PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]COMBIVIR

lamivudine and zidovudine tablets, Manufacturer's Standard

Tablets, 150 mg lamivudine and 300 mg zidovudine, oral

Antiretroviral Agent

ViiV Healthcare ULC
75 Queen Street, Suite 1400
Montreal, Quebec
Canada
H3C 2N6

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RECENT MAJOR LABEL CHANGES

Section	Date
1 INDICATIONS	05/2023
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	03/2022
7 WARNINGS AND PRECAUTIONS, General	03/2022
7 WARNINGS AND PRECAUTIONS, General	[Removed] 05/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

COMBIVIR (lamivudine and zidovudine), in combination with other antiretrovirals, is indicated for the treatment of HIV infection.

1.1 Pediatrics

Pediatrics (< 12 years of age): The safety and efficacy of COMBIVIR in pediatric patients less than 12 years of age have not been established. 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 **4 DOSAGE AND ADMINISTRATION** section).

1.2 Geriatrics

Geriatrics (> 65 years of age): No specific data are available, however special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of hematological parameters.

2 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 **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section.
- Due to the active ingredient zidovudine, COMBIVIR is contraindicated in patients with abnormally low neutrophil counts (< 0.75 x 10^9/L) or abnormally low hemoglobin levels (< 7.5 g/dL or 4.65 mmol/L)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 with or without hepatitis (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

- **Post-Treatment Exacerbation of Hepatitis B**
  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 coinfected with HBV and HIV. Exacerbations of hepatitis B have been reported in patients after the discontinuation of antiretroviral therapy. Patients coinfected 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 **8 ADVERSE REACTIONS** section).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

COMBIVIR may be administered with or without food.

Because COMBIVIR is a fixed dose tablet, it should not be prescribed for patients requiring dosage adjustments, such as pediatric patients who weigh less than 40 kg with renal impairment (creatinine clearance <50 mL/min).

4.2 Recommended Dose and Dosage Adjustment

Adults and Adolescents (> 12 years of age) weighing at least 30 kg
The recommended oral dose of COMBIVIR for adults and adolescents weighing at least 30 kg 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: pediatric patients weighing less than 30 kg or patients requiring dosing adjustments due to adverse events. See complete prescribing information for 3TC and RETROVIR (AZT) for dosage adjustments.

Geriatrics

No specific data are available, however special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of hematological parameters.

Hepatic Insufficiency

It is recommended that COMBIVIR not be used in patients with hepatic impairment. For these patients, it is recommended that 3TC (lamivudine) and RETROVIR (AZT) (zidovudine) be administered as separate tablets.

Renal Insufficiency

It is recommended that COMBIVIR not be used in patients with reduced renal function (creatinine clearance less than 30 mL/min). For these patients, it is recommended that 3TC (lamivudine) and RETROVIR (AZT) (zidovudine) be administered as separate tablets. The individual Product Monographs for 3TC (lamivudine) and RETROVIR (AZT) (zidovudine) should be consulted for appropriate dosage adjustments.

Patients with renal impairment (creatinine clearance 30 – 49 mL/min)

Adult patients with a creatinine clearance between 30 and 49 mL per min receiving COMBIVIR may experience a 1.6- to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥50 mL per min. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of hematologic toxicities (neutropenia and anemia), although discontinuations due to neutropenia or anemia each occurred in <1% of subjects. Patients with a sustained creatinine clearance between 30 and 49 mL per min who receive COMBIVIR should be monitored for hematologic toxicities. If new or worsening neutropenia or anemia develop, dose adjustment of lamivudine, per lamivudine prescribing information, is recommended. If lamivudine dose adjustment is indicated, COMBIVIR should be discontinued and the individual components should be used to construct the treatment regimen.

4.5 Missed Dose

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

5 OVERDOSAGE

There is no known antidote for COMBIVIR.

If overdosage 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.

No specific signs or symptoms have been identified following acute overdose with lamivudine or zidovudine apart from those listed as adverse reactions.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Form, Strength, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets/ 150 mg lamivudine and 300 mg zidovudine	colloidal silicon dioxide, hydroxypropyl methyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

COMBIVIR 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.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

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

COMBIVIR is a fixed-dose combination of lamivudine and zidovudine. COMBIVIR should not be administered concomitantly with other products containing either lamivudine or zidovudine including 3TC Tablets and oral solution; RETROVIR Syrup and Solution for infusion, KIVEXA Tablets, DELSTRIGO Tablets, DOVATO Tablets, or TRIUMEQ Tablets.

COMBIVIR should also not be administered concomitantly with emtricitabine containing products, including ATRIPLA Tablets, EMTRIVA Capsules, TRUVADA Tablets, COMPLERA Tablets, STRIBILD Tablets, BIKTARVY Tablets, DESCOVY Tablets, GENVOYA Tablets, ODEFSEY Tablets, or SYMTUZA Tablets.

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.

Endocrine and Metabolism

- **Lipoatrophy**

Treatment with zidovudine has been associated with loss of subcutaneous fat. The incidence and severity of lipoatrophy are related to cumulative exposure. This fat loss, which is most evident in the

face, limbs and buttocks, may be only partially reversible and improvement may take several months when switching to a zidovudine-free regimen.

Patients should be regularly assessed for signs of lipoatrophy during therapy with zidovudine and other zidovudine containing products (RETROVIR), and if feasible, therapy should be switched to an alternative regimen if there is suspicion of lipoatrophy development.

- **Serum lipids and blood glucose**

Serum lipid and blood glucose levels may increase during antiretroviral therapy.

Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.

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 **8 ADVERSE REACTIONS**). Hematological parameters should therefore be carefully monitored (see **2 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/mm^3 or hemoglobin < 9.5 g/dL. In patients with advanced symptomatic disease, anemia and granulocytopenia were the most significant adverse events observed (see **8 ADVERSE REACTIONS**). 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 hemoglobin less than 9 g/dL (5.59 mmol/l) or neutrophil count less than 1.0 x 10^9/L. As dosage adjustment of COMBIVIR is not possible separate preparations of zidovudine and lamivudine should be used (see **2 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, 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 with or without hepatitis (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

COMBIVIR, a fixed dose combination, is not recommended for patients with impaired hepatic function as a reduction in daily dose of zidovudine may be necessary in patients with hepatic impairment (See **4 DOSAGE AND ADMINISTRATION**).

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 **9 DRUG INTERACTIONS**).

- **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 anemia 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 anemia.

- **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 Inflammatory Syndrome (IRIS)**

Immune reconstitution inflammatory syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including COMBIVIR. During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections [such as Mycobacterium avium-complex (MAC), cytomegalovirus (CMV), Pneumocystis jirovecii pneumonia (PCP), and tuberculosis (TB)], which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, autoimmune hepatitis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Musculoskeletal

- **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 <30 mL/min) (See **4 DOSAGE AND ADMINISTRATION**)

7.1 Special Populations

7.1.1 Pregnant Women

The safe use of COMBIVIR in human pregnancy has not been established in adequate and well-controlled trials investigating congenital abnormalities. Therefore administration of COMBIVIR in pregnancy should be considered only if the expected benefit outweighs the possible risk to the fetus.

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. Lamivudine and zidovudine have been shown to cross the placenta in humans (see **10 CLINICAL PHARMACOLOGY**). The use of zidovudine in pregnant women, with subsequent treatment of the newborn infants, has been shown to reduce the rate of maternal fetal transmission of HIV.

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 embryolethality when lamivudine was administered to pregnant rabbits at exposure levels comparable to those achieved in man.

Lamivudine and zidovudine have been associated with findings in animal reproductive studies (see **16 NON-CLINICAL TOXICOLOGY**). Pregnant women considering using COMBIVIR during pregnancy should be made aware of these findings.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to ART (antiretroviral therapy), including COMBIVIR, an Antiretroviral Pregnancy Registry has been established. Healthcare professionals are encouraged to register patients:

http://www.apregistry.com
Telephone: (800) 258-4263
Fax: (800) 800-1052

Lamivudine and zidovudine has been evaluated in the Antiretroviral Pregnancy Registry in over 11,000, and 13,000 women respectively during pregnancy and postpartum. Available human data from the

Antiretroviral Pregnancy Registry do not show an increased risk of major birth defects for lamivudine or zidovudine compared to the background rate (see **10 CLINICAL PHARMACOLOGY)**

The Antiretroviral Pregnancy Registry has received reports of over 11,000 exposures to lamivudine during pregnancy resulting in live birth. These consist of over 4,500 exposures during the first trimester, over 7,200 exposures during the second/third trimester and included 143 and 207 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.1% (2.6, 3.7%) and in the second/third trimester, 2.9% (2.5, 3.3%). The APR has received reports of over 13,000 exposures to zidovudine during pregnancy resulting in live birth. These consist of over 4,100 exposures during the first trimester, over 9,300 exposures during the second/third trimester and included 133 and 264 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.2% (2.7, 3.8%) and in the second/third trimester, 2.8% (2.5, 3.2%). These proportions are not significantly higher than those reported in the two population based surveillance systems (2.72 per 100 live births and 4.17 per 100 live births respectively). The Antiretroviral Pregnancy Registry does not show an increased risk of major birth defects for lamivudine or zidovudine compared to the background rate.

7.1.2 Breast-feeding

HIV-1 infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Both lamivudine and zidovudine are excreted in human milk at similar concentrations to those found in serum. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving COMBIVIR.**

7.1.3 Pediatrics

There are no data on the use of COMBIVIR in pediatric patients (see **10.3 Pharmacokinetics**).

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 **4 DOSAGE AND ADMINISTRATION**).

7.1.4 Geriatrics

No specific data are available, however special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of hematological parameters.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 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 2).

Table 2 Selected clinical adverse events (≥ 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%

Adverse Event	3TC plus RETROVIR (AZT) (n=251)
Musculoskeletal	
Musculoskeletal pain	12%
Myalgia	8%
Arthralgia	5%

Other clinical adverse events reported in controlled clinical trials in association with 3TC 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.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Selected laboratory abnormalities observed during therapy are listed in Table 3.

Table 3 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

8.5 Post-Market Adverse 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:	Loss of subcutaneous fat (see **7 WARNINGS AND PRECAUTIONS**: Lipoatrophy 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 **7 WARNINGS AND PRECAUTIONS**)
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, *Candida* 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.
Immune System:	Immune Reconstitution Inflammatory Syndrome (see **7 WARNINGS AND PRECAUTIONS:** Immune section)
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.

9 DRUG INTERACTIONS

9.2 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 **10 CLINICAL PHARMACOLOGY**).

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

Effect of lamivudine on the pharmacokinetics of other agents

In vitro, lamivudine demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistance protein (BCRP) or P-glycoprotein (Pgp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K or organic cation transporter 3 (OCT3). Lamivudine is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters.

Lamivudine is an inhibitor of OCT1 and OCT2 in vitro with IC50 values of 17 and 33 µM, respectively, however lamivudine has low potential to affect the plasma concentrations of OCT1 and OCT2 substrates at therapeutic drug exposures (up to 300 mg).

Effect of other agents on the pharmacokinetics of lamivudine

Lamivudine is a substrate of MATE1, MATE2-K and OCT2 *in vitro*. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations, however this interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

Lamivudine is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

Lamivudine is a substrate of Pgp and BCRP, however due to its high bioavailability it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore co-administration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 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 *Pneumocystis jiroveci* pneumonia (often referred to as 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.

Proper name	Effect	Clinical comment
Emtricitabine	Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these drugs in combination therapy may be limited.	Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.
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.

Proper name	Effect	Clinical comment
Sorbitol	Coadministration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC_∞) and 28%, 52%, and 55% in the C_{max} of lamivudine in adults.	When possible, avoid chronic coadministration of sorbitol-containing medicines with lamivudine. Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.
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.
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.

Proper name	Effect	Clinical comment
Other agents		Some drugs such as trimethoprim-sulfamethoxazole, pyrimethamine, and acyclovir may be necessary for the management or prevention of opportunistic infections. Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with these medicinal products. Although, there is an isolated published report of neurotoxicity (profound lethargy) associated with concomitant use of Zidovudine and acyclovir, this isolated case is not understood and unlikely to be of general relevance. 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		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. 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.

10 CLINICAL PHARMACOLOGY

10.1 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 ($-N_3$) 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.

10.3 Pharmacokinetics

The single-dose pharmacokinetic properties of COMBIVIR 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 5. 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.

Table 5 Summary Table of Measured Comparative Bioavailability Data for COMBIVIR 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)

	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**
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
T½ (h)	1.48 1.50 (15.73)	9.66 9.98 (27.85)	1.43 1.45 (16.24)	9.52 9.79 (24.71)	1.48 1.53 (26.78)	9.80 10.52 (50.61)	NA	NA	NA	NA

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%.

Absorption

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)

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.

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% ± 1.4% (mean ± 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 times 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 ± SD), representing 71% ± 16% (mean ± 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 ($t_{½}$) ranged from 18 to 19 hours. Oral clearance was 0.37 ± 0.05 L/hr/kg (mean ± 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 and Conditions

- **Pediatrics:** 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% ± 26% (mean ± SD), which is less than the 86% ± 16% (mean ± 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, Cmax was 1.2 ± 0.5 µg/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 T1/2 across the range of doses. AUC and Cmax 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.

- **Geriatrics:** 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.
- **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 **9 DRUG INTERACTIONS**).

Following oral administration, lamivudine pharmacokinetics in late pregnancy were similar to non pregnant adults.

- **Breast-feeding:** See **7.1.2 Breast-feeding**.

  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.

- **Ethnic Origin:** There are no significant differences in pharmacokinetic properties of lamivudine among races.

- **Renal Insufficiency:** 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 **7 WARNINGS AND PRECAUTIONS**).

  The pharmacokinetic properties of lamivudine were determined in a small group of HIV-infected adults with impaired renal function, and are summarized in Table 6.

Table 6 Pharmacokinetic Parameters (Mean ± SD) 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. Tmax 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 **4 DOSAGE AND ADMINISTRATION**).

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 well tolerated 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.

11 STORAGE, STABILITY AND DISPOSAL

COMBIVIR tablets should be stored between 2°C and 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

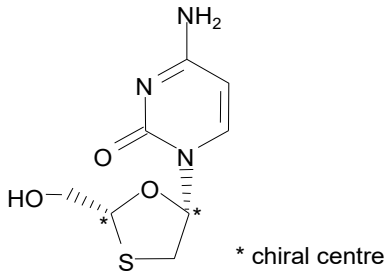
Drug Substance

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.

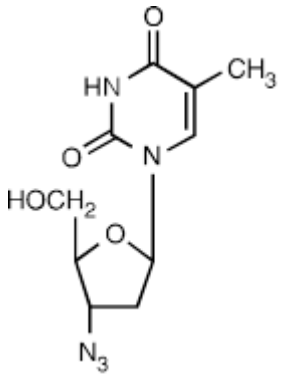
Drug Substance

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.

14 CLINICAL TRIALS

Please refer to **10 CLINICAL PHARMACOLOGY**.

15 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 using HIV-1-infected MT-4 cells as the test system. No antagonistic effects were seen *in vitro* with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine, zalcitabine, and zidovudine). No antagonistic effects were seen *in vitro* with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine, lamivudine and interferon-alpha).

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 [^{3}H]-thymidine uptake (Td) assays. In the CP assay, lamivudine was the least toxic of the four compounds. [^{3}H]-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 [^{3}H]-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. ID_{50} 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 ID_{50} of 5 µg/mL. Moreover, in a colony-forming unit assay designed to assess the toxicity of zidovudine for human bone marrow, an ID_{50} 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.

16 NON-CLINICAL 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.

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, respectively). 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.

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 7 below. Rats and monkeys received zidovudine by gavage, dogs were administered zidovudine capsules.

Table 7 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.

Species	No. per Group		Dose Levels (mg/kg/day)	Duration (weeks)	Effects
	M	F			
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.

Reproductive and Developmental Toxicology

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 F_1 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 F_0 and F_1 generation animals, and the development of the F_1 and F_2 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 embryolethal 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]COMBIVIR

lamivudine and zidovudine tablets

Read this carefully before you start taking **COMBIVIR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **COMBIVIR**.

Serious Warnings and Precautions

Lactic Acidosis and Severe Liver Problems: 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 healthcare professional will monitor you closely for any signs that you may be developing lactic acidosis.

Worsening of Hepatitis B: If you have hepatitis B infection, you should not stop COMBIVIR without instructions from your healthcare professional, as you may have recurrence of your hepatitis.

Pancreatitis in Pediatric Patients: COMBIVIR should be used with caution in pediatric patients with a history of prior antiretroviral drug exposure or a history of pancreatitis (inflammation of the pancreas). Treatment with COMBIVIR should be stopped immediately if signs of pancreatitis occur, such as nausea, vomiting and severe stomach cramps.

What is COMBIVIR used for?

COMBIVIR is used with other antiretrovirals to treat Human Immunodeficiency Virus (HIV) infection.

How does COMBIVIR work?

COMBIVIR contains the medicinal ingredients lamivudine and zidovudine. This belongs to a group of antiretroviral medicines called nucleoside analogue reverse transcriptase inhibitors (NRTIs), which are used to treat HIV infection.

HIV is a retrovirus (a type of virus). Infection with HIV damages the immune system and can lead to Acquired Immune Deficiency Syndrome (AIDS) and other related illnesses.

COMBIVIR does not cure HIV infection; it reduces the amount of virus in your body, and keeps it at a low level. It also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important in helping your body fight infection.

What are the ingredients in COMBIVIR?

Medicinal ingredients: lamivudine and zidovudine.

Non-medicinal ingredients: colloidal silicon dioxide, hydroxypropyl methyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

COMBIVIR comes in the following dosage forms:

150 mg lamivudine and 300 mg zidovudine tablets.

Do not use COMBIVIR if:

- you have had an allergic reaction to COMBIVIR or to any of the ingredients in the product.
- you have a very low red blood cell count (anemia) or very low white blood cell count (neutropenia).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take COMBIVIR. Talk about any health conditions or problems you may have, including if you:

- ever had to stop taking this or another medication for this illness because you were allergic to them or they caused problems.
- have any kidney issues.
- have any liver issues, particularly hepatitis B or C infection.
- have a very low red blood cell count (severe anemia), very low white blood cell count (neutropenia) or any type of blood disorder.

Other warnings you should know about:

COMBIVIR can cause serious side effects, including:

Risk of Infections: 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 your healthcare professional.

Your healthcare professional will arrange regular blood tests to check for side effects.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Blood Tests: Your blood sugar levels (glucose) or levels of fats (lipids) in your blood may increase with HIV treatment. Your healthcare professional may order blood tests for you.

Pregnancy and Newborns: If you are pregnant, or planning to become pregnant soon, tell your healthcare professional before taking any medicine. The safe use of COMBIVIR in pregnancy has not been established. Your healthcare professional will decide whether you should continue to be treated with COMBIVIR if you are pregnant. If you take COMBIVIR while you are pregnant, talk to your healthcare professional about how you can be included in the Antiretroviral Pregnancy Registry.

Breastfeeding: It is recommended that HIV infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV from mother to child. The active substances in COMBIVIR are likely to be found in breast milk. You are recommended **not** to breastfeed your baby while taking COMBIVIR.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

COMBIVIR should not be taken with stavudine, emtricitabine, ribavirin, lamivudine or zidovudine.

The following may interact with COMBIVIR:

- phenytoin, valproic acid, to treat epilepsy
- oxazepam, lorazepam, to treat anxiety and sleep problems (insomnia)

- codeine, morphine, methadone, acetylsalicylic acid, indomethacin, ketoprofen, naproxen, to treat pain
- dapsone, to prevent pneumonia and treat skin infections
- rifampicin, co-trimoxazole (trimethoprim and sulfamethoxazole), fluconazole, amphotericin, flucytosine, to treat bacterial and fungal infections
- vincristine, vinblastine, doxorubicin, to treat cancer
- cimetidine, to treat heartburn and ulcers
- probenecid, to treat gout
- clofibrate, to treat high cholesterol
- atovaquone, pentamidine, pyrimethamine, to treat parasitic infections
- interferon, ganciclovir, to treat viral infections
- isoprinosine, to treat viral infections
- clarithromycin to be taken 2 hours before or 2 hours after taking COMBIVIR, to treat bacterial infections
- sorbitol-containing medicines (usually liquids) used regularly

How to take COMBIVIR:

- Take your medicine as your healthcare professional has told you. If you are not sure, ask your healthcare professional.
- Never share your medicine with someone else. It may harm them even if their symptoms are the same as yours.
- You can take COMBIVIR with or without food

Usual dose:

Adults and Adolescents weighing at least 30 kg:

One tablet by mouth twice a day at the same time each day.

If you have kidney or liver problems and your dose needs to be reduced your healthcare professional may have you take 3TC (lamivudine) and RETROVIR (zidovudine) as separate medicines.

Overdose:

If you think you, or a person you are caring for, have taken too much COMBIVIR, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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.

What are possible side effects from using COMBIVIR?

These are not all the possible side effects you may have when taking COMBIVIR. If you experience any side effects not listed here, tell your healthcare professional.

Treatment with COMBIVIR or other medicines that contain zidovudine may cause a loss of fat from legs, arms and face (lipoatrophy). Your healthcare professional should monitor for signs of lipoatrophy. Tell your healthcare professional if you notice any loss of fat from your legs, arms, and face. When

these signs occur, your healthcare professional will assess if COMBIVIR should be stopped and your HIV treatment changed. If you stop taking COMBIVIR, it may take several months to see any lost fat return. You may not regain all of your lost body fat.

Side effects may include:

Very common side effects (> 1 in 10 people)

- headache

Common side effects (≤ 1 in 10 people)

- feeling dizzy
- hair loss

Common side effects that may show up in blood tests are:

- an increase in the level of liver enzymes

Uncommon side effects (≤ 1 in 100 people)

- wind/gas (flatulence)
- itching

Uncommon side effects that may show up in blood tests are:

- a decrease in the number of cells involved in blood clotting (thrombocytopenia), or in all kinds of blood cells (pancytopenia).

Rare side effects (≤ 1 in 1000 people)

- difficulty in sleeping (insomnia)
- fits (convulsions)
- feeling depressed or anxious, not being able to concentrate, feeling drowsy
- indigestion, taste disturbance
- changes in the colour of your nails, your skin, or the skin inside your mouth
- a flu-like feeling — chills and sweating
- loss of appetite
- breakdown of muscle tissue
- passing urine more often
- enlarged breasts in men
- cough
- sweating
- itchy, bumpy rash (hives)
- tingly feelings in the skin (pins and needles)

Rare side effects that may show up in blood tests are:

- increase in an enzyme called amylase
- a failure of the bone marrow to produce new red blood cells (pure red cell aplasia).

Very rare side effects that may show up in blood tests are:

- a failure of the bone marrow to produce new red or white blood cells (aplastic anaemia).

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	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.			✓
UNCOMMON			
Blood problems and symptoms such as anemia (lowered red blood cell count) resulting in fatigue, breathlessness, or neutropenia (low white blood cell count), making you prone to infections.			✓
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 Liver Problems: 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.			✓
FREQUENCY NOT KNOWN			
Immune Reconstitution Inflammatory Syndrome and Autoimmune Disorders: fever, redness, rash or swelling, fatigue, joint or muscle pain , numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, chest pain or rapid heart rate, yellowing of the eyes and skin		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to

interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store COMBIVIR tablets between 2 °C and 30 °C.

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

Keep out of reach and sight of children.

If you want more information about COMBIVIR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.viivhealthcare.com, or by calling 1-877-393-8448.

This leaflet was prepared by ViiV Healthcare ULC

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