Thr215→Tyr or Phe, and Lys219→Gln) have been described in viruses with decreased *in vitro* susceptibility to zidovudine inhibition. Viruses acquire phenotypic resistance to thymidine analogues through the combination of mutations at codons 41 and 215 or by accumulation of at least four to six mutations. These thymidine analogue mutations alone do not cause high-level cross-resistance to any of the other nucleosides, allowing for subsequent use of any other approved reverse transcriptase inhibitors.

For isolates collected in clinical studies, phenotypic and genotypic resistance data showed that resistance to lamivudine monotherapy or combination therapy with lamivudine plus zidovudine developed in most patients within 12 weeks. Evidence in isolates from antiretrovirally-naïve patients suggests that the combination of lamivudine and zidovudine delays the emergence of mutations conferring resistance to zidovudine. Combination therapy with lamivudine plus zidovudine did not prevent phenotypic resistance to lamivudine. However, phenotypic resistance to lamivudine did not limit the antiretroviral activity of combination therapy with lamivudine plus zidovudine. In antiretroviral therapy-naïve patients, phenotypic resistance to lamivudine emerged more slowly on combination therapy than on lamivudine monotherapy. In the zidovudine-experienced patients on lamivudine plus zidovudine, no consistent pattern of changes in phenotypic resistance to lamivudine or zidovudine was observed.

Cross-Resistance

The potential for cross-resistance between HIV reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved. 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 the combination of zidovudine and didanosine or zalcitabine. The pattern of resistant mutations in the combination therapy was different (Ala62→Val, Val75→Ile, Phe77→Leu, Phe116→Tyr and Gln151→Met) from monotherapy, with mutation 151 being most significant for multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also result in resistance to zalcitabine, lamivudine, and stavudine. A second pattern, typically involving a T69S mutation plus a 6 base-pair inserted at the same position, results in a phenotypic resistance to zidovudine as well as to the other approved nucleoside reverse transcriptase inhibitors. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

Cytotoxicity

The results of cytotoxicity studies in various assays have shown little cytotoxic action with lamivudine. Cytotoxicity of lamivudine was compared with that of zidovudine, zalcitabine, and didanosine in four T-lymphoblastoid cell lines; one monocyte/macrophage-like cell line; one B-lymphoblastoid cell line; and peripheral blood lymphocytes (PBLs) using both cell proliferation (CP) and [³H]-thymidine uptake (Td) assays. In the CP assay, lamivudine was the least toxic of the four compounds. [³H]-thymidine uptake results demonstrated a similar trend to those from the CP assays. Lamivudine had no cytotoxic effect when incubated for 10 days with phytohemagglutinin (PHA)-activated human lymphocytes or human macrophages.

The cytotoxicity of combinations of lamivudine with zidovudine, zalcitabine, or didanosine was evaluated in PHA-activated PBLs and CEM cells by measuring cellular uptake of [³H]-thymidine. Lamivudine greatly reduced the cytotoxicity of zalcitabine, slightly reduced the cytotoxicity of zidovudine in some cases, and did not alter the cytotoxicity of didanosine.

In myelotoxicity studies *in vitro*, lamivudine demonstrated no toxic effects against erythroid, granulocyte-macrophage, pluripotent, or stromal progenitor cells from healthy human donors. Lamivudine was not toxic to human hematopoietic supportive stroma, nonadherent hematopoietic cells, or stromal fibroblasts, and produced minimal changes in cytokine (GM-CSF) production from mitogen-stimulated bone marrow stromal cells. Lamivudine was less toxic than zidovudine, zalcitabine, ara-C, 3FT, and stavudine in these studies. In another study, lamivudine was not toxic to activated human T-cells.

The cytotoxicity of zidovudine for various cell lines was determined using a cell growth inhibition assay. ID₅₀ values for several human cell lines showed little growth inhibition by zidovudine except at concentrations > 50 µg/mL. However, one human T-lymphocyte cell line was sensitive to the cytotoxic effect of zidovudine with an ID₅₀ of 5 µg/mL. Moreover, in a colony-forming unit assay designed to assess the toxicity of zidovudine for human bone marrow, an ID₅₀ value of < 1.25 µg/mL was estimated. Two of 10 human lymphocyte cultures tested were found to be sensitive to zidovudine at 5 µg/mL or less.

TOXICOLOGY

Acute Toxicity

Acute toxicity studies with lamivudine and zidovudine have been performed in the mouse and rat. The acute oral administration of very high doses of lamivudine (two doses of 2000 mg/kg) in mice was associated with transient increases in sexual activity in males and general activity in males and females. There were no deaths and no evidence of target organ toxicity. Therefore the maximum non-lethal oral dose of lamivudine in mice is greater than two doses of 2000 mg/kg.

The acute intravenous administration of lamivudine at 2000 mg/kg was well tolerated by both mice and rats and was not associated with any target organ toxicity. A number of non-specific clinical signs were observed which were more severe in rats but were all of relatively short duration.

Acute toxicity studies with zidovudine in mice and rats at doses up to 750 mg/kg produced only one death, in a mouse given 487 mg/kg of zidovudine. Death was preceded by chronic convulsions. Decreased activity, ptosis and laboured breathing were noted in other animals for up to 35 minutes post-dose. No effects were seen during the 14-day post-dose observation period.

In a second set of acute toxicity studies at higher doses of zidovudine, the median lethal doses for mice were 3568 mg/kg and 3062 mg/kg for male and female, respectively. In rats, the median lethal doses were 3084 mg/kg for males and 3683 mg/kg for females.

Clinical signs noted prior to death included ptosis, decreased activity, ataxia, body tremors, urine stains and prostration in mice. In rats, decreased activity and salivation occurred in most animals; the males receiving 5000 mg/kg also exhibited rough coats and lacrimation.

Long-Term Toxicity

In repeat-dose toxicity studies, lamivudine was very well tolerated in the rat at oral doses up to 2000 mg/kg b.i.d. for 6 months. Treatment-related effects were restricted to minor hematological (mainly red cell parameters), clinical chemistry and urinalysis changes, and the mucosal hyperplasia of the cecum (in the 6-month study). The no (toxicologically important) effect level was 450 mg/kg b.i.d.

In the dog, oral doses of lamivudine 1500 mg/kg b.i.d. in males and 1000 mg/kg b.i.d. in females for a period of 12 months were well tolerated. Treatment-related changes included reductions in red cell counts at all dose levels, associated with increased MCV and MCH, and reductions in total leucocyte, neutrophil and lymphocyte counts in high dose animals, but with no effect on bone marrow cytology. Deaths were seen in females dosed with 1500 mg/kg b.i.d. in a 3 month study but not in a 12 month study, using a dose of 1000 mg/kg b.i.d.

When administered orally for one month, at a dose of 1000 mg/kg b.i.d., lamivudine demonstrated low hematotoxic potential in the mouse, and did not significantly enhance the hematotoxicity of zidovudine or interferon α .

The results of long-term toxicity studies with zidovudine in rats, dogs and monkeys are presented in the table below. Rats and monkeys received zidovudine by gavage, dogs were administered zidovudine capsules.

Table 6: Long-term Toxicity Studies with Zidovudine in Rats, Dogs and Monkeys.

Species	No. per Group		Dose Levels (mg/kg/day)	Duration (weeks)	Effects
	M	F			
CD Rat	5	5	0, 60, 125, 250, 500	2	Post-dose salivation. Weight loss in mid-dose (1/5) and high-dose (1/5) males.
CD Rat	12	12	0, 56, 167, 500	13	Anogenital staining in high-dose rats. Increased blood glucose levels in high-dose females at term. Occasional decreases in SGOT in both sexes at high dose.
CD Rat	25	25	0, 50, 150, 450	52	Salivation at high dose for the first 4 weeks. Moderate, reversible macrocytic anemia, with reticulocytosis, in the high-dose animals. Increased urine output in some high-dose animals.
Dog	1	1	0, 125, 250, 500	2	High-dose female sacrificed day 14, following 2 days emesis. High-dose male had bloody vomitus on days 11, 14, 16. Marked leukopenia and thrombocytopenia in all treated dogs, most severe in high-dose. Alk. phos., BUN and creatinine increased in high-dose female. Slight increase in kidney weight in both high-dose dogs and in mid-dose male. Focal to diffuse hemorrhage in GI tract and mesentery of both high-dose dogs and mid-dose female. Moderate hypoactivity in the lymph nodes, involution of the thymus (mid- and high-dose females, high-dose male) and splenic lymphoid atrophy (high-dose male only). Dose-related mild to marked hypocellularity of the bone marrow at all dose levels.
Monkey (Cynomolgus)	1	1	0, 125, 250, 500	2	Emesis in high-dose male. Decreased RBC, hematocrit and hemoglobin in all groups (all values within normal range). Increased SGPT in mid- and high-dose males, more marked in high-dose females.
Monkey (Cynomolgus)	4	4	0, 34, 100, 300	13	Emesis in one high-dose male. Mild to moderate decrease in RBC, HCT and HB; slight to mild increase in MCV in mid- and high-dose groups. Slight decrease in WBC in high-dose males.
Monkey (Cynomolgus)	5	5	0, 35, 100, 300	26	Decreased RBC, HCT and HB in all groups, generally dose-related. Increase in MCV and MCH more prominent in males. Dose-related retardation of bone marrow cell maturation, particularly in erythroid elements. Slight, inconsistent increase in platelets in mid- and high-dose group.
Monkey (Cynomolgus)	6	6	Males-35, 100, 300 Females-35, 100, 300	52	Dose-related macrocytic anemia (i.e., decreased RBC, HCT and HB, increased MCV and MCH) maximized by week 26 at latest. After 4 weeks, recovery, the bone marrow smears were similar in control and treated animals. The severity of anemia was similar to that in the 3-month and 6-month study.

Carcinogenicity and Mutagenicity

Lamivudine

Traditional 24-month carcinogenicity studies using lamivudine have been conducted in mice and rats at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at recommended therapeutic doses. The following results should be noted. In mice, there appeared to be an increased incidence of histiocytic sarcoma in female mice treated with 180 mg/kg/day (6 of 60 mice) and 2000 mg/kg/day (5 of 60 mice) when compared to control mice (two control groups with 1 of 60 and 2 of 60 mice). There did not appear an increased incidence in histiocytic sarcoma in female mice treated with 600 mg/kg/day (3 of 60 mice). It should be noted that the control incidence of this type of tumour in this strain of mice can be as high as 10%, similar to that found in the 180 and 2000 mg/kg/day groups. In rats, there appeared to be an increased incidence of endometrial epithelial tumours in female rats treated with 3000 mg/kg/day (5 of 55 rats) when compared to control rats (two control groups each with 2 of 55 rats). There did not appear to be an increased incidence for endometrial tumours in rats treated with 1000 mg/kg/day (2 of 55 rats) or 300 mg/kg/day (1 of 55 rats). It should be noted that there did not appear to be an increased incidence of any proliferative non-neoplastic epithelial lesions in treated female rats when compared to control rats, and the incidence of adenocarcinoma (5/55 or 9%) was only slightly higher than recorded controls at the laboratory where the study was conducted (4/50 or 8%). The statistical significance of the findings in mice and rats varied with the statistical analysis conducted, and therefore, the statistical and hence, the clinical, significance of these findings are uncertain. However, based on the similarity to historical control data, it was concluded that the results of long-term carcinogenicity studies in mice and rats for lamivudine did not seem to show a carcinogenic potential relevant for humans.

Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg (approximately 65 times the recommended human dose based on body surface area comparisons).

Zidovudine

Zidovudine was administered orally at three 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 per day in mice and 80, 220, and 600 mg/kg per day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg per 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 per day on day 279.

In mice, seven late-appearing (after 19 months) vaginal neoplasms (five non-metastasizing squamous cell carcinomas, one squamous cell papilloma, and one 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 tumours were found at the lowest dose.

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

At doses that produced tumours in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 8 times (mouse) and 57 times (rat) the estimated human exposure following a single dose of 300 mg.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg per day or 40 mg/kg per 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 three times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumours was noted with no increase in tumours 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 tumours 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.

No evidence of mutagenicity (with or without metabolic activation) was observed in the Ames *Salmonella* mutagenicity assay at concentrations up to 10 µg per plate, which was the maximum concentration that could be tested because of the antimicrobial activity of zidovudine against the *Salmonella* species. In a mutagenicity assay conducted in L5178Y/TK+/- mouse lymphoma cells, zidovudine was weakly mutagenic in the absence of metabolic activation only at the highest concentrations tested (4,000 and 5000 µg/mL). In the presence of metabolic activation, the drug was weakly mutagenic at concentrations of 1,000 µg/mL and higher. In an *in vitro* mammalian cell transformation assay, zidovudine was positive at concentrations of 0.5 µg/mL and higher. In an *in vitro* cytogenetic study performed in cultured human lymphocytes, zidovudine induced dose-related structural chromosomal abnormalities at concentrations of 3 µg/mL and higher. No such effects were noted at the two lowest concentrations tested, 0.3 and 1 µg/mL. In an *in vivo* cytogenetic study in rats given a single intravenous injection of zidovudine at doses of 37.5 to 300 mg/kg, there were no treatment-related structural or numerical chromosomal alterations in spite of plasma levels that were as high as 453 µg/mL 5 minutes after dosing.

In two *in vivo* micronucleus studies (designed to measure chromosome breakage or mitotic spindle apparatus damage) in male mice, oral doses of zidovudine 100 to 1,000 mg/kg per day administered once daily for approximately 4 weeks induced dose-related increases in micronucleated erythrocytes. Similar results were also seen after 4 or 7 days of dosing at 500 mg/kg per day in rats and mice.

In a study involving 11 AIDS patients, it was reported that the seven patients who were receiving zidovudine (1,200 mg/day) as their only medication for 4 weeks to 7 months showed a chromosome breakage frequency of 8.29 ± 2.65 breaks per 100 peripheral lymphocytes. This was significantly ($p < 0.05$) higher than the incidence of 0.5 ± 0.29 breaks per 100 cells that was observed in the four AIDS patients who had not received zidovudine. A pilot study has demonstrated that zidovudine is incorporated into leukocyte nuclear DNA of adults, including pregnant women, taking zidovudine as treatment for HIV-1 infection, or for the prevention of mother to child viral transmission. Zidovudine was also incorporated into DNA from cord blood leukocytes of infants from zidovudine-treated mothers. The clinical significance of these findings is unknown.

Reproduction and Teratology

Zidovudine

In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation.

No effect on male or female fertility (judged by conception rates) was seen in rats given zidovudine orally at doses up to 450 mg/kg/day.

In a fertility and reproduction study, male rats were dosed for 85 days prior to mating and females for 26 days prior to mating and throughout gestation and lactation. No fetal malformations or variations occurred, but the mid- and high-doses were both embryotoxic, increasing the number of early resorptions and decreasing litter sizes. No embryotoxic effects occurred in untreated females mated with treated males.

No evidence of teratogenicity was found in rats given oral doses of zidovudine of up to 500 mg/kg/day on days 6 through 15 of gestation. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats of 66 to 226 times the peak human plasma concentrations.

In a second teratology study in rats, an oral dose of 3000 mg/kg/day (very near the oral median lethal dose in rats of 3683 mg/kg/day) caused marked maternal toxicity and an increase in the incidence of fetal malformations including absent tail, anal atresia, fetal edema, situs inversus, diaphragmatic hernia, bent limb bones, atlas occipital defect and vertebral and/or rib anomalies. There was also a significant increase in the number of litters with bent ribs, reduced ossification of the vertebral arches, and presacral vertebrae. This dose resulted in peak zidovudine plasma concentrations 117 times peak human plasma concentrations. (Estimated area-under-the-curve AUC in rats at this dose level was 327 times the daily AUC in humans following a single dose of 300 mg). No evidence of teratogenicity was seen in the experiment at doses of 600 mg/kg/day or less.

In one of two studies in pregnant rabbits, the incidence of fetal resorptions was increased in rabbits given 500 mg/kg/day. There was no evidence of a teratogenic effect at any dose level. The doses used in these studies resulted in peak zidovudine plasma concentrations in rabbits of 5 to 49 times mean peak human plasma concentrations achieved following a single 300 mg. dose of zidovudine.

Peri- and Postnatal Studies

A separate peri- and postnatal study was conducted in pregnant rats given doses of 0, 50, 150 and 400 mg/kg/day from day 17 of gestation through to day 21 of lactation. There were no adverse effects noted in either generation. The reproductive capacity of those F₁ generation pups that were raised to sexual maturity was not affected.

Neonatal animals were given 0, 80, 250 or 750 mg/kg/day for two months, starting on lactation day 8. Treatment-related alterations occurred only in the high-dose group and were reversible macrocytic anemia and increased urine output in both sexes, and decreased body weight gain in males. Mild to moderate increases in spleen weights were also noted.

Lamivudine

A range of studies has been performed to assess the effects of repeated oral administration of lamivudine upon mammalian reproduction and development.

In a rat fertility study, except for a few minor changes in high dose (2000 mg/kg b.i.d.) animals, the overall reproductive performance of the F₀ and F₁ generation animals, and the development of the F₁ and F₂ generation, was unaffected by treatment with lamivudine.

Lamivudine was not teratogenic in the rat or rabbit, at doses up to 2000 mg/kg b.i.d. and 500 mg/kg b.i.d., respectively. In the rabbit a slight increase in the incidence of pre-implantation loss at doses 20 mg/kg b.i.d. and above indicates a possible early embryo-lethal effect. There was no such effect in the rat. These marginal effects occurred at relatively low doses, which produced plasma levels comparable to those achieved in patients.

In a peri-/postnatal/juvenile toxicity study in rats, some histological inflammatory changes at the ano-rectal junction and slight diffuse epithelial hyperplasia of the cecum were observed in dams and pups at the high dose level. An increased incidence of urination upon handling was also seen in some offspring receiving 450 or 2000 mg/kg. In addition, a reduction in testes weight was observed in juvenile males at 2000 mg/kg which was associated with slight to moderate dilatation of the seminiferous tubules.

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PART III: CONSUMER INFORMATION**Pr**COMBIVIR[®]
lamivudine and zidovudine

This leaflet is part III of a three-part "Product Monograph" published when COMBIVIR[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about COMBIVIR[®]. Please read this leaflet carefully before you start to take your medicine. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

The name of your medicine is COMBIVIR[®] (lamivudine and zidovudine). COMBIVIR[®] is a treatment that contains a combination of two active ingredients that are currently available as separate medicines: 3TC[®] (lamivudine) and RETROVIR[®] (AZT) (zidovudine). COMBIVIR[®] can only be obtained with a prescription from your doctor. You should not be taking RETROVIR[®] (AZT) (zidovudine) nor 3TC[®] (lamivudine) while taking COMBIVIR[®].

What it does:

The Human Immunodeficiency Virus (HIV) is a retrovirus. Infection with HIV damages the immune system and can lead to Acquired Immune Deficiency Syndrome (AIDS) and other related illnesses.

COMBIVIR[®] is an antiretroviral medication. COMBIVIR[®] does not cure AIDS or kill the HIV virus, but helps to prevent further damage to the immune system by slowing down the production of new viruses.

When it should not be used:

Do not use COMBIVIR[®]:

- If you previously had an allergic reaction to COMBIVIR[®] or to any of the ingredients in the product (See what the nonmedicinal ingredients are).
- If you have a very low red blood cell count (anemia) or very low white blood cell count (neutropenia).

The coadministration of COMBIVIR[®] with 3TC[®] or RETROVIR[®] (AZT) is not recommended.

What the medicinal ingredient is:

Each COMBIVIR[®] tablet contains 150 mg of lamivudine and 300 mg of zidovudine.

What the important nonmedicinal ingredients are:

Each COMBIVIR[®] tablet also contains the non-medicinal ingredients colloidal silicon dioxide, hydroxypropyl methyl cellulose, magnesium stearate, microcrystalline cellulose,

polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

What dosage forms it comes in:

Each COMBIVIR[®] tablet contains 150 mg of lamivudine and 300 mg of zidovudine.

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

- **lactic acidosis (high levels of acid in the blood) with severe hepatomegaly with steatosis (swollen and fatty liver).** (See Warnings and Precautions and Side Effects)
- **worsening of hepatitis B** (See Warnings and Precautions, Side Effects)
- **pancreatitis (inflammation of the pancreas).** (See Warnings and Precautions, Side Effects)

BEFORE you use COMBIVIR[®] talk to your doctor or pharmacist if:

- You ever had to stop taking this or another medication for this illness because you were allergic to them or they caused problems.
- You had, or you have, any diseases of the kidney.
- You had, or you have, any diseases of the liver, particularly hepatitis B infection.
- You had, or you have, very low red blood cell count (severe anemia) or very low white blood cell count (neutropenia).
- You are taking ribavirin as it could cause or worsen anemia (symptoms of tiredness, shortness of breath). Your doctor will advise whether you should stop taking COMBIVIR[®].

If your answer is **yes** to any of these questions, tell your doctor or pharmacist as soon as possible, if you have not already done so.

Remember that treatment with COMBIVIR[®] does not reduce the risk of passing the infection onto others. You will still be able to pass HIV by sexual contact or by blood transfusion and you should use appropriate precautions.

While taking COMBIVIR[®] or any other therapy for HIV disease, you may continue to develop other infections and other complications of HIV infection. Therefore, you should keep in regular contact with the doctor who is treating your condition.

Because your medicine helps to control your condition but does not cure it, you will need to take it every day. Do not stop taking your medicine without first talking to your doctor.

It is important that your doctor knows about all your symptoms even if you think they are not related to HIV infection. Your doctor may need to change the dose of your medicine.

Use of this medicine during pregnancy and breastfeeding

If you are pregnant, or likely to become pregnant soon, or if you are breastfeeding, please inform your doctor before taking any drugs, including COMBIVIR®.

Administration of COMBIVIR® in the first 3 months of pregnancy is not recommended.

Babies and infants exposed to Nucleoside Reverse Transcriptase Inhibitors (NRTIs) during pregnancy and labour, show minor temporary increases in blood levels of lactate. The clinical importance of these temporary increases is unknown.

There have been very rare reports of disease that affect the nervous system such as delayed development and seizures.

These findings do not affect the current recommendations to use antiretroviral therapy in pregnant women to prevent transmission of HIV to their babies.

It is recommended that HIV-infected women do not breastfeed their infants in order to avoid transmission of HIV. The active substances in COMBIVIR® are found in human breast milk. Mothers taking COMBIVIR® should not breastfeed their infants.

Pancreatitis in Pediatric Patients

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, COMBIVIR® should be used with caution. Treatment with COMBIVIR® should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS section).

Other special warnings

The class of medicines to which COMBIVIR® belongs (NRTIs) can cause a condition called lactic acidosis (excess of lactic acid in your blood), together with an enlarged liver. Symptoms of lactic acidosis include feeling of weakness, loss of appetite, sudden unexplained weight loss, upset stomach and difficulty breathing. This rare but serious side effect occurs more often in women. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with COMBIVIR® your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

If you have hepatitis B infection, you should not stop COMBIVIR® without instructions from your doctor, as you may have recurrence of your hepatitis. This may occur due to you suddenly stopping the active substance lamivudine in COMBIVIR®.

INTERACTIONS WITH THIS MEDICATION

It is important that your doctor know about all your medicines so that you get the best possible treatment. Tell your doctor about all your medicines, including vitamin supplements, herbal remedies or homeopathic remedies, including those you have bought yourself. COMBIVIR® should not be taken with stavudine or zalcitabine.

It is important that you tell your doctor if you are taking any of the medicines below. Ask your doctor if you are not sure:

- phenytoin, valproic acid, oxazepam, lorazepam
- acetylsalicylic acid, codeine, morphine, methadone, rifampicin, indomethacin, ketoprofen, naproxen, cimetidine, clofibrate, isoprinosine, probenacid
- pentamidine, pyrimethamine, co-trimoxazole, dapsone, atovaquone, amphotericin, flucytosine, interferon
- vincristine, vinblastine, doxorubicin
- clarithromycin

PROPER USE OF THIS MEDICATION

Usual dose:

Take your medicine as your doctor has advised you. The label on it will usually tell you the amount to take, and how frequently. If it does not, or you are not sure, ask your doctor or pharmacist.

Adults and Adolescents (at least 12 years old)

As a general guide, swallow one tablet twice a day. COMBIVIR® can be taken with or without food.

If your doctor wishes to reduce your dose of COMBIVIR®, for example if you have kidney problems, then your medicine may be changed to lamivudine and zidovudine taken as separate medicines, 3TC® and RETROVIR® (AZT).

If you are also taking clarithromycin, your doctor may advise you to take this medication at least 2 hours before or 2 hours after COMBIVIR®, to avoid a drug interaction.

Overdose:

Accidentally taking too much of your medicine is unlikely to cause any serious problems. However, you should **immediately** contact either your doctor, your hospital emergency department or the nearest poison control centre.

Missed Dose:

If you forget to take your medicine, take it as soon as you remember. Then continue as before.

Do not double dose to make up for a forgotten dose. Then continue as before.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Consult your doctor at your next visit if any of the following undesirable events occur:

Headaches, nausea, vomiting, diarrhea, fever, rash, fatigue, a general feeling of being unwell, or a numbness, tingling sensation or sensation of weakness in your limbs.

COMBIVIR® may also cause a decrease in certain types of blood counts (including red blood cells, white blood cells and platelets) and an increase in certain liver enzymes.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amounts of fat in the upper back and neck (“buffalo hump”), breasts, and around the trunk. 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 at this time.

Always tell your doctor or pharmacist about any undesirable effects, even those not mentioned in this leaflet.

If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency	Side Effect/ Symptom	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Serious allergic reaction and symptoms of sudden wheeziness and chest pain or tightening, swelling of eyelids, face or lips, skin rash or ‘hives’ anywhere on the body.			✓
Rare	Pancreatitis (inflammation of the pancreas and symptoms such as nausea, vomiting and severe stomach cramps). Lactic acidosis (high level of acid in the blood) and symptoms such as weight loss, fatigue, malaise, abdominal pain, shortness of breath, severe hepatomegaly (swollen liver), with symptoms of liver problems such as nausea, vomiting, abdominal pain, weakness and diarrhea.			✓
Uncommon	Blood problems and symptoms such as anemia (lowered red blood cell count) resulting in fatigue, breathlessness, low white blood cell count making you prone to infections.			✓

This is not a complete list of side effects. For any unexpected effects while taking COMBIVIR®, contact your doctor or pharmacist.

HOW TO STORE IT

Store COMBIVIR[®] tablets between 2° and 30°C.

As with all medicines, keep COMBIVIR[®] out of reach of children.

Do not take your medicine after the expiry date shown on the bottle and the carton.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Remember this medicine is for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

This leaflet does not tell you everything about your medicine. If you have any questions or are not sure about anything, then ask your doctor or pharmacist. You may need to read this leaflet again. Please do not throw it away until you are no longer taking COMBIVIR[®] (lamivudine and zidovudine).

This document plus the full product monograph prepared for health professionals can be found at:
www.viivhealthcare.com
or by contacting the sponsor, ViiV Healthcare Shire Canada at:
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