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DUOVIR Tablets (Lamivudine + Zidovudine)

Black Box Warning

Hematologic toxicity, myopathy, lactic acidosis and severe hepatomegaly with steatosis, and exacerbations of hepatitis B

Zidovudine, a component of DUOVIR (zidovudine and lamivudine), has been associated with hematologic toxicity, including neutropenia and severe anemia, particularly in patients with advanced human immunodeficiency virus-1 (HIV-1) disease (see warnings and precautions).

Prolonged use of zidovudine has been associated with symptomatic myopathy (see warnings and precautions).

Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Discontinue zidovudine and lamivudine if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur (see warnings and precautions).

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 DUOVIR. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue DUOVIR and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see warnings and precautions).

Composition

Duovir tablet

Each film-coated tablet contains:

Lamivudine ..... 150 mg

Zidovudine ..... 300 mg

Dosage Form

Film-coated tablet

Description

DUOVIR tablet is a combination of lamivudine and zidovudine, which belong to the nucleoside analog class of antiretroviral drugs. Each tablet of DUOVIR contains half of the commonly prescribed daily doses of both lamivudine and zidovudine. With the availability of this combination tablet, patients may be better able to adhere to complex drug treatment regimens, thereby enhancing compliance.

Pharmacology

▶ Pharmacodynamics

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 transciptase (RT) via DNA chain termination after incorporation of the nucleoside 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.

▶ Pharmacokinetics

Pharmacokinetics in Adults

One lamivudine/zidovudine tablet was bioequivalent to 1 lamivudine tablet (150 mg) plus 1 zidovudine 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'-amin--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 1.

Table 1: Pharmacokinetic parametersa 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	n=38[c]	0.60	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 .

[c] Children.

[d] Adults.

[e] Approximate range.

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

Special Populations

Renal Impairment

Lamivudine/Zidovudine: The effect of renal impairment on the combination of lamivudine and zidovudine has not been evaluated (see the prescribing information for the individual lamivudine and zidovudine components).

Hepatic Impairment

Lamivudine/Zidovudine: The effect of hepatic impairment on the combination of lamivudine, and zidovudine has not been evaluated (see the 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 patients 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.

Indications

DUOVIR, a combination of two nucleoside analogues, is indicated in combination with other antiretrovirals for the treatment of HIV-1 infection.

Dosage And Administration

▶ Recommended dosage adults and adolescents

The recommended dosage of DUOVIR tablet 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.

▶ Not Recommended Due to Lack of Dosage Adjustment

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

- pediatric patients weighing less than 30 kg (see WARNING and PRECAUTIONS)
- patients with creatinine clearance less than 50 mL per min(see WARNING and PRECAUTIONS)
- patients with hepatic impairment(see WARNING and PRECAUTIONS)
- patients experiencing dose-limiting adverse reactions.

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

Contraindications

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

Warnings And Precautions

▶ Drug Interactions

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

▶ Hematologic Toxicity/Bone Marrow Suppression

Zidovudine, a component of Zidovudine/Lamivudine tablets, has been associated with hematologic toxicity, including neutropenia and anemia, particularly in patients with advanced HIV-1 disease. Zidovudine/Lamivudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count less than 1000 cells/mm^3 or hemoglobin less than 9.5 grams per dL (see UNDESIRABLE EFFECTS).

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

▶ 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 Zidovudine/Lamivudinetablet.

▶ Lactic Acidosis and 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 lamivudine and zidovudine.

Treatment with Zidovudine/Lamivudine 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).

▶ Patients with Hepatitis B Virus Co-infection

Post-treatment Exacerbations of Hepatitis

Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. See full prescribing information for 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 variants associated with resistance to lamivudine has also 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 lamivudine.

▶ Use with Interferon- and Ribavirin-Based Regimens

Patients receiving interferon alfa with or without ribavirin and Zidovudine/lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decomposition, neutropenia, and anemia. See full prescribing information for lamivudine and zidovudine. Discontinuation of lamivudine and zidovudine 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 (eg, Childs Pugh greater than 6) (see the complete prescribing information for interferon and ribavirin).
Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Co-administration of ribavirin and zidovudine is not advised.

▶ Pancreatitis

Zidovudine/lamivudine should be used with caution in patients with a history of pancreatitis or other significant risk factors for the development of pancreatitis. Treatment with Zidovudine/lamivudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see UNDESIRABLE EFFECTS).

▶ Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including lamivudine and zidovudine. 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 , 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.

▶ 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.

▶ Patients with Impaired Renal Function

Zidovudine/lamivudine is not recommended for patients with creatinine clearance less than 50 mL per min because it is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of the lamivudine or zidovudine is required for patients with renal impairment, then the individual components should be used (see DOSAGE AND ADMINISTRATION).

▶ Patients with Impaired Hepatic Function

Zidovudine/lamivudine is a fixed-dose combination and the 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 functions, which may increase the risk of hematologic toxicity. Frequent monitoring of hematologic toxicities is advised.

Pregnancy

Risk Summary

Available data from the APR show no difference in the overall risk of birth defects for lamivudine or zidovudine compared with the background rate for birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program (MACDP) reference population . The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks gestation. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The background risk for major birth defects and miscarriage for the indicated population is unknown.

In animal reproduction studies, oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at systemic exposure (AUC) similar to the recommended clinical dose; however, no adverse development effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (Cmax) 35 times the recommended clinical dose. Administration of oral zidovudine to female rats prior to mating and throughout gestation resulted in embryotoxicity at doses that produced systemic exposure (AUC) approximately 33 times higher than exposure at the recommended clinical dose. However, no embryotoxicity was observed after oral administration of zidovudine to pregnant rats during organogenesis at doses that produced systemic exposure (AUC) approximately 117 times higher than exposures at the recommended clinical dose. Administration of oral zidovudine to pregnant rabbits during organogenesis resulted in embryotoxicity at doses that produced systemic exposure (AUC) approximately 108 times higher than exposure at the recommended clinical dose. However, no embryotoxicity was observed at doses that produced systemic exposure (AUC) approximately 23 times higher than exposures at the recommended clinical dose.

Data

Human Data

Lamivudine: Based on prospective reports to the APR of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,500 exposed in the first trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of birth defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.8% (95% CI: 2.5% to 3.3%) following second/third trimester exposure to lamivudine-containing regimens.

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical studies 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. These trials were not designed or powered to provide efficacy information. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of lamivudine were 3.9 (1.2 to 12.8)–fold greater compared with paired maternal serum concentration (n = 8).

Zidovudine: Based on prospective reports to the APR of over 13,000 exposures to zidovudine during pregnancy resulting in live births (including over 4,000 exposed in the first trimester), there was no difference between the overall risk of birth defects for zidovudine compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of birth defects in live births was 3.2% (95% CI: 2.7% to 3.8%) following first trimester exposure to zidovudine-containing regimens and 2.8% (95% CI: 2.5% to 3.2%) following second/third trimester exposure to

zidovudine-containing regimens.
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. Of the 363 neonates that were evaluated, 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.
Zidovudine has been shown to cross the placenta and concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery.
Animal Data
Lamivudine: Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300, and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day) during organogenesis (on gestation Days 7 through 16 and 8 through 20, respectively). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (Cmax) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryolethality was seen in the rabbit at system exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (Cmax) 35 times higher than human exposure at the recommended daily dose. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the pre-and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg per kg per day (from gestation Day 6 through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, was not affected by maternal administration of lamivudine.
Zidovudine
A study in pregnant rats (at 50, 150, or 450 mg per kg per day starting 26 days prior to mating through gestation to postnatal Day 21) showed increased fetal resorptions at doses that produced systemic exposures (AUC) approximately 33 times higher than exposure at the recommended daily human dose (300 mg twice daily). However, in an oral embryo-fetal development study in rats (at 125, 250, or 500 mg per kg per day on gestation Days 6 through 15), no fetal resorptions were observed at doses that produced systemic exposure (AUC) approximately 117 times higher than exposures at the recommended daily human dose. An oral embryo-fetal development study in rabbits (at 75, 150, or 500 mg per kg per day on gestation Days 6 through 18) showed increased fetal resorptions at the 500 mg-per-kg-per-day dose, which produced systemic exposures (AUC) approximately 108 times higher than exposure at the recommended daily human dose; however, no fetal resorptions were noted at doses up to 150 mg per kg per day, which produced systemic exposure (AUC) approximately 23 times higher than exposures at the recommended daily human dose. These oral embryo-fetal development studies in the rat and rabbit revealed no evidence of fetal malformations with zidovudine. In another developmental toxicity study, pregnant rats (dosed at 3,000 mg per kg per day from Days 6 through 15 of gestation) showed marked maternal toxicity and an increased incidence of fetal malformations at exposures greater than 300 times the recommended daily human dose based on AUC. However, there were no signs of fetal malformations at doses up to 600 mg per kg per day.

▶ Lactation

Risk Summary
The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers should not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Lamivudine and zidovudine are present in human milk.

There is no information on the effects of lamivudine or zidovudine on the breastfed infant or the effects of the drugs on milk production. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving Zidovudine/lamivudine.
Although no studies of lamivudine/zidovudine excretion in breast milk have been performed, lactation studies performed with lamivudine and zidovudine show that both drugs are excreted in human breast milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine. In another study, after administration of a single dose of 200 mg zidovudine to 13 HIV-1-infected women, the mean concentration of zidovudine was similar in human milk and serum.

▶ Pediatric Use

Zidovudine/lamivudine 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.

▶ Geriatric Use

Clinical trials of Zidovudine/lamivudine did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of Zidovudine/lamivudine in elderly patient reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Undesirable Effects

The following are the adverse reactions are discussed in other sections of the labelling:
Hematologic toxicity, including neutropenia and anemia (see BOXED WARNING, WARNINGS AND PRECAUTIONS)
Symptomatic myopathy (see BOXED WARNING, WARNINGS AND PRECAUTIONS).
Lactic acidosis and severe hepatomegaly with steatosis (see BOXED WARNING, WARNINGS AND PRECAUTIONS).
Exacerbations of hepatitis B (see BOXED WARNING, WARNINGS AND PRECAUTIONS).
Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C (see WARNINGS AND PRECAUTIONS)
Exacerbation of anemia in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine (see WARNINGS AND PRECAUTIONS).
Pancreatitis (see WARNINGS AND PRECAUTIONS).
Immune reconstitution syndrome (see WARNINGS AND PRECAUIONS)
Fat redistribution (see WARNING AND PRECAUTIONS)

▶ 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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Lamivudine Plus Zidovudine Administered As Separate Formulations
In 4 randomized, controlled trials of lamivudine 300 mg per day plus zidovudine 600 mg per day, the following selected adverse reactions and laboratory abnormalities were observed (see tables 2 and 3).

Table 2: Selected clinical adverse reactions (greater than or equal to 5% frequency) in 4 controlled clinical trials with lamivudine 300 mg per day and zidovudine 600 mg per day

Adverse Reaction	Lamivudine plus Zidovudine (n = 251)
Body as a whole	
Headache	35%
Malaise and fatigue	27%
Fever or chills	10%
Digestive	
Nausea	33%
Diarrhea	18%
Nausea and vomiting	13%
Anorexia and/or decreased appetite	10%
Abdominal pain	9%
Abdominal cramps	6%
Dyspepsia	5%
Nervous system	
Neuropathy	12%
Insomnia and other sleep disorders	11%
Dizziness	10%
Depressive disorders	9%
Respiratory	
Nasal signs and 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 lamivudine in controlled clinical trials (see WARNINGS AND PRECAUTIONS).

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

Table 3: Frequencies of selected laboratory abnormalities among adults in 4 controlled clinical trials of lamivudine 300 mg per day plus zidovudine 600 mg per daya

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

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

▶ 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).
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, post-treatment exacerbation of hepatitis B (see BOXED WARNING; warnings and precautions).
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.
If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com . You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.
By reporting side effects, you can help provide more information on the safety of this product.

Overdosage

There is no known specific treatment for overdose with Zidovudine/lamivudine. If overdose occurs, the patients 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 exposure 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--
-D-glucopyranuronosylthymidine (GZDV), is enhanced.

Packaging Information

DUOVIR .....Blister pack of 10 tablets and Container of 60 tablets

Last updated: June 2018

Last reviewed: June 2018

DUOVIR Tablets
