HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use COMBIVIR safely and effectively. See full prescribing information for COMBIVIR.

COMBIVIR (lamivudine and zidovudine) tablets
Initial U.S. Approval: 1997

WARNING: HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, and EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

Hematologic Toxicity

- **Hematologic toxicity, including neutropenia and anemia, has been associated with the use of zidovudine, a component of COMBIVIR. (5.1)**

Myopathy

- **Symptomatic myopathy associated with prolonged use of zidovudine. (5.2)**

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.(5.3)**

Exacerbations of Hepatitis B

- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of COMBIVIR. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.4)**

---------- RECENT MAJOR CHANGES ----------

Warnings and Precautions (5) 09/2015

---------- INDICATIONS AND USAGE ----------

COMBIVIR, a combination of 2 nucleoside analogue reverse transcriptase inhibitors, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Adults and Adolescents weighing greater than or equal to 30 kg: 1 tablet orally twice daily. (2.1)
- Pediatrics weighing greater than or equal to 30 kg: 1 tablet orally twice daily. (2.2)
- Because COMBIVIR is a fixed-dose tablet and cannot be dose adjusted, COMBIVIR is not recommended in patients requiring dosage adjustment or with hepatic impairment or experiencing dose-limiting adverse reactions. (2.3, 4)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: Scored 150 mg lamivudine and 300 mg zidovudine (3)

----------CONTRAINDICATIONS----------

COMBIVIR is contraindicated in patients with a previous hypersensitivity reaction to lamivudine or zidovudine. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- COMBIVIR should not be administered with other lamivudine- or zidovudine-containing products or emtricitabine-containing products. (5.5)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with/without ribavirin. Discontinue COMBIVIR as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.6)
- Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Coadministration of ribavirin and zidovudine is not advised. (5.6)
- Pancreatitis: Use with caution in patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.7)
- Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.8, 5.9)

---------- ADVERSE REACTIONS ----------

- Most commonly reported adverse reactions (incidence greater than or equal to 15%) in clinical trials of combination lamivudine and zidovudine were headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Agents antagonistic with zidovudine: Concomitant use should be avoided. (7.1)
- Hematologic/bone marrow suppressive/cytotoxic agents: May increase the hematologic toxicity of zidovudine. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, and EXACERBATIONS OF HEPATITIS B

Hematologic Toxicity

Zidovudine, a component of COMBIVIR® (lamivudine and zidovudine) tablets, has been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced Human Immunodeficiency Virus (HIV-1) disease *[see Warnings and Precautions (5.1)]*.

Myopathy

Prolonged use of zidovudine has been associated with symptomatic myopathy *[see Warnings and Precautions (5.2)]*.

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 and other antiretrovirals. Discontinue COMBIVIR if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Warnings and Precautions (5.3)]*.

Exacerbations of Hepatitis B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine, which is one component of COMBIVIR. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue COMBIVIR and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.4)]*.

1 INDICATIONS AND USAGE

COMBIVIR, a combination of 2 nucleoside analogues, is indicated in combination with other antiretrovirals for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Adults and Adolescents

The recommended dosage of COMBIVIR in HIV-1-infected adults and adolescents weighing greater than or equal to 30 kg is 1 tablet (containing 150 mg of lamivudine and 300 mg of zidovudine) taken orally twice daily.

2.2 Recommended Dosage for Pediatric Patients

The recommended dosage of scored COMBIVIR tablets for pediatric patients who weigh greater than or equal to 30 kg and for whom a solid oral dosage form is appropriate is 1 tablet administered orally twice daily.

Before prescribing COMBIVIR tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a COMBIVIR tablet, the liquid oral formulations should be prescribed: EPIVIR® (lamivudine) oral solution and RETROVIR® (zidovudine) syrup.

2.3 Not Recommended Due to Lack of Dosage Adjustment

Because COMBIVIR is a fixed-dose tablet and cannot be dose adjusted, COMBIVIR is not recommended for:

- pediatric patients weighing less than 30 kg *[see Use in Specific Populations (8.4)]*.
- patients with creatinine clearance less than 50 mL per minute *[see Use in Specific Populations (8.6)]*.
- patients with hepatic impairment *[see Use in Specific Populations (8.7)]*.
- patients experiencing dose-limiting adverse reactions.

Liquid and solid oral formulations of the individual components of COMBIVIR are available for these populations.

3 DOSAGE FORMS AND STRENGTHS

COMBIVIR tablets contain 150 mg of lamivudine and 300 mg of zidovudine. The tablets are white, scored, film-coated, modified capsule-shaped tablets, debossed on both tablet faces, such that when broken in half, the full “GX FC3” code is present on both halves of the tablet (“GX” on one face and “FC3” on the opposite face of the tablet).

4 CONTRAINDICATIONS

COMBIVIR is contraindicated in patients with a previous hypersensitivity reaction to lamivudine or zidovudine.

5 WARNINGS AND PRECAUTIONS

5.1 Hematologic Toxicity/Bone Marrow Suppression

Zidovudine, a component of COMBIVIR, has been associated with hematologic toxicity including neutropenia and anemia, particularly in patients with advanced HIV-1 disease. COMBIVIR should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count less than 1,000 cells per mm^3 or hemoglobin less than 9.5 grams per dL *[see Adverse Reactions (6.1)]*.

Frequent blood counts are strongly recommended in patients with advanced HIV-1 disease who are treated with COMBIVIR. Periodic blood counts are recommended for other HIV-1-infected patients. If anemia or neutropenia develops, dosage interruption may be needed.

5.2 Myopathy

Myopathy and myositis, with pathological changes similar to that produced by HIV-1 disease, have been associated with prolonged use of zidovudine, and therefore may occur with therapy with COMBIVIR.

5.3 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 and other antiretrovirals. See full prescribing information for EPIVIR (lamivudine) and RETROVIR (zidovudine). Treatment with COMBIVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.4 Patients with Hepatitis B Virus Co-infection

Posttreatment Exacerbations of Hepatitis

Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. See full prescribing information for EPIVIR (lamivudine). Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Emergence of Lamivudine-resistant HBV

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV. Emergence of hepatitis B virus variants associated with resistance to lamivudine has been reported in HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. See full prescribing information for EPIVIR (lamivudine).

5.5 Related Products that are Not Recommended

COMBIVIR is a fixed-dose combination of 2 nucleoside analogue reverse transcriptase inhibitors (lamivudine and zidovudine). Concomitant administration of COMBIVIR with other products containing lamivudine or zidovudine is not recommended. In addition, do not administer COMBIVIR in combination with products containing emtricitabine.

5.6 Use with Interferon- and Ribavirin-based Regimens

Patients receiving interferon alfa with or without ribavirin and COMBIVIR should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. See full prescribing information for EPIVIR (lamivudine) and RETROVIR

(zidovudine). 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 greater than 6) (see full prescribing information for interferon and ribavirin).

Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Coadministration of ribavirin and COMBIVIR is not advised.

5.7 Pancreatitis

COMBIVIR should be used with caution in patients with a history of pancreatitis or other significant risk factors for the development of pancreatitis. Treatment with COMBIVIR should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur *[see Adverse Reactions (6.1)]*.

5.8 Immune Reconstitution Syndrome

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

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré 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.

5.9 Fat Redistribution

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

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Hematologic toxicity, including neutropenia and anemia *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Symptomatic myopathy *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Lactic acidosis and severe hepatomegaly with steatosis *[see Boxed Warning, Warnings and Precautions (5.3)]*.

- Exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.4)]*.
- Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C *[see Warnings and Precautions (5.6)]*.
- Exacerbation of anemia in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine *[see Warnings and Precautions (5.6)]*.
- Pancreatitis *[see Warnings and Precautions (5.7)]*.
- Immune reconstitution syndrome *[see Warnings and Precautions (5.8)]*.
- Fat redistribution *[see Warnings and Precautions (5.9)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Lamivudine plus Zidovudine Administered as Separate Formulations

In 4 randomized, controlled trials of EPIVIR 300 mg per day plus RETROVIR 600 mg per day, the following selected adverse reactions and laboratory abnormalities were observed (see Tables 1 and 2).

Table 1. Selected Clinical Adverse Reactions (Greater than or Equal to 5% Frequency) in 4 Controlled Clinical Trials with EPIVIR 300 mg per day and RETROVIR 600 mg per day

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

Pancreatitis was observed in 9 of the 2,613 adult subjects (0.3%) who received EPIVIR in controlled clinical trials *[see Warnings and Precautions (5.7)]*.

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

Table 2. Frequencies of Selected Laboratory Abnormalities among Adults in 4 Controlled Clinical Trials of EPIVIR 300 mg per day plus RETROVIR 600 mg per day[a]

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

ULN = Upper limit of normal.
ANC = Absolute neutrophil count.
n = Number of subjects assessed.
[a] Frequencies of these laboratory abnormalities were higher in subjects with mild laboratory abnormalities at baseline.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole

Redistribution/accumulation of body fat *[see Warnings and Precautions (5.9)]*.

Cardiovascular

Cardiomyopathy.

Endocrine and Metabolic

Gynecomastia, hyperglycemia.

Gastrointestinal

Oral mucosal pigmentation, stomatitis.

General

Vasculitis, weakness.

Hemic and Lymphatic

Anemia, (including pure red cell aplasia and anemias progressing on therapy), lymphadenopathy, splenomegaly.

Hepatic and Pancreatic

Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.3), (5.4), (5.7)]*.

Hypersensitivity

Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal

Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous

Paresthesia, peripheral neuropathy, seizures.

Respiratory

Abnormal breath sounds/wheezing.

Skin

Alopecia, erythema multiforme, Stevens-Johnson syndrome.

7 DRUG INTERACTIONS

7.1 Zidovudine

Agents Antagonistic with Zidovudine

Concomitant use of zidovudine with the following drugs should be avoided since an antagonistic relationship has been demonstrated in vitro:

- Stavudine
- Doxorubicine
- Nucleoside analogues e.g., ribavirin

Hematologic/Bone Marrow Suppressive/Cytotoxic Agents

Coadministration with the following drugs may increase the hematologic toxicity of zidovudine:

- Ganciclovir
- Interferon alfa
- Ribavirin
- Other bone marrow suppressive or cytotoxic agents

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to COMBIVIR during pregnancy. Physicians are encouraged to register patients by calling the Antiretroviral Pregnancy Registry at 1-800-258-4263.

Fetal Risk Summary

There are no adequate and well-controlled trials of COMBIVIR (lamivudine and zidovudine) in pregnant women. Clinical trial data demonstrate that maternal zidovudine treatment during pregnancy reduces vertical transmission of HIV-1 infection to the fetus. Animal reproduction studies performed with lamivudine and zidovudine showed increased embryotoxicity and fetal malformations (zidovudine), and increased embryolethality (lamivudine). COMBIVIR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Treatment of HIV during pregnancy optimizes the health of both mother and fetus. Clinical trial data reviewed by FDA demonstrate that maternal zidovudine treatment significantly reduces vertical transmission of HIV-1 infection to the fetus *[see Clinical Studies (14.2)]*. Published data suggest that combination antiretroviral regimens may reduce the rate of vertical transmission even further.

Pharmacokinetics of lamivudine and zidovudine in pregnant women are similar to the pharmacokinetics in non-pregnant women. No dose adjustments are needed during pregnancy.

In a clinical trial, adverse events among HIV-1-infected women were not different among untreated women and women treated with zidovudine. It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared with other HIV-1-infected patients (see Human data below).

Data

Human Data: Lamivudine: Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trial assessed pharmacokinetics in:
16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine,
10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and
10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

Zidovudine: In a randomized, double-blind, placebo-controlled trial was conducted in HIV-1-infected pregnant women to determine the utility of zidovudine for the prevention of maternal-fetal HIV-1 transmission. Zidovudine treatment during pregnancy reduced the rate of maternal-fetal HIV-1 transmission from 24.9% for infants born to placebo-treated mothers to

7.8% for infants born to mothers treated with zidovudine. There were no differences in pregnancy-related adverse events between the treatment groups. Congenital abnormalities occurred with similar frequency between neonates born to mothers who received zidovudine and neonates born to mothers who received placebo. The observed abnormalities included problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of trial drug *[see Clinical Studies (14.2)]*.

Zidovudine pharmacokinetics were studied in a Phase 1 trial of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine were similar to that of non-pregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery.

Animal Data: Lamivudine: Animal reproduction studies performed at oral doses up to 130 and 60 times the adult dose in rats and rabbits, respectively, revealed no evidence of teratogenicity due to lamivudine. Increased early embryolethality occurred in rabbits at exposure levels similar to those in humans. However, there was no indication of this effect in rats at exposure levels up to 35 times those in humans. Based on animal studies, lamivudine crosses the placenta and is transferred to the fetus *[see Nonclinical Toxicology (13.2)]*.

Zidovudine: Increased fetal resorptions occurred in pregnant rats and rabbits treated with doses of zidovudine that produced drug plasma concentrations 66 to 226 times (rats) and 12 to 87 times (rabbits) the mean steady-state peak human plasma concentration following a single 100-mg dose of zidovudine. There were no other reported developmental anomalies. In another developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that produced peak plasma concentrations 350 times peak human plasma concentrations (300 times the daily exposure [AUC] in humans given 600 mg per day zidovudine). This dose was associated with marked maternal toxicity and an increased incidence of fetal malformations. However, there were no signs of teratogenicity at doses up to one-fifth the lethal dose *[see Nonclinical Toxicology (13.2)]*.

8.2 Lactation

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of the potential for HIV-1 transmission mothers should be instructed not to breastfeed.

8.4 Pediatric Use

COMBIVIR is not recommended for use in pediatric patients who weigh less than 30 kg because it is a fixed-dose combination tablet that cannot be adjusted for this patient population *[see Dosage and Administration (2.2)]*.

8.5 Geriatric Use

Clinical trials of COMBIVIR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of COMBIVIR in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Patients with Impaired Renal Function

COMBIVIR is not recommended for patients with creatinine clearance less than 50 mL per min because COMBIVIR is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of the lamivudine or zidovudine components of COMBIVIR is required for patients with renal impairment then the individual components should be used *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

8.7 Patients with Impaired Hepatic Function

COMBIVIR is a fixed-dose combination and the dosage of the individual components cannot be adjusted. Zidovudine is primarily eliminated by hepatic metabolism and zidovudine concentrations are increased in patients with impaired hepatic function, which may increase the risk of hematologic toxicity. Frequent monitoring of hematologic toxicities is advised.

10 OVERDOSAGE

There is no known specific treatment for overdose with COMBIVIR. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

Lamivudine

Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

Zidovudine

Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. No specific symptoms or signs have been identified following acute overdosage with zidovudine apart from those listed as adverse events such as fatigue, headache, vomiting, and occasional reports of hematological disturbances. Patients recovered without permanent sequelae. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, 3′-azido-3′-deoxy-5′-*O*-β-*D*-glucopyranuronosylthymidine (GZDV), is enhanced.

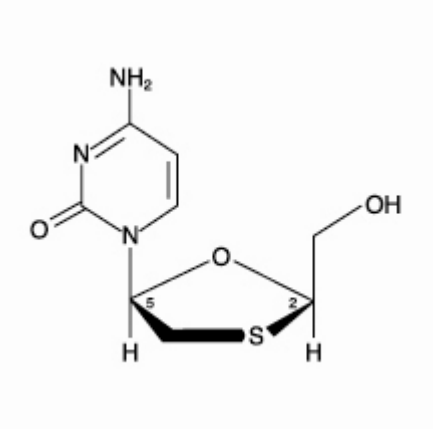
11 DESCRIPTION

COMBIVIR tablets are combination tablets containing lamivudine and zidovudine. Lamivudine (EPIVIR) and zidovudine (RETROVIR, azidothymidine, AZT, or ZDV) are synthetic nucleoside analogues with activity against HIV-1.

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

Lamivudine

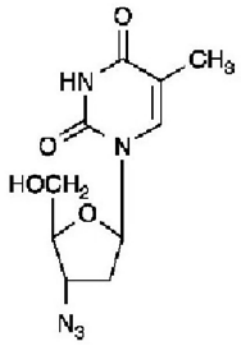
The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$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



Lamivudine is a white to off-white crystalline solid and is soluble in water.

Zidovudine

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



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COMBIVIR is an antiretroviral agent *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Pharmacokinetics in Adults

One COMBIVIR tablet was bioequivalent to 1 EPIVIR tablet (150 mg) plus 1 RETROVIR tablet (300 mg) following single-dose administration to fasting healthy subjects (n = 24).

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

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

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

The pharmacokinetic properties of lamivudine and zidovudine in fasting subjects are summarized in Table 3.

Table 3. Pharmacokinetic Parameters[a] for Lamivudine and Zidovudine in Adults

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

[a] Data presented as mean ± standard deviation except where noted.
[b] Median [range].
[c] Children.
[d] Adults.
[e] Approximate range.

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

Special Populations

Renal Impairment: COMBIVIR: The effect of renal impairment on the combination of lamivudine and zidovudine has not been evaluated (see the U.S. prescribing information for the individual lamivudine and zidovudine components).

Hepatic Impairment: COMBIVIR: The effect of hepatic impairment on the combination of lamivudine, and zidovudine has not been evaluated (see the U.S. prescribing information for the individual lamivudine and zidovudine components).

Pregnancy: Lamivudine: Lamivudine pharmacokinetics were studied in 36 pregnant women during 2 clinical trials conducted in South Africa. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

Zidovudine: Zidovudine pharmacokinetics have been studied in a Phase 1 trial of 8 women during the last trimester of pregnancy. Zidovudine pharmacokinetics were similar to those of non-pregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery.

Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics.

Geriatric Patients

The pharmacokinetics of lamivudine and zidovudine have not been studied in subjects over 65 years of age.

Gender

There are no significant or clinically relevant gender differences in the pharmacokinetics of the individual components (lamivudine or zidovudine) based on the available information that was analyzed for each of the individual components.

Race

Lamivudine: There are no significant or clinically relevant racial differences in lamivudine pharmacokinetics based on the available information that was analyzed for the individual lamivudine component.

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

Drug Interactions

No drug interaction trials have been conducted using COMBIVIR tablets.

Lamivudine and Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 hours).

Other interactions

Interferon Alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects *[see Warnings and Precautions (5.5)]*.

Table 4 presents drug interaction information for the individual components of COMBIVIR.

Table 4. Effect of Coadministered Drugs on Lamivudine and Zidovudine AUC[a]

Coadministered Drug and Dose	Drug and Dose	n	Concentrations of Lamivudine or Zidovudine		Concentration of Coadministered Drug
			AUC	Variability	
Nelfinavir 750 mg every 8 h x 7 to 10 days	Lamivudine single 150 mg	11	↑10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	Lamivudine single 300 mg	14	↑43%	90% CI: 32% to 55%	↔
Atovaquone 750 mg every 12 h with food	Zidovudine 200 mg every 8 h	14	↑31%	Range 23% to 78%[b]	↔
Clarithromycin 500 mg twice daily	Zidovudine 100 mg every 4 h x 7 days	4	↓12%	Range ↓34% to ↑14%	Not Reported
Fluconazole 400 mg daily	Zidovudine 200 mg every 8 h	12	↑74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	Zidovudine 200 mg every 4 h	9	↑43%	Range 16% to 64%[b]	↔
Nelfinavir 750 mg every 8 h x 7 to 10 days	Zidovudine single 200 mg	11	↓35%	Range 28% to 41%	↔
Probenecid 500 mg every 6 h x 2 days	Zidovudine 2 mg/kg every 8 h x 3 days	3	↑106%	Range 100% to 170%[b]	Not Assessed
Rifampin 600 mg daily x 14 days	Zidovudine 200 mg every 8 h x 14 days	8	↓47%	90% CI: 41% to 53%	Not Assessed
Ritonavir 300 mg every 6 h x 4 days	Zidovudine 200 mg every 8 h x 4 days	9	↓25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg	Zidovudine 100 mg every	6	↑80%	Range 64% to	Not Assessed

every 8 h x 4 days	8 h x 4 days			130%[b]	

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

[a] This table is not all inclusive.

[b] Estimated range of percent difference.

12.4 Microbiology

Mechanism of Action

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.

Zidovudine: Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is phosphorylated to its active 5′-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue.

Antiviral Activity

Lamivudine plus Zidovudine: In HIV-1–infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and fresh human peripheral blood lymphocytes (PBMCs) using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC_{50} values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. The EC_{50} values against HIV-2 isolates (n = 4) ranged from 0.003 to 0.120 microM in PBMCs. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

Zidovudine: The antiviral activity of zidovudine against HIV-1 was assessed in a number of cell lines including monocytes and fresh human peripheral blood lymphocytes. The EC_{50} and EC_{90} values for zidovudine were 0.01 to 0.49 microM (1 microM = 0.27 mcg per mL) and 0.1 to 9 microM, respectively. HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC_{50} values of 0.011 microM (range: 0.005 to 0.110 microM) from Virco (n = 92 baseline samples) and 0.0017 microM (range: 0.006 to 0.0340 microM) from Monogram Biosciences (n = 135 baseline samples). The EC_{50} values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 microM, and

against HIV-2 isolates from 0.00049 to 0.004 microM. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell culture.

Neither lamivudine nor zidovudine were antagonistic to tested anti-HIV agents, with the exception of stavudine where an antagonistic relationship with zidovudine has been demonstrated in cell culture. See full prescribing information for EPIVIR (lamivudine) and RETROVIR (zidovudine).

Resistance

In subjects receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most subjects became phenotypically and genotypically resistant to lamivudine within 12 weeks.

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from subjects after prolonged lamivudine/zidovudine therapy. Dual resistance required the presence of multiple amino acid substitutions, the most essential of which may be G333E. The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.

Lamivudine: Lamivudine-resistant isolates of HIV-1 have been selected in cell culture and have also been recovered from subjects treated with lamivudine or lamivudine plus zidovudine. Genotypic analysis of isolates selected in cell culture and recovered from lamivudine-treated subjects showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

Zidovudine: HIV-1 isolates with reduced susceptibility to zidovudine have been selected in cell culture and were also recovered from subjects treated with zidovudine. Genotypic analyses of the isolates selected in cell culture and recovered from zidovudine-treated subjects showed thymidine analog mutation (TAM) substitutions in HIV-1 RT (M41L, D67N, K70R, L210W, T215Y or F, and K219E/R/H/Q/N) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of substitutions.

In some subjects harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine.

Cross-resistance

Cross-resistance has been observed among NRTIs. Cross-resistance between lamivudine and zidovudine has not been reported. In some subjects treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a substitution at codon 184, which confers resistance to lamivudine.

TAM substitutions are selected by zidovudine and confer cross-resistance to abacavir, didanosine, stavudine, and tenofovir.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the recommended dose of 300 mg.

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

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

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

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

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

Mutagenicity

Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

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

Impairment of Fertility

Lamivudine: Lamivudine did not affect male or female fertility in rats at a dose associated with exposures approximately 130 times higher than the exposure in humans at the dose of 300 mg.

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

13.2 Animal Toxicology and/or Pharmacology

Lamivudine

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

Zidovudine

Oral teratology studies in the rat and in the rabbit at doses up to 500 mg per kg per day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg per kg per day and rabbits given 500 mg per kg per day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg per kg per day (very near the oral median lethal dose in rats of 3,683 mg per kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated AUC in rats at this dose level was 300 times the daily AUC in humans given 600 mg per day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg per kg per day or less.

14 CLINICAL STUDIES

One COMBIVIR tablet given twice daily is an alternative regimen to EPIVIR tablets 150 mg twice daily plus RETROVIR 600 mg per day in divided doses.

14.1 Adults

The NUCB3007 (CAESAR) trial was conducted using EPIVIR 150-mg tablets (150 mg twice daily) and RETROVIR 100-mg capsules (2 x 100 mg 3 times daily). CAESAR was a

multi-center, double-blind, placebo-controlled trial comparing continued current therapy (zidovudine alone [62% of subjects] or zidovudine with didanosine or zalcitabine [38% of subjects]) to the addition of EPIVIR or EPIVIR plus an investigational non-nucleoside reverse transcriptase inhibitor, randomized 1:2:1. A total of 1,816 HIV-1-infected adults with 25 to 250 (median 122) CD4 cells per mm^3 at baseline were enrolled: median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median duration on trial was 12 months. Results are summarized in Table 5.

Table 5. Number of Subjects (%) with at Least 1 HIV-1 Disease-progression Event or Death

Endpoint	Current Therapy (n = 460)	EPIVIR plus Current Therapy (n = 896)	EPIVIR plus a NNRTI[a] plus Current Therapy (n = 460)
HIV-1 progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

[a] An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United States.

14.2 Prevention of Maternal-Fetal HIV-1 Transmission

The utility of zidovudine alone for the prevention of maternal-fetal HIV-1 transmission was demonstrated in a randomized, double-blind, placebo-controlled trial conducted in HIV-1-infected pregnant women with CD4+ cell counts of 200 to 1,818 cells per mm^3 (median in the treated group: 560 cells per mm^3) who had little or no previous exposure to zidovudine. Oral zidovudine was initiated between 14 and 34 weeks of gestation (median 11 weeks of therapy) followed by IV administration of zidovudine during labor and delivery. Following birth, neonates received oral zidovudine syrup for 6 weeks. The trial showed a statistically significant difference in the incidence of HIV-1 infection in the neonates (based on viral culture from peripheral blood) between the group receiving zidovudine and the group receiving placebo. Of 363 neonates evaluated in the trial, the estimated risk of HIV-1 infection was 7.8% in the group receiving zidovudine and 24.9% in the placebo group, a relative reduction in transmission risk of 68.7%. Zidovudine was well tolerated by mothers and infants. There was no difference in pregnancy-related adverse events between the treatment groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

COMBIVIR tablets, containing 150 mg lamivudine and 300 mg zidovudine, are white, scored, film-coated, modified-capsule-shaped tablets, debossed on both tablet faces, such that when broken in half, the full “GXFC3” code is present on both halves of the tablet (“GX” on one face and “FC3” on the opposite face of the tablet). They are available as follows:

60 Tablets/Bottle (NDC 49702-202-18).

Unit Dose Pack of 120 (NDC 49702-202-29).

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

17 PATIENT COUNSELING INFORMATION

Neutropenia and Anemia

Inform patients that the important toxicities associated with zidovudine are neutropenia and/or anemia. Inform them of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced HIV-1 disease *[see Boxed Warning, Warnings and Precautions (5.1)]*.

Myopathy

Inform patients that myopathy and myositis with pathological changes, similar to that produced by HIV-1 disease, have been associated with prolonged use of zidovudine *[see Warnings and Precautions (5.2)]*.

Lactic Acidosis/Hepatomegaly

Inform patients that some HIV medicines, including COMBIVIR, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) *[see Warnings and Precautions (5.3)]*.

Patients with Hepatitis B or C Co-infection

Advise patients co-infected with HIV-1 and HBV that worsening of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Advise patients to discuss any changes in regimen with their physician *[see Warnings and Precautions (5.4)]*.

Inform patients with HIV-1/HCV co-infection that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.6)]*.

Related Products that are Not Recommended

Inform patients that they should not take COMBIVIR with ATRIPLA®, COMPLERA®, DUTREBIS™, EMTRIVA®, EPIVIR, EPIVIR-HBV®, EPZICOM®, RETROVIR, STRIBILD®, TRIUMEQ®, TRIZIVIR®, or TRUVADA® *[see Warnings and Precautions (5.5)]*.

Drug Interactions

Caution patients about the use of other medications, including ganciclovir, interferon alfa, and ribavirin, which may exacerbate the toxicity of zidovudine *[see Drug Interactions (7.3)]*.

Immune Reconstitution Syndrome

In some patients with advanced HIV infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection *[see Warnings and Precautions (5.8)]*.

Redistribution/Accumulation of Body Fat

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.9)]*.

Information about HIV-1 Infection

COMBIVIR is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients must remain on continuous HIV therapy to control HIV-1 infection and decrease HIV-related illness. Inform patients that sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death.

Advise patients to remain under the care of a physician when using COMBIVIR.

Advise patients to take all HIV medications exactly as prescribed.

Advise patients to avoid doing things that can spread HIV-1 infection to others.

Advise patients not to re-use or share needles or other injection equipment.

Advise patients not to share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.

Advise patients to always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Female patients should be advised not to breastfeed. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Instruct patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Manufactured for:

ViiV Healthcare
Research Triangle Park, NC 27709

by:

GlaxoSmithKline
Research Triangle Park, NC 27709

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Basingstoke, UK

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