

Zidovudine and Lamivudine Tablets

DUOVIR

WARNINGS

RISK OF HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B

ZIDOVUDINE, ONE OF THE TWO ACTIVE INGREDIENTS IN DUOVIR, HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY, INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HIV-1 DISEASE (SEE WARNINGS AND PRECAUTIONS). PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

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

SEVERE AND 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 OF THE COMPONENTS OF THE COMBINATION. 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 Tablets

Each film-coated tablet contains:

Lamivudine 150 mg

Zidovudine 300 mg USP

DOSAGE FORM

Film-coated tablet

DESCRIPTION

DUOVIR Tablets are a combination of lamivudine and zidovudine, which belong to the nucleoside analog class of antiretroviral drugs. Each tablet of **DUOVIR Tablets** 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 analog. 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 nucleoside analog. 3TC-TP is a weak inhibitor of mammalian DNA polymerases alpha and beta and mitochondrial DNA polymerase gamma.

Zidovudine: Zidovudine is a synthetic nucleoside analog. 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. ZDV-TP is a weak inhibitor of the cellular DNA polymerase alpha and mitochondrial DNA polymerase gamma, and has been reported to be incorporated into the DNA of cells in culture.

Pharmacokinetics in Adults

Lamivudine: The pharmacokinetic properties of lamivudine in fasting patients are summarized in Table 1. Following oral administration, lamivudine is rapidly absorbed and extensively distributed, the oral bioavailability being 86% and plasma concentration (C_{max}) being 1.5 mcg/ml. Lamivudine distributes into extravascular spaces and the volume of distribution is independent of dose and does not correlate with body weight. Metabolism of lamivudine is a minor route of elimination, with an elimination half-life of 5–7 hours. Within 12 hours after a single oral dose of lamivudine, approximately 5% of the dose is excreted as the trans-sulfoxide metabolite in the urine.

Zidovudine: The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 1. Following oral administration, zidovudine is rapidly absorbed and extensively distributed, with peak serum concentrations occurring within 0.5–1.5 hours, and an oral bioavailability of 63%. Zidovudine is eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is 3'-azido-3'-deoxy-5'-O-(beta)-D-glucopyranuronosylthymidine (GZDV), which has an elimination half-life of 1 hour. GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively.

A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one-fifth of the zidovudine AUC.

| Table 1: Pharmacokinetic Parameters * for Lamivudine/Zidovudine in Adults | | | | |
|--|------------------------|--------|------------------------|--------|
| Parameter | Lamivudine | | Zidovudine | |
| Oral bioavailability (%) | 86 ± 16 | n=12 | 64 ± 10 | n=5 |
| Apparent volume of distribution (L/kg) | 1.3 ± 0.4 | n=20 | 1.6 ± 0.6 | n=8 |
| Plasma protein binding (%) | <36 | | <38 | |
| CSF:Plasma ratio † | 0.12 [0.04 to 0.47] | n=38 ‡ | 0.60 [0.04 to 2.62] | n=39 § |
| Systemic clearance (L/hr/kg) | 0.33 ± 0.06 | n=20 | 1.6 ± 0.6 | n=6 |
| Renal clearance (L/hr/kg) | 0.22 ± 0.06 | n=20 | 0.34 ± 0.05 | n=9 |
| Elimination half-life (hr) # | 5 to 7 | | 0.5 to 3 | |
| * Data presented as mean ± standard deviation except where noted. | | | | |
| † Median [range]. | | | | |
| ‡ Children. | | | | |
| § Adults. | | | | |
| # Approximate range. | | | | |

INDICATIONS

DUOVIR Tablets are indicated for the treatment of HIV infection, as part of combination therapy.

DOSAGE AND ADMINISTRATION

Adults and Adolescents

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

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

A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Because **DUOVIR Tablets** are a fixed-dose combination that cannot be adjusted for this patient

population, they are not recommended for patients with impaired hepatic function.

CONTRAINDICATIONS

DUOVIR Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (eg, anaphylaxis, Stevens-Johnson Syndrome) to any of the components of the product.

WARNINGS AND PRECAUTIONS

Hematologic Toxicity/Bone Marrow Suppression

Zidovudine, a component of **DUOVIR Tablets**, has been associated with hematologic toxicity, including neutropenia and anemia, particularly in patients with advanced HIV-1 disease. **DUOVIR Tablets** should be used with caution in patients who have bone marrow compromise, evidenced by granulocyte counts less than 1000 cells/mm³ or hemoglobin less than 9.5 g/dL (see **UNDESIRABLE EFFECTS**).

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

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 alone or in combination, including zidovudine, lamivudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Particular caution should be exercised when administering **DUOVIR Tablets** to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with **DUOVIR Tablets** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Myopathy

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

Patients with HIV And HBV Co-infection

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response. Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with HBV. Post-treatment exacerbations of hepatitis have also been reported (see **WARNINGS and PRECAUTIONS**).

Post-Treatment Exacerbations of Hepatitis

In clinical trials in non-HIV-1-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to the re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from postmarketing experience after changes from lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of post-treatment exacerbations of hepatitis.

Other Lamivudine-, Zidovudine-, and/or Emtricitabine-Containing Products

DUOVIR Tablets are a fixed-dose combination of lamivudine and zidovudine. **DUOVIR Tablets** should not be administered concomitantly with other lamivudine- or zidovudine-containing products, including lamivudine tablets and oral solution; lamivudine-HBV tablets and oral solution; zidovudine tablets, capsules, syrup and I.V. infusion; abacavir sulfate and lamivudine tablets; abacavir sulfate, lamivudine, and zidovudine tablets; or emtricitabine-containing products, including efavirenz, emtricitabine, and tenofovir, or emtricitabine, or emtricitabine and tenofovir.

Interferon- and Ribavirin-Based Regimens

In vitro studies have shown that ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (eg, loss of HIV-1/HCV virologic suppression) was seen when ribavirin was co-administered with lamivudine in HIV-1/HCV co-infected patients, **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.** Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic

decompensation. Discontinuation of lamivudine 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 >6) (see the complete prescribing information for interferon and ribavirin).

Pancreatitis

DUOVIR Tablets should be used with caution in patients with a history of pancreatitis or other significant risk factors for the development of pancreatitis. Treatment with **DUOVIR Tablets** should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including zidovudine. During the initial phase of combination antiretroviral treatment, patients whose immune system responds 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.

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.

Drug Interactions

Ribavirin

In vitro data indicate that ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (eg, plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (eg, loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), or stavudine (n = 10), or zidovudine (n = 6) was co-administered as part of a multi-drug regimen to HIV-1/HCV co-infected patients (see **WARNINGS AND PRECAUTIONS**).

Antiretroviral Agents

Lamivudine :

Zalcitabine: Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of **DUOVIR Tablets** in combination with zalcitabine is not recommended.

Zidovudine:

Stavudine: Concomitant use of **DUOVIR Tablets** with stavudine should be avoided since an antagonistic relationship with zidovudine has been demonstrated *in vitro*.

Nucleoside Analogues Affecting DNA Replication

Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the *in vitro* antiviral activity of zidovudine against HIV-1; hence, concomitant use of such drugs should be avoided.

Doxorubicin

Zidovudine: Concomitant use of **DUOVIR Tablets** with doxorubicin should be avoided since an antagonistic relationship with zidovudine has been demonstrated *in vitro*.

Hematologic/Bone Marrow Suppressive/Cytotoxic Agents

Zidovudine: Co-administration of ganciclovir, interferon alfa, ribavirin, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Interferon- and Ribavirin-Based Regimens

Lamivudine: Although no evidence of a pharmacokinetic or pharmacodynamic interaction (eg, loss of HIV-I/HCV virologic suppression) was seen when ribavirin was co-administered with lamivudine in HIV-I/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-I/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin (see **WARNINGS AND PRECAUTIONS**;).

Trimethoprim/Sulfamethoxazole (TMP/SMX)

Lamivudine: No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX, such as those used to treat PCP.

Lamivudine Plus Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV -I-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).

Table 2: Effect of Co-administered Drugs on Lamivudine and Zidovudine AUC*

Note: ROUTINE DOSE MODIFICATION OF LAMIVUDINE AND ZIDOVUDINE IS NOT WARRANTED WITH CO-ADMINISTRATION OF THE FOLLOWING DRUGS

| Drugs That May Alter Lamivudine Blood Concentrations | | | | | |
|---|-----------------|----|---------------------------|-----------------------|--------------------------------------|
| Coadministered Drug and Dose | Lamivudine Dose | n | Lamivudine Concentrations | | Concentration of Coadministered Drug |
| | | | AUC | Variability | |
| Nelfinavir 750 mg q 8 hr x 7 to 10 days | single 150 mg | 11 | ↑AUC 10% | 95% CI: 1% to 20% | ↔ |
| Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days | single 300 mg | 14 | ↑AUC 43% | 90% CI: 32% to 55% | ↔ |

| Drugs That May Alter Zidovudine Blood Concentrations | | | | | |
|--|-------------------------|----|---------------------------|------------------------------------|--------------------------------------|
| Coadministered Drug and Dose | Zidovudine Dose | n | Zidovudine Concentrations | | Concentration of Coadministered Drug |
| | | | AUC | Variability | |
| Atovaquone 750 mg q 12 hr with food | 200 mg q 8 hr | 14 | ↑AUC 31% | Range 23% to 78% [†] | ↔ |
| Fluconazole 400 mg daily | 200 mg q 8 hr | 12 | ↑AUC 74% | 95% CI: 54% to 98% | Not Reported |
| Methadone 30 to 90 mg daily | 200 mg q 4 hr | 9 | ↑AUC 43% | Range 16% to 64% [†] | ↔ |
| Nelfinavir 750 mg q 8 hr x 7 to 10 days | single 200 mg | 11 | ↓AUC 35% | Range 28% to 41% | ↔ |
| Probenecid 500 mg q 6 hr x 2 days | 2 mg/kg q 8 hr x 3 days | 3 | ↑AUC 106% | Range 100% to 170% [†] | Not Assessed |
| Rifampin 600 mg daily x 14 days | 200 mg q 8 hr X 14 days | 8 | ↓AUC 47% | 90% CI: 41% to 53% | Not Assessed |
| Ritonavir 300 mg q 6 hr x 4 days | 200 mg q 8 hr x 4 days | 9 | ↓AUC 25% | 95% CI: 15% to 34% | ↔ |

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

* This table is not all-inclusive.

† Estimated range of percent difference.

Renal Impairment

Reduction of the dosages of lamivudine and zidovudine is recommended for patients with impaired renal function. Patients with creatinine clearance <50 mL/min should not receive **DUOVIR Tablets** because they are a fixed-dose combination that cannot be adjusted.

Hepatic Impairment

A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. **DUOVIR Tablets** are not recommended for patients with impaired hepatic function because they are a fixed-dose combination that cannot be adjusted.

Pregnancy

Category C: There are no adequate and well-controlled studies of lamivudine/zidovudine in pregnant women. Reproduction studies with lamivudine and zidovudine have been performed in animals. **DUOVIR Tablets** should be used during pregnancy only if the potential benefits outweigh the risks.

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. 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 nonpregnant 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).

Human Data: Lamivudine: Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical studies conducted in South Africa. The study 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 nonpregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

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

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 embryoletality 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.

Zidovudine: Increased fetal resorptions occurred in pregnant rats and rabbits treated with doses of zidovudine that produced drug plasma concentrations 66 to 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 AUC in humans given 600 mg/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.

Lactation

The Centers for Disease Control and Prevention recommend that HIV-infected mothers should not breastfeed their infants to avoid risking post-natal transmission of HIV-1 infection. No data are available on this combination or lamivudine. But, both zidovudine and lamivudine are excreted in human breast milk. Therefore, there is a potential for adverse effects in nursing infants.

Mothers should be instructed not to breastfeed if they are receiving DUOVIR Tablets.

Although no studies have been performed regarding the excretion of **DUOVIR Tablets** in breast milk, 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

DUOVIR Tablets should not be administered to pediatric patients less than 12 years of age because they are a fixed-dose combination that cannot be adjusted for this patient population.

Geriatric Use

Clinical studies of Lamivudine plus zidovudine did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **DUOVIR Tablets** are not recommended for patients with impaired renal function (ie, creatinine clearance <50mL/min) (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

UNDESIRABLE EFFECTS

Zidovudine and Lamivudine

In four randomized, controlled trials of lamivudine 300 mg per day plus zidovudine 600 mg per day, the following selected clinical and laboratory adverse events were observed (see Tables 3 and 4).

Table 3: Selected Clinical Adverse Events (≥5% Frequency) in Four Controlled Clinical Trials with Lamivudine 300 mg/day and Zidovudine 600 mg/day

| Adverse Event | 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 2613 adult patients (0.3%) who received lamivudine in controlled clinical trials. Selected laboratory abnormalities observed during therapy are listed in Table 4 .

Table 4: Frequencies of Selected Laboratory Abnormalities Among Adults in Four Controlled Clinical Trials of Lamivudine 300 mg/day Plus Zidovudine 600 mg/day*

| 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.

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

Observed During Clinical Practice:

The following events have been identified during post-approval use of lamivudine, zidovudine, and/or lamivudine/zidovudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine, zidovudine, and/or lamivudine/zidovudine.

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

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 severe anemias progressing on therapy), lymphadenopathy, splenomegaly.

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, post-treatment exacerbation of hepatitis B (see **BOXED WARNINGS; 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.

OVERDOSAGE

There is no known antidote for **DUOVIR Tablets**.

Lamivudine: One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs noted and hematologic tests remained normal. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

Zidovudine: Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposure up to 50 grams. The only consistent findings were nausea and vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy, confusion, and one report of grand mal seizure. Hematologic changes were transient. All patients recovered.

Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, GZDV, is enhanced.

PACKAGING INFORMATION

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

Last updated: May 2009